CLINICAL GUIDELINES PROGRAM
NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV • HCV • STIs • SUBSTANCE USE • LGBTQ+ HEALTH

# PrEP to Prevent HIV and Promote Sexual Health

## Updates, Authorship, and Related Resources

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|---|---|
| Date of current publication | October 16, 2025 |
| Highlights of changes, additions, and updates in the October 16, 2025 edition | • Comprehensive update (text and references updated throughout)<br>• Recommendations and text added throughout on subcutaneous lenacapavir (SC LEN) as pre-exposure prophylaxis (PrEP)<br>• Text added throughout on tenofovir alafenamide/emtricitabine (TAF/FTC) as an alternative PrEP option for HIV exposures through receptive vaginal sex for individuals in whom tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is not tolerated or not desired<br>• Choosing and Prescribing a PrEP Regimen > Alternative Oral Dosing: On-Demand PrEP section: Text added on "2-1-1-1" on-demand dosing of TDF/FTC for receptive vaginal HIV exposures |
| Intended users | Clinicians recommending, initiating, or maintaining PrEP care for individuals at risk of acquiring HIV |
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| Writing group | Sanjiv S. Shah, MD, MPH, AAHIVS; Steven M. Fine, MD, PhD; Joseph P. McGowan, MD, FACP, FIDSA, AAHIVS; Samuel T. Merrick, MD, FIDSA; Asa E. Radix, MD, MPH, PhD, FACP, AAHIVS; Anne K. Monroe, MD, MSPH; Jessica Rodrigues, MPH, MS; Christopher J. Hoffmann, MD, MPH, MSc, FACP; Brianna L. Norton, DO, MPH; Charles J. Gonzalez, MD |
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| Related NYSDOH AI resources | **Guidelines**<br>• Diagnosis and Management of Acute HIV Infection<br>• Doxycycline Post-Exposure Prophylaxis to Prevent Bacterial Sexually Transmitted Infections<br>• Hepatitis C Virus Screening, Testing, and Diagnosis in Adults<br>• HIV Testing<br>• Immunizations for Adults With HIV<br>• Prevention and Management of Hepatitis B Virus Infection in Adults With HIV<br>• Primary Care for Adults With HIV<br>• PEP to Prevent HIV Infection<br>• Rapid ART Initiation<br>• Selecting an Initial ART Regimen<br>• Substance Use Harm Reduction in Medical Care<br>• Substance Use Screening, Risk Assessment, and Use Disorder Diagnosis in Adults<br>**Guidance**<br>• Drug-Drug Interaction Guide: From HIV Prevention to Treatment<br>• GOALS Framework for Sexual History Taking in Primary Care<br>• U=U Guidance for Implementation in Clinical Settings<br>**Podcast**<br>• *Viremic—Cases in HIV* |

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**Committee:** Medical Care Criteria Committee
**Date of original publication:** October 10, 2019

## Contents

# Purpose of This Guideline

HIV prevention with pre-exposure prophylaxis (PrEP) is the use of antiretroviral medications by individuals who do not have HIV to reduce their risk of acquiring HIV. PrEP is a cornerstone of HIV prevention and is strongly endorsed by New York State. However, it is underutilized, particularly by communities disproportionately affected by HIV.

The New York State Ending the Epidemic (ETE) initiative presents strategies to decrease HIV prevalence and end the AIDS epidemic in New York State. The third pillar of the 3-pillar ETE plan is facilitating access to PrEP as a proven strategy to prevent HIV acquisition among individuals at risk. Its inclusion as a pillar of this initiative emphasizes the safety and effectiveness of PrEP as an HIV prevention method. This guideline was developed by the Medical Care Criteria Committee of the NYSDOH AI Clinical Guidelines Program to help clinicians successfully start and continue PrEP for individuals at risk of acquiring HIV.

In support of the ETE initiative and to reduce new HIV infections in New York State, the goals of this guideline are to:

- Increase clinician awareness and knowledge of PrEP efficacy.
- Assist clinicians in identifying candidates for PrEP and increasing PrEP awareness, access, and uptake among individuals at risk of acquiring HIV through sexual and drug use exposures.
- Discuss barriers to PrEP access and encourage clinicians to assist PrEP candidates in reducing or eliminating these barriers.
- Provide clinicians with the information needed to help a PrEP candidate make the best choice regarding oral versus injectable PrEP and daily versus on-demand PrEP.
- Provide evidence-based recommendations for PrEP initiation, management, monitoring, and discontinuation.

**Note on "experienced" HIV care providers:** The NYSDOH AI Clinical Guidelines Program defines an "experienced HIV care provider" as a practitioner who has been accorded HIV Specialist status by the American Academy of HIV Medicine. Nurse practitioners (NPs) and licensed midwives who provide clinical care to individuals with HIV in collaboration with a physician may be considered experienced HIV care providers if all other practice agreements are met; NPs with more than 3,600 hours of qualifying experience do not require collaboration with a physician (8 NYCRR 79-5:1; 10 NYCRR 85.36; 8 NYCRR 139-6900). Physician assistants who provide clinical care to individuals with HIV under the supervision of an HIV Specialist physician may also be considered experienced HIV care providers (10 NYCRR 94.2).

# Improving PrEP Equity, Uptake, and Persistence Through Structural Support and Patient-Centered Choice

**PrEP uptake:** Although new HIV infections and diagnoses have steadily declined in New York State, these decreases have not been uniform across all groups. Men who have sex with men (MSM), particularly young MSM, and people of color continue to be overrepresented among those newly infected and diagnosed with HIV [NYSDOH 2023]. Computer simulation modeling suggests that increased PrEP uptake will be the single largest contributor to further reductions in new HIV infections and key to ending the HIV epidemic in New York State [Martin, et al. 2020]. However, data indicate that people of color, cisgender women, and individuals accessing Medicaid, 3 groups overrepresented among people with HIV, are accessing PrEP at lower levels than other groups in whom the disease burden is high [Ending the Epidemic Dashboard 2025]. For example, in 2023, 20.9% of new HIV diagnoses in New York State were in cisgender women and people assigned female at birth [NYSDOH 2023] but just 8% of all individuals who accessed PrEP in New York State were women [Ending the Epidemic Dashboard 2025]. When broken down by race, 43% of PrEP prescriptions were written for White individuals, 12% for Black individuals, 10% for Hispanic individuals, 27% for "unknown," 4% for Asian/Pacific Islander individuals, and 4% for "other" individuals [Ending the Epidemic Dashboard 2025].

**Barriers to PrEP access, use, and persistence:** PrEP uptake, adherence, and persistence vary widely across populations and are influenced by structural, care provider, and individual-level factors. Suboptimal awareness and acceptance of PrEP among at-risk individuals and their care providers remain key barriers to initiation [Townes, et al. 2021; Bazzi, et al. 2018; Mayer, et al. 2018].

Among Black MSM, low perceived HIV risk, stigma, and medical mistrust rooted in systemic racism significantly impede PrEP use. Those unaware of PrEP often have lower HIV testing rates, limited HIV knowledge, and higher rates of transactional sex [Russ, et al. 2021]. Additional structural barriers include lack of insurance and limited access to culturally competent care. Women who engage in sex work and use drugs face unique challenges including competing survival needs, low risk perception, and difficulty with daily adherence. Effective strategies include nonjudgmental care provider communication,

integrated HIV and substance use care, and adherence support. Clinicians may struggle with limited infrastructure and discomfort discussing sex work [Harris, et al. 2024]. Young MSM of color face care provider bias and a lack of culturally concordant care. Hiring staff with shared identities, providing affirming services, and LGBTQ+ cultural competency training can improve PrEP engagement [Ribas Rietti Souto, et al. 2024]. Individuals who inject drugs have low to moderate levels of PrEP awareness and very low PrEP uptake, varying from 0% to 3% in a systematic review [Mistler, et al. 2021]. There has been little research into effective ways to increase PrEP uptake in people who inject drugs. Addressing structural and stigma-related barriers for this population is essential. One study found that conversations about HIV prevention at syringe-exchange programs significantly increased PrEP awareness [Walters, et al. 2020].

Despite increased availability of oral PrEP (tenofovir disoproxil fumarate/emtricitabine [TDF/FTC] or tenofovir alafenamide/emtricitabine (TAF/FTC]) in high-burden settings, persistence (sustained PrEP use) remains low. Long-acting injectable PrEP with intramuscular cabotegravir (CAB LA) or subcutaneous lenacapavir (SC LEN) is highly acceptable and may improve adherence, although PrEP rollout faces challenges such as limited clinician capacity, high cost, lack of self-injection option, and concerns about potential integrase resistance with use of CAB LA. PrEP implementation strategies include task-shifting (e.g. home HIV self-testing or involvement of community health workers), clinician and staff training, establishment of billing and procurement protocols, development of appointment tracking systems, and integration into sexual health services [Joseph Davey, et al. 2025]. Expanding the number of PrEP prescribers beyond HIV and sexual health specialists to include primary care providers is essential. Additionally, clinicians must address unconscious bias, avoid assumptions about sexual or drug use behavior, and gain comfort with taking sexual histories [Calabrese, et al. 2018; Edelman, et al. 2017; Calabrese, et al. 2014]. If a patient requests PrEP and it is not medically contraindicated, it should be prescribed with appropriate follow-up.

Successful PrEP programs will address stigma, mistrust, low HIV risk perception, and structural inequities through culturally responsive, patient-centered care and offer flexible PrEP options, including the ability to switch modalities.

**PrEP persistence and episodic use:** PrEP effectiveness depends on sustained use, yet discontinuation remains common. A meta-analysis of oral PrEP use found that 41% of users discontinued within 6 months and 35.6% between 7 and 12 months, with discontinuation strongly associated with increased HIV incidence (2.1–3.6 vs. 0.0–0.1 per 100 person-years) [Guo, et al. 2024]. Discontinuation is more likely among younger people, individuals using substances (especially methamphetamine), women, and those with lower education or high out-of-pocket costs. Medicaid coverage, affordability, and living in an Ending the HIV Epidemic (EHE) county are associated with improved persistence [Dawit, et al. 2024]. Public transportation reliance is associated with lower continuation [Sharpe, et al. 2023], while use of health-system specialty pharmacies (HSSPs) improves persistence at 6, 12, and 18 months [Whelchel, et al. 2023].

Frequent required visits and laboratory testing can be experienced as “overmedicalization” and deter continuation. Although quarterly laboratory monitoring is standard for oral PrEP, it is not evidence-based and should be adapted to patient needs. At-home HIV testing or conveniently located external laboratory centers with annual in-person visits and telemedicine options can reduce structural barriers [Siegler, et al. 2019].

PrEP use may be noncontinuous, with individuals cycling on and off based on perceived HIV risk. Discontinuation does not always reflect program failure [Reed, et al. 2021]. For individuals who wish to stay on PrEP, removing barriers and tailoring care are essential.

**PrEP choice:** Offering individuals a choice of HIV prevention modalities including oral PrEP, long-acting injectable PrEP, and post-exposure prophylaxis (PEP) improves uptake, adherence, persistence, and satisfaction. In the SEARCH trial, a dynamic choice model allowing participants to switch modalities led to more than 5-fold higher biomedical coverage (69.7% vs. 13.3%) and reduced HIV incidence (0% vs. 1.8%) compared with standard of care [Kamya, et al. 2024]. A modeling analysis projected that structured choice, including the option of CAB LA, could reduce HIV incidence by one-third over 10 years and be cost-effective across eastern and southern Africa [Phillips, et al. 2025]. In the ImPrEP CAB Brasil study, 83% of participants opted for CAB LA over oral PrEP after receiving options counseling, citing challenges with daily pills and confidence in injectables [Grinsztejn, et al. 2025]. PrEP options counseling significantly increased CAB LA uptake and satisfaction, highlighting the importance of decision-support tools in personalized HIV prevention. The approval of SC LEN adds another important PrEP choice and may further increase uptake and persistence.

**Gender-affirming care and PrEP:** Transgender women experience a disproportionate burden of HIV, and PrEP uptake is likely to have a high impact in transgender women who are sexually active and for whom PrEP is indicated [Malone, et al. 2021]. Transgender women have low rates of PrEP uptake and high rates of discontinuation [Scott, et al. 2019], and gender-affirming care and access to hormone therapy can increase PrEP uptake and adherence [Sevelius, et al. 2016]. Gender-affirming care has been shown to improve health outcomes for transgender people, and providing gender-affirming hormone therapy in the context of primary care was associated with reduced rates of HIV seropositivity in the LEGACY study [Reisner,

et al. 2025]. Concerns about interactions between PrEP medications and estrogen may lead to avoidance or missed doses, although studies show that TDF/FTC, TAF/FTC, CAB LA, and SC LEN do not significantly affect hormone levels [Kelley, et al. 2025; Blumenthal, et al. 2022; Grant, et al. 2021; Blair, et al. 2020; Hiransuthikul, et al. 2019]. Providing reassurance about this lack of interaction can also increase uptake.

**Comprehensive services and support:** To enhance PrEP success, it is essential that clinicians collaborate with others inside and outside their organizations to address individuals' social determinants of health and offer services such as:

- Mental health and substance use treatment
- Case management and navigation
- Housing assistance and benefits counseling
- Support groups and peer networks

**→ KEY POINTS**

- Offering PrEP choice improves uptake, adherence, persistence, and satisfaction.
- Individualized strategies to support PrEP adherence may improve PrEP persistence.
- PrEP use may be episodic as individuals start and stop based on fluctuations in risk.
- Providing gender-affirming care to transgender individuals can increase their engagement in PrEP care.
- TDF/FTC, TAF/FTC, CAB LA, and SC LEN are not expected to lower estrogen levels, and addressing this directly with transgender women may improve their willingness to take and adhere to PrEP.

## PrEP Coverage

**Coverage under the Affordable Care Act (ACA):** In 2023, the U.S. Preventive Services Task Force published an updated grade A recommendation that clinicians should "prescribe preexposure prophylaxis using effective antiretroviral therapy to persons at increased risk of HIV acquisition to decrease the risk of acquiring HIV" [USPSTF 2023]. This federal recommendation recognizes PrEP as a preventive service to be covered under the ACA, a significant step toward increasing access to PrEP, and further affirms PrEP as a highly effective HIV prevention strategy clinicians can and should provide to their patients. Of note, ACA plans and Medicare Part B and D not only cover PrEP medications but also testing and monitoring without cost-sharing [CMS 2024].

**Coverage in New York State:** New York State Senate Bill S825 (2023-2024 Legislative Session) mandates that certain large group policies cover HIV PrEP and PEP. New York State Medicaid and the Essential Plan cover PrEP medications, visits, monitoring, and testing without cost-sharing (see NYS Medicaid Coverage for HIV PrEP Related Services).

**◊ RESOURCES**

- Ending the AIDS Epidemic in New York State
- NYSDOH AI Provider Directory
- PrEP Patient Assistance Program
- PrEP Assistance Program Participating Providers
- Payment Options for Adults and Adolescents for PrEP
- Educational Materials for Consumers
- NYSDOH PrEP for Sex
- NYSDOH FAQs About PrEP
- NYSDOH AI Clinical Education Initiative (CEI) and HIV Education and Training Programs offer training in motivational counseling methods and prevention interventions.

# FDA-Approved PrEP Agents

**Tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg in a fixed-dose tablet (TDF/FTC; Truvada):** TDF/FTC is approved by the U.S. Food and Drug Administration (FDA) for use as PrEP as part of a comprehensive HIV prevention strategy for all individuals at risk of acquiring HIV. Multiple randomized, placebo-controlled clinical trials have demonstrated the efficacy of TDF/FTC as PrEP for preventing HIV infection in all risk populations when taken daily as directed [McCormack, et al. 2016; Choopanya, et al. 2013; Baeten, et al. 2012; Grant, et al. 2010]. Based on 2 large clinical trials, TDF/FTC can also be taken before and after sex (on-demand dosing) for appropriate candidates (see guideline section Choosing and Prescribing a PrEP Regimen > Alternative Oral Dosing: On-Demand PrEP), although this dosing strategy is not FDA-approved.

**Tenofovir alafenamide 25 mg/emtricitabine 200 mg in a fixed-dose tablet (TAF/FTC; Descovy):** TAF/FTC was noninferior to TDF/FTC in a study of men who have sex with men (MSM) and a small number of transgender women who have sex with men [Mayer, et al. 2020]. Daily TAF/FTC was approved by the FDA in October 2019 for HIV prevention through sexual exposure in those groups [FDA(b) 2025]. On-demand dosing of TAF/FTC has not been studied.

In the PURPOSE 1 trial, rates of HIV seroconversion with TAF/FTC were not different from the background rates of HIV seroconversion in cisgender adolescent and adult women overall [Bekker, et al. 2024]. However, in a subanalysis of the study TAF/FTC was effective when taken with medium to high adherence and reduced HIV incidence by 89% with 2 or more doses per week [Kiweewa, et al. 2025]. Although TAF/FTC is not FDA-approved for receptive vaginal sex, given the data noted above it is reasonable as part of shared decision-making to offer TAF/FTC as an alternative PrEP option for HIV exposures through receptive vaginal sex for individuals in whom TDF/FTC is not tolerated or not desired.

**Long-acting injectable cabotegravir (CAB LA; Apretude):** CAB LA is an integrase strand transfer inhibitor given as an intramuscular injection every 2 months after an optional 4-week lead-in of oral CAB (Vocabria) and 2 initial injections given 4 weeks apart. CAB LA was statistically superior to oral TDF/FTC as PrEP (due to imperfect adherence to oral PrEP) in MSM, transgender women, and cisgender women [Delany-Moretlwe, et al. 2022; Landovitz, et al. 2021]. CAB LA was approved by the FDA in December 2021 for prevention of HIV via all sexual exposures [FDA 2021].

**Subcutaneous lenacapavir (SC LEN; Yeztugo):** SC LEN is a capsid inhibitor dosed subcutaneously every 6 months along with an initial oral loading dose of two 300 mg tablets on the day of the initial injections and again on the next day after the injections. In the PURPOSE 1 trial in cisgender adolescent and adult women [Bekker, et al. 2024] and PURPOSE 2 trial in men and gender-diverse populations who have sex with men [Kelley, et al. 2025], SC LEN was statistically superior to TDF/FTC (PURPOSE 1 and 2) and to TAF/FTC (PURPOSE 1) in preventing HIV infection for all sexual exposures (due to imperfect adherence to oral PrEP). The PURPOSE 3 (cisgender women in the United States), PURPOSE 4 (people who inject drugs), and PURPOSE 5 (individuals at high risk of HIV in France and the United Kingdom) trials are ongoing. SC LEN was approved by the FDA in June 2025 for prevention of HIV via all sexual exposures [FDA(d) 2025].

# Who Should Use PrEP

**☑ RECOMMENDATIONS**

**PrEP Candidates**

- Clinicians should assess all individuals for HIV risk as a routine part of primary care. (A3)
- Clinicians should recommend PrEP for individuals, including adolescents, who do not have but are at risk of acquiring HIV. (A1)
- Clinicians should prescribe PrEP for any individual who self-identifies as being at risk of acquiring HIV. (A*)
- For individuals who are completing a course of nPEP and remain at risk of acquiring HIV, clinicians should recommend PrEP be initiated immediately upon completion of nPEP. (A3)

**Contraindications to PrEP**

- Clinicians should not prescribe oral or injectable PrEP for any patient with a documented HIV diagnosis; none of the available PrEP regimens are adequate for HIV treatment. (A1)
- Clinicians should recommend individuals with confirmed HIV immediately initiate a fully suppressive ART regimen. (A1)

**☑ RECOMMENDATIONS**

- Clinicians should not initiate TDF/FTC as PrEP for any individual with a confirmed CrCl <60 mL/min and should discontinue it in patients with a confirmed CrCl <50 mL/min; in such cases, TDF/FTC as PrEP is contraindicated. (A1)
- Clinicians should not prescribe TAF/FTC as PrEP for any individual with a confirmed CrCl <30 mL/min; in such cases, TAF/FTC as PrEP is contraindicated. (A1)

**Abbreviations:** ART, antiretroviral therapy; CrCl, creatinine clearance; nPEP, non-occupational post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; TAF/FTC, tenofovir alafenamide/emtricitabine (Descovy); TDF/FTC; tenofovir disoproxil fumarate/emtricitabine (Truvada).

# PrEP Candidates

PrEP is part of a comprehensive HIV prevention plan and should be offered to individuals, including adolescents who meet the prescribing criteria, and who are assessed as or who self-identify as being at increased risk of acquiring HIV through sexual or injection drug exposure.

**☆ NEW YORK STATE LAW**

- New York Consolidated Laws, Public Health Law – PBH Article 2305 has long established the legal capacity of minors to consent to treatment and preventive services for sexually transmitted diseases (STDs). Provisions in Article 2305 require that the Commissioner of Health promulgate a list of STDs. A 2017 amendment to Article 2305 added HIV to the list of STDs, thereby bringing minor capacity to consent to HIV treatment and preventive services on par with other STDs. In addition, under Article 2305, medical or billing records may not be released or made available to the parent or guardian without the minor patient's permission. For more information, see New York State Register/April 12, 2017: Rule Making Activities.

Box 1, below, shows candidates who should be offered PrEP and factors that do not disqualify candidates from PrEP. See Appendix B: Studies That Support the Use of PrEP in Different Populations for a discussion of the studies that support the use of PrEP in different populations.

**Box 1: Candidates for Pre-exposure Prophylaxis**

**Offer pre-exposure prophylaxis (PrEP) to individuals who are candidates, including those who:**

- Self-identify as being at risk without disclosing specific risk behaviors
- Engage in condomless sex with partners whose HIV status is unknown, who have untreated HIV, or who are being treated for HIV but have unsuppressed virus
- Are attempting to conceive with a partner with HIV who is not consistently virally suppressed or whose suppression status is unknown, or want the further reassurance of HIV prevention via PrEP
- Are at ongoing risk of HIV acquisition during pregnancy through inconsistent condom use with sex partners who have unsuppressed virus [Heffron, et al. 2016]
- Have multiple or anonymous sex partners or are involved with partners who do
- Engage in sexual activity at parties and other high-risk venues or have sex partners who do
- Are involved in or have sex partners who may be involved in transactional sex (i.e., sex for money, drugs, food, or housing), including commercial sex workers and their clients
- Have been diagnosed with at least 1 bacterial sexually transmitted infection (STI) in the previous 12 months [LaLota, et al. 2011; Zetola, et al. 2009]
- Report recreational use of mood-altering substances during sex, including but not limited to alcohol, methamphetamine, cocaine, ecstasy, and gamma hydroxybutyrate [Grov, et al. 2013; Smith, et al. 2012; Koblin, et al. 2011; Zule, et al. 2007; Buchacz, et al. 2005] (see NYSDOH AI Chemsex: Questions and Answers for more information)
- Report injecting substances or having sex partners who inject substances, including illicit drugs, hormones, or silicone
- Are receiving non-occupational post-exposure prophylaxis (nPEP) and anticipate ongoing risk or have used multiple courses of nPEP [Heuker, et al. 2012]

**Box 1: Candidates for Pre-exposure Prophylaxis**

- Request the protection of PrEP even if their sex partners have an undetectable HIV viral load (see discussion of HIV-serodifferent couples in Appendix B: Studies That Support the Use of PrEP in Different Populations)
- Acknowledge the possibility of or anticipate engaging in risk behaviors soon

***Do not withhold PrEP* from eligible candidates who:**

- Are pregnant or planning to conceive
- Inconsistently use condoms or other risk-reduction methods
- Engage in substance use
- Have mental health disorders of any severity
- Experience intimate partner violence
- Have unstable housing or limited social support
- Have recently had an STI
- Have a partner with HIV who has an undetectable viral load

# Contraindications to PrEP

**Exposure to HIV in the previous 72 hours:** Individuals with potential HIV exposure in the previous 72 hours should be prescribed PEP and provided a 4-week follow-up to transition to PrEP. See the NYSDOH AI guideline PEP to Prevent HIV Infection.

**HIV infection:** The 2-drug PrEP regimens of TDF/FTC and TAF/FTC and the single-drug regimens of long-acting injectable cabotegravir (CAB LA) and subcutaneous lenacapavir (SC LEN) are inadequate for treating established HIV infection; therefore, PrEP should not be initiated unless an individual is tested for HIV at initiation or within 1 week before the proposed initiation. If HIV infection is confirmed, PrEP should immediately be converted to a fully suppressive HIV treatment regimen. See guideline section Managing a Positive HIV Test Result.

**Renal dysfunction:** TDF is contraindicated for individuals with a CrCl <60 mL/min at the time of PrEP initiation and should be discontinued if CrCl drops to <50 mL/min [FDA 2024]. TAF/FTC can be prescribed in individuals with a CrCl ≥30 mL/min. Serum creatinine levels can vary and be affected by factors other than renal disease; therefore, before a decision is made to forgo or discontinue oral PrEP, decreased CrCl should be verified through repeat testing, and other causes of spurious creatinine elevation (e.g., use of creatine-containing protein supplements) or reversible causes (e.g., use of nonsteroidal anti-inflammatory drugs) should be ruled out. CAB LA and SC LEN are safe to use in individuals with renal dysfunction.

**Fillers, implants, and silicone in the buttocks and hips:** Caution should be exercised when considering CAB LA as PrEP in individuals with silicone and implants in buttocks and hips, as absorption of CAB LA may be compromised.

**Drug-drug interactions:** CAB LA as PrEP is contraindicated with some antiseizure medications and rifamycins. There are several important drug-drug interactions for SC LEN that require dose adjustment and consideration of alternative PrEP options. Check for drug-drug interactions before prescribing PrEP. See NYSDOH AI Drug-Drug Interaction Guide: From HIV Prevention to Treatment and University of Liverpool HIV Drug Interactions.

**Other HIV prevention methods:** Discuss other HIV prevention methods, such as condom use and safer sex practices, in the context of PrEP, particularly for individuals with contraindications or intolerance to current PrEP options.

# Comparing PrEP Regimens

All current pre-exposure prophylaxis (PrEP) options are highly effective when taken as directed. Shared decision-making allows patient preferences and clinical considerations to guide the choice of the best PrEP option for each candidate (see Table 1 and Table 2, below).

**Table 1: Key Clinical and Logistical Factors in Choosing a PrEP Regimen**
(details provided in discussion that follows; also see Checklist 1: Key Factors in Choice of PrEP Regimen)

| **TDF/FTC** (tenofovir disoproxil fumarate/ emtricitabine; Truvada) | **TAF/FTC** (tenofovir alafenamide/ emtricitabine; Descovy) | **CAB LA** (long-acting injectable cabotegravir; Apretude) | **SC LEN** (long-acting injectable lenacapavir; Yeztugo) | **Comments** |
|---|---|---|---|---|
| *Indications* | | | | |
| Sexual and injection drug use exposures in adults and adolescents weighing ≥35 kg | • Sexual exposures in adults and adolescents weighing ≥35 kg<br>• Not studied for injection drug exposure | • Sexual exposures in adults and adolescents weighing ≥35 kg<br>• Not studied for injection drug exposure | • Sexual exposures in adults and adolescents weighing ≥35 kg<br>• Under study for injection drug use | • A 2017 amendment to the NYCRR grants minors capacity to consent to PrEP and PEP without parental/guardian involvement.<br>• Although not FDA indicated, TAF/FTC is an oral PrEP option for HIV exposure through receptive vaginal sex if TDF/FTC is not tolerated or desired or there is preexisting bone or renal disease, with shared decision-making.<br>• Although TAF/FTC and CAB LA have not been studied for injection drug use exposure and data are still pending for SC LEN, it is reasonable to think these PrEP options will be effective for exposures from injection drug use. |
| *Time to Protection* [a] | | | | |
| • All exposures: within 7 days of daily dosing<br>• All sexual exposures: 2 hours after initiating with a double dose of TDF/FTC | Not defined, but expected to be ≤7 days | Estimated efficacy at 7 days | 2 hours after second oral loading dose | See guideline section Comparing PrEP Regimens > Time to Protection |

| **Table 1: Key Clinical and Logistical Factors in Choosing a PrEP Regimen**<br>(details provided in discussion that follows; also see Checklist 1: Key Factors in Choice of PrEP Regimen) | | | | |
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| **TDF/FTC**<br>(tenofovir disoproxil fumarate/ emtricitabine; Truvada) | **TAF/FTC**<br>(tenofovir alafenamide/ emtricitabine; Descovy) | **CAB LA**<br>(long-acting injectable cabotegravir; Apretude) | **SC LEN**<br>(long-acting injectable lenacapavir; Yeztugo) | **Comments** |
| *Renal Safety* | | | | |
| • Do not initiate if confirmed CrCl <60 mL/min.<br>• Discontinue if confirmed CrCl <50 mL/min.<br>• Potential effect on renal tubular function; meta-analysis shows good safety [Pilkington, et al. 2018] | • Improved renal biomarkers compared with TDF<br>• Do not initiate if confirmed CrCl <30 mL/min. | Increased monitoring for adverse effects is recommended if CrCl <30 mL/min. | Increased monitoring for adverse effects is recommended if CrCl <15 mL/min. | More frequent monitoring may be required for individuals at increased risk of renal disease (i.e., hypertension, diabetes, age >40 years). |
| *Bone Safety* | | | | |
| Potential decrease in bone mineral density; meta-analysis shows good safety [Pilkington, et al. 2018] | • Favorable bone biomarkers for TAF compared with TDF<br>• Preferred oral regimen for adults with osteopenia or osteoporosis<br>• Preferred for adolescents aged ≤19 years | Preferred option for prevention of sexual exposures in all individuals with osteopenia or osteoporosis | Preferred option for prevention of sexual exposures in all individuals with osteopenia or osteoporosis | — |
| *Weight and LDL Cholesterol* | | | | |
| • Weight neutral<br>• Small decreases in LDL | • Minimal weight gain was observed in studies<br>• Small increases in LDL | • Minimal weight gain was observed in MSM and transgender women<br>• No significant effect on lipids | No information on weight or cholesterol reported | — |

**Table 1: Key Clinical and Logistical Factors in Choosing a PrEP Regimen**
(details provided in discussion that follows; also see Checklist 1: Key Factors in Choice of PrEP Regimen)

| **TDF/FTC** (tenofovir disoproxil fumarate/ emtricitabine; Truvada) | **TAF/FTC** (tenofovir alafenamide/ emtricitabine; Descovy) | **CAB LA** (long-acting injectable cabotegravir; Apretude) | **SC LEN** (long-acting injectable lenacapavir; Yeztugo) | **Comments** |
|---|---|---|---|---|
| *Dosing* | | | | |
| • Daily dosing<br>• On-demand dosing for sexual exposures is an option in cisgender MSM and transgender women.<br>• On-demand dosing for sexual exposures with 1 additional day of medication is an option, with shared decision-making, for receptive vaginal exposures.<br>• On-demand dosing is not appropriate for injection exposures. | Daily dosing only | • Optional 30-day oral CAB lead-in<br>• First 2 IM injections administered 4 weeks apart; thereafter, injections given every 2 months | • Initial loading dose of LEN 600 mg oral daily for 2 days<br>• Subcutaneous injections every 6 months | — |
| *Same-Day Initiation* | | | | |
| Generic TDF/FTC is a preferred insurance option and is usually available for same-day initiation. | May require prior insurance authorization | • May require prior insurance authorization for oral or injectable CAB<br>• Implementation challenges may interfere | • May require prior insurance authorization<br>• Implementation challenges may interfere | — |
| *Common Adverse Effects* | | | | |
| Diarrhea (6%), nausea (5%) [Glidden, et al. 2016] | Diarrhea (5%), nausea (4%) [Mayer, et al. 2020] | Injection site reactions (32% to 81%) [Delany-Moretlwe, et al. 2022; Landovitz, et al. 2021], which are mostly mild and greatest initially | Injection site reactions including potential pain, nodules, and erythema (69% to 83%) [Kelley, et al. 2025; Bekker, et al. 2024], mostly grades 1 and 2, affected by injection technique | — |

| **Table 1: Key Clinical and Logistical Factors in Choosing a PrEP Regimen**<br>(details provided in discussion that follows; also see Checklist 1: Key Factors in Choice of PrEP Regimen) | | | | |
|---|---|---|---|---|
| **TDF/FTC**<br>(tenofovir disoproxil fumarate/ emtricitabine; Truvada) | **TAF/FTC**<br>(tenofovir alafenamide/ emtricitabine; Descovy) | **CAB LA**<br>(long-acting injectable cabotegravir; Apretude) | **SC LEN**<br>(long-acting injectable lenacapavir; Yeztugo) | **Comments** |
| *Use During or When Planning Pregnancy* | | | | |
| May be continued through pregnancy and breast/chestfeeding | May be continued through pregnancy and breast/chestfeeding | • No significant differences in maternal adverse events or pregnancy outcomes between CAB LA and TDF/FTC, but data are limited<br>• Use shared decision-making when considering CAB LA for pregnant individuals. | • Pregnancy outcomes similar to those in the general population, but data are limited<br>• Use shared decision-making when considering SC LEN for pregnant individuals. | • HIV acquisition risk is increased during pregnancy and highest late in pregnancy and early postpartum.<br>• Acute seroconversion significantly increases the risk of perinatal transmission during pregnancy and while breast/chestfeeding.<br>• Suppressive ART (TasP) for a partner with HIV is important for risk reduction.<br>• Prospectively report information regarding PrEP use during pregnancy to the Antiretroviral Pregnancy Registry. |
| *Use With Oral Contraceptives* | | | | |
| No interaction expected based on pharmacokinetic data | No interaction expected based on pharmacokinetic data | No interaction expected based on pharmacokinetic data | May increase concentrations of oral contraceptives but no dose adjustment needed | No dose adjustment of emergency contraception needed for all PrEP regimens |
| *Use With Gender-Affirming Hormones* | | | | |
| No significant interaction with estrogen or testosterone | No significant interaction with estrogen or testosterone | No significant interaction with estrogen or testosterone | • Mild increases in levels of feminizing hormones and androgens are possible but no dose adjustments are needed.<br>• Monitor gender-affirming hormone levels and adjust dosages as needed. | — |

**Table 1: Key Clinical and Logistical Factors in Choosing a PrEP Regimen**
(details provided in discussion that follows; also see Checklist 1: Key Factors in Choice of PrEP Regimen)

| **TDF/FTC** (tenofovir disoproxil fumarate/ emtricitabine; Truvada) | **TAF/FTC** (tenofovir alafenamide/ emtricitabine; Descovy) | **CAB LA** (long-acting injectable cabotegravir; Apretude) | **SC LEN** (long-acting injectable lenacapavir; Yeztugo) | **Comments** |
|---|---|---|---|---|
| *Patients With Active Chronic HBV* [b,c] | | | | |
| • Active against and FDA-approved for treatment of HBV infection<br>• Daily dosing required when used for PrEP and HBV treatment | Active against and FDA-approved for treatment of HBV infection | Not active against HBV infection | Not active against HBV infection | Monitor closely for rebound HBV viremia if TDF/FTC or TAF/FTC is discontinued in a patient with chronic HBV |
| *Drug-Drug Interactions* | | | | |
| See NYSDOH AI Drug-Drug Interaction Guide: From HIV Prevention to Treatment > TDF and TAF Interactions | See NYSDOH AI Drug-Drug Interaction Guide: From Prevention to Treatment > TDF and TAF Interactions | See NYSDOH AI Drug-Drug Interaction Guide: From Prevention to Treatment > CAB Interactions | See NYSDOH AI Drug-Drug Interaction Guide: From Prevention to Treatment > LEN Interactions | Drug-drug interactions for SC LEN may require additional dosing or an alternative PrEP regimen. |
| *Generic Formulation Availability* | | | | |
| Generic TDF/FTC is available | Brand only | Brand only | Brand only | TAF/FTC, CAB LA, and SC LEN may require prior insurance authorization. |

**Abbreviations:** 3TC, lamivudine; ART, antiretroviral therapy; CrCl, creatinine clearance; FDA, U.S. Food and Drug Administration; HBV, hepatitis B virus; IM, intramuscular; LDL, low-density lipoprotein; MSM, men who have sex with men; NYCRR, New York Codes, Rules and Regulations; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; TasP, treatment-as-prevention.

**Notes:**

a. Time to protection has not been definitively established for any available PrEP regimen (see guideline section Comparing PrEP Regimens > Time to Protection).
b. TDF and TAF are approved by the FDA for HBV treatment. FTC is also active against HBV but is not FDA-approved for HBV treatment. TDF or TAF in combination with FTC or 3TC (which is FDA-approved for HBV treatment and is molecularly similar to FTC) is commonly used in patients with HIV/HBV coinfection as part of an ART regimen to treat both infections.
c. For individuals with chronic HBV who are not eligible for, cannot tolerate, or decide against TDF/FTC or TAF/FTC for PrEP, evaluate for an alternative HBV treatment (see NYSDOH AI guideline Prevention and Management of Hepatitis B Virus Infection in Adults With HIV).

| Table 2: Benefits, Limitations, and Risks of Available PrEP Regimens | | | |
|---|---|---|---|
| **All PrEP Regimens** | **Oral PrEP With TDF/FTC or TAF/FTC** | **Injectable PrEP With CAB LA** | **Injectable PrEP With SC LEN** |
| *Benefits* | | | |
| • Highly effective when taken as directed<br>• May decrease anxiety regarding HIV acquisition<br>• Engages sexually active at-risk individuals in care who are then screened regularly for STIs | • 99% effective in reducing the risk of HIV acquisition when used as prescribed<br>• **TDF/FTC:** Indicated for all sexual and injection exposures<br>• **TAF/FTC:** Use for all sexual exposures (with shared decision-making for receptive vaginal sex)<br>• Single tablet taken daily, and for TDF/FTC can also be taken before and after sex<br>• Good safety profiles in people without HIV<br>• Minimal adverse effects, most of which are manageable or resolve quickly<br>• Appear to be safe for use during attempts to conceive and during pregnancy<br>• Treats HBV infection | • Statistical superiority to TDF/FTC has been attributed to a lack of adherence to the oral regimen<br>• Indicated for all sexual exposures<br>• Administered intramuscularly once every 2 months<br>• Directly observed therapy<br>• Advantageous option when adherence to oral PrEP may be challenged by ongoing substance use or mental health concerns, neurocognitive disorders, difficulty swallowing pills, privacy concerns, or other | • Statistical superiority to TDF/FTC and TAF/FTC has been attributed to a lack of adherence to the oral regimen<br>• Indicated for all sexual exposures<br>• Administered subcutaneously once every 6 months<br>• Directly observed therapy<br>• Advantageous option when adherence to oral PrEP may be challenged by ongoing substance use or mental health concerns, neurocognitive disorders, difficulty swallowing pills, privacy concerns, or other |
| *Limitations* | | | |
| • Protection correlates with adherence to the dosing schedule<br>• No significant protection against STIs other than HIV (some protection against HSV reported in heterosexual populations without HIV [Celum, et al. 2014]) | • Requires daily adherence<br>• Requires planning and adherence when TDF/FTC is dosed on-demand<br>• Requires additional monitoring in patients with chronic HBV<br>• Cost of TAF/FTC (no generic available)<br>• No data on TAF/FTC for individuals who inject drugs | • Requires deep intramuscular injection<br>• No data for individuals who inject drugs<br>• Requires oral medications as bridging therapy when injections are missed<br>• Requires ≥6 in-person healthcare visits per year<br>• Does not treat HBV coinfection<br>• Potential absorption issue for individuals with injectable silicone or | • Increased risk of long-term impactful medication interactions<br>• Data pending for individuals who inject drugs<br>• Requires oral medications as bridging therapy when injections are missed<br>• Does not treat HBV coinfection<br>• Implementation logistics<br>• Cost (no generic available) |

| Table 2: Benefits, Limitations, and Risks of Available PrEP Regimens | | | |
|---|---|---|---|
| **All PrEP Regimens** | **Oral PrEP With TDF/FTC or TAF/FTC** | **Injectable PrEP With CAB LA** | **Injectable PrEP With SC LEN** |
| | | other fillers in the gluteal area; discuss risks and consider ultrasound for assessment and alternative PrEP options<br>• Implementation logistics<br>• Cost (no generic available) | |
| *Risks* | | | |
| Continued use after undiagnosed HIV infection may result in development of drug-resistant virus | • Safety concerns for individuals with impaired kidney function<br>• Compared with TAF, TDF may be associated with reversible decreases in bone density in adults and irreversible bone density loss in individuals aged ≤19 years | • Potential injection site reactions and other adverse events, including pyrexia<br>• Potential for delayed detection of HIV infection using standard HIV testing algorithms<br>• Long tail phase once treatment is discontinued<br>• Rare breakthrough infections despite on-time injections<br>• Breakthrough infection may eliminate first-line ART options | • Injection site reactions are common (nodules, pain, and erythema at injection site)<br>• Long tail phase once treatment is discontinued<br>• Rare breakthrough infections despite on-time injections |

**Abbreviations:** ART, antiretroviral therapy; CAB LA, long-acting injectable cabotegravir (Apretude); HBV, hepatitis B virus; HSV, herpes simplex virus; SC LEN, subcutaneous lenacapavir (Yeztugo) PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide/emtricitabine (Descovy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (Truvada).

## HBV Infection

Daily tenofovir-containing PrEP is preferred for individuals with chronic hepatitis B virus (HBV). Unlike tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and tenofovir alafenamide/emtricitabine (TAF/FTC), long-acting injectable cabotegravir (CAB LA) and subcutaneous lenacapavir (SC LEN) do not prevent or treat HBV infection. When considering or switching to a long-acting injectable PrEP regimen, perform HBV testing if an individual's hepatitis serologies are unknown or if there was borderline or low-level immunity in the past. Unrecognized chronic HBV can flare when tenofovir-containing regimens are discontinued. Individuals with chronic HBV who are switching from an oral PrEP regimen will need to continue oral tenofovir or other HBV treatment options while using CAB LA or SC LEN. Non–HBV-immune individuals should be offered routine vaccination to prevent HBV infection. See the NYSDOH AI guideline Prevention and Management of Hepatitis B Virus Infection in Adults With HIV.

## Time to Protection

The time to protection against HIV infection after PrEP initiation is not definitively established. Whether the key to protection is drug levels in genital and rectal tissue, plasma blood mononuclear cells (PBMCs), or more likely, a combination of tissue and PBMC levels is under debate. Most of what is known is from animal studies, human tissue studies, and pharmacokinetic modeling. There are no studies with clinical endpoints. In animal models and observational studies, post-exposure prophylaxis (PEP) has been effective if initiated within 72 hours after exposure, which raises questions about the specific drug concentrations in tissue required to protect against HIV infection.

**TDF/FTC:** Early pharmacokinetic modeling data demonstrated that 7 days of daily TDF/FTC for PrEP are required to achieve maximal protective concentrations in rectal tissue, and 20 days of daily dosing are required to achieve maximal protective concentrations in cervicovaginal tissue [Louissaint, et al. 2013; Anderson, et al. 2012; Patterson, et al. 2011]. Newer pharmacokinetic modeling data suggest that TDF/FTC is likely protective within 1 week of dosing in both rectal and genital compartments and PBMCs [Hendrix, et al. 2016; Seifert, et al. 2016]. Emtricitabine triphosphate (active metabolite of emtricitabine) reaches steady-state and therapeutic concentrations very quickly in vaginal tissue, and tenofovir diphosphate (active metabolite of tenofovir) reaches concentrations more slowly, potentially affording vaginal protection quite early from emtricitabine triphosphate while tenofovir diphosphate concentrations accumulate [Cottrell, et al. 2016; Seifert, et al. 2016].

Studies have shown that initiating PrEP with a double dose (2 tablets) of TDF/FTC confers protective levels after 2 hours both rectally and vaginally [Chawki, et al. 2024; Cottrell, et al. 2016]. Therefore, a double dose of TDF/FTC at initiation, when more immediate protection is desired, is recommended, otherwise daily dosing for 7 days will achieve optimal protective levels of medication in PBMCs and genital and rectal tissue, acknowledging that protection is likely conferred earlier.

**TAF/FTC:** Time to protection for TAF/FTC is also unclear. TAF had a faster time to 90% effective concentrations ($EC_{90}$) than TDF (4 hours vs. 3 days) and significantly higher steady-state concentrations in PBMCs than TDF/FTC as PrEP [Ogbuagu, et al. 2021], which may confer a clinical benefit in terms of time to protection and adherence forgiveness, but this is preliminary evidence and further evaluation is needed. It is reasonable to assume protection at 7 days, and likely earlier. There are no data on a double dose at initiation for more immediate protection.

**CAB LA:** CAB LA is estimated to be protective 7 days after the initial injection [Han(a), et al. 2024]. If switching from oral PrEP, individuals should be advised to continue oral PrEP for an additional 7 days to maintain protection while CAB LA levels are rising, otherwise counsel individuals on additional HIV prevention techniques, including barrier protection and abstinence, during this time.

**SC LEN:** Rapid increases have been observed in plasma concentrations of LEN after the initial oral loading dose and first injection, reaching therapeutic levels within 2 hours after the second oral loading dose on day 2 [Gilead 2025; Jogiraju, et al. 2025], and it is reasonable to assume protection at that point. Individuals initiating SC LEN who are not already using PrEP should be counseled on using additional HIV prevention techniques, including barrier protection and abstinence, during the oral loading period. Individuals switching from oral PrEP to SC LEN are protected from HIV on the day of the initial injection. If the second oral loading dose is missed, the time to protection increases to up to 28 days [Gilead 2025].

**→ KEY POINTS**

- Time to protection after initiation of TDF/FTC as PrEP is based on pharmacokinetic modeling studies and has not been clinically determined but is estimated to be 7 days of daily dosing, and likely earlier, or 2 hours after a loading dose of 2 tablets taken simultaneously on the day of initiation.
- Time to protection for TAF/FTC is estimated to be 7 days, and likely earlier.
- Time to protection for CAB LA is estimated to be 7 days.
- Time to protection for SC LEN is estimated to be 2 hours after the second oral loading dose, or up to 28 days if the second oral dose is missed.

# Choosing and Prescribing a PrEP Regimen

## ☑ RECOMMENDATIONS

**Choice of Regimen**

- Clinicians should engage in shared decision-making with PrEP candidates to identify an optimal and safe regimen and dosing strategy based on patient preference, clinical considerations, and individual patient factors. (A3)

**TDF/FTC**

- In the absence of contraindications, clinicians should recommend TDF/FTC as the preferred oral PrEP regimen for adults and adolescents aged 19 years or older who are at risk of acquiring HIV through rectal and genital sexual or injection drug use exposures. (A1)

**TAF/FTC**

- Clinicians should recommend TAF/FTC as the preferred oral PrEP regimen for sexual exposures in adults who have preexisting renal disease or osteoporosis. (A1)
  - TAF/FTC is an alternative oral PrEP regimen if TDF/FTC is not tolerated or desired. (A3)
- Clinicians should recommend TAF/FTC as a preferred PrEP regimen for individuals aged 19 years or younger, given the potential for irreversible bone loss in this age group. (A2)

**Patients With HBV**

- Clinicians should recommend daily TDF/FTC or TAF/FTC as the preferred PrEP regimen for patients who require HBV treatment. (A2†)
- Clinicians should closely monitor patients with chronic HBV for potential viral rebound when PrEP with TDF/FTC or TAF/FTC is discontinued and develop an alternative treatment plan if necessary. (A2)

**CAB LA**

- Clinicians should recommend CAB LA as a preferred PrEP regimen for protection against HIV through sexual exposure for individuals who are willing to receive regular IM injections and have no contraindications or barriers to its use. (A1)
- An oral CAB lead-in is optional before initiation of CAB LA injections; if challenges adhering to daily oral medication have been identified, clinicians should engage patients in shared decision-making to weigh the risk of HIV acquisition against the benefit of an oral CAB lead-in. (A3)
- Clinicians should administer CAB LA as indicated in Box 2: Preparation and Administration of Long-Acting Injectable Cabotegravir as Pre-Exposure Prophylaxis. (A1)
- If a patient at ongoing risk of HIV acquisition discontinues CAB LA, the clinician should recommend an alternative PrEP regimen be started 2 months after the last injection and continued for at least 1 year to prevent potential acquisition of INSTI-resistant HIV. (A3)
- Clinicians should discuss potential risks and benefits and engage individuals who are or may become pregnant in shared decision-making when considering CAB LA as PrEP. (A3)

**SC LEN**

- Clinicians should recommend SC LEN as a preferred PrEP regimen for protection against HIV through sexual exposure for individuals who are willing to receive subcutaneous injections every 6 months and have no contraindications or barriers to its use. (A1)
- Clinicians should administer SC LEN as indicated in Box 3: Dosing, Preparation, and Administration of Subcutaneous Lenacapavir as Pre-Exposure Prophylaxis. (A1)
- If a patient at ongoing risk of HIV acquisition discontinues SC LEN, the clinician should recommend an alternative PrEP regimen be started 6 months after the last injection and continued for 6 months to prevent potential acquisition of capsid inhibitor–resistant HIV.
- Clinicians should discuss potential risks and benefits and engage individuals who are or may become pregnant in shared decision-making when considering SC LEN as PrEP. (A3)

**Resources:** Checklist 1: Key Factors in Choice of PrEP Regimen; Checklist 2: Assessment and Counseling Before PrEP Initiation

**Abbreviations:** CAB LA, long-acting injectable cabotegravir (Apretude); CrCl, creatinine clearance; HBV, hepatitis B virus; IM, intramuscular; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; oral CAB, oral cabotegravir (Vocabria); PrEP, pre-exposure prophylaxis; SC LEN, subcutaneous lenacapavir (Yeztugo); TAF/FTC, tenofovir alafenamide/emtricitabine (Descovy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (Truvada).

# Preferred Oral Regimen for Daily Dosing: TDF/FTC

TDF/FTC is the preferred oral HIV PrEP regimen because of its proven efficacy and safety in clinical trials, suitability for use in all populations, including individuals who inject drugs, and cost, which is significantly lower than that of TAF/FTC. However, for adults with preexisting renal disease or osteoporosis and for adolescents aged 19 years or younger, TAF/FTC is the preferred oral regimen (see discussion below).

**Daily dosing:** The U.S. Food and Drug Administration (FDA)-approved dosing of TDF/FTC as PrEP is 1 tablet daily by mouth with or without food [FDA 2024].

**Common adverse effects:** In clinical trials of TDF/FTC as PrEP, the most common adverse effects were nausea, headache, abdominal pain, and dizziness, which were mild and short-lived [McCormack, et al. 2016; Thigpen, et al. 2012; Grant, et al. 2010]. Most adverse effects peaked at 1 month and generally resolved within 3 months [Glidden, et al. 2016]. In a study comparing TAF/FTC and TDF/FTC as PrEP, both regimens were well tolerated, with diarrhea the only treatment-related adverse effect in >10% of individuals in either study arm [Mayer, et al. 2020].

**Renal impairment and loss of bone density:** Both renal impairment and loss of bone density have been observed in individuals taking TDF/FTC as HIV treatment, predominantly in studies of TDF/FTC combined with a third drug containing the pharmacokinetic booster ritonavir or cobicistat. Studies comparing unboosted TDF/FTC and TAF/FTC for HIV treatment found no difference in adverse events between the 2 regimens [Hill, et al. 2018]. A meta-analysis of 13 trials of TDF/FTC used as PrEP found no difference in serious adverse events between TDF/FTC and placebo but did find a borderline statistically significant difference in creatinine elevation of all grades when adding in grade 1 and 2 elevations [Pilkington, et al. 2018].

The DISCOVER study, which compared TDF/FTC with TAF/FTC as PrEP, found a small but statistically significant difference between biomarkers of renal and bone dysfunction favoring TAF/FTC, although no difference was found in clinical adverse outcomes [Mayer, et al. 2020]. Although renal dysfunction is uncommon in individuals taking TDF/FTC as PrEP, and especially those who are younger than 50 years [Gandhi, et al. 2016], regular laboratory monitoring is necessary during use of TDF/FTC or TAF/FTC (see Table 4: Recommended Routine Laboratory Testing for Individuals Using PrEP). If an increase in serum creatinine or a decrease in calculated CrCl is observed, evaluate potential causes other than TDF use. Discontinuation or interruption of TDF/FTC as PrEP is appropriate if other causes are ruled out or if CrCl drops to <50 mL/min (confirmed on 2 readings) for any reason. TAF/FTC is indicated for sexual exposures when CrCl ≥30 mL/min. When appropriate, on-demand dosing of TDF/FTC can also be considered to decrease drug exposure for individuals with borderline renal function.

Bone density losses with TDF/FTC as PrEP are minimal, have not been associated with bone fractures, and are reversible in individuals aged 20 years and older [Havens, et al. 2020; Spinelli, et al. 2019]. However, bone loss did not completely reverse in individuals aged 19 years and younger [Havens, et al. 2020]; therefore, TDF/FTC is not the preferred option in this age group (see Appendix B: Studies That Support the Use of PrEP in Different Populations > Adolescents > Oral PrEP).

# Alternative Oral Regimen for Daily Dosing: TAF/FTC

TAF/FTC is an alternative oral HIV PrEP regimen for all sexual exposures. However, it is the preferred oral regimen (for all sexual exposures) for individuals with preexisting renal disease or osteoporosis and for individuals aged 19 years and younger. TAF/FTC may also be preferable when there are multiple risk factors for renal disease or osteoporosis.

**Daily dosing:** The FDA-approved dosing of TAF/FTC as PrEP is 1 tablet daily by mouth with or without food [FDA(b) 2025]. On-demand dosing has not been studied for TAF/FTC.

**TAF/FTC for receptive vaginal exposure:** Based on the PURPOSE 1 trial results showing 89% lower rates of HIV acquisition in cisgender women who took 2 or more doses per week [Kiweewa, et al. 2025], use of TAF/FTC is appropriate for receptive vaginal sex in those whom TDF/FTC is not appropriate, tolerated or desired.

**Common adverse effects:** As noted above, in a study comparing TAF/FTC and TDF/FTC as PrEP, both regimens were well tolerated, with diarrhea the only adverse effect in >10% of individuals in either arm [Mayer, et al. 2020].

# Managing Adverse Effects of Oral PrEP

Two weeks after oral PrEP initiation, follow up with the individual either in person or by telephone to assess and address adverse effects and offer advice for management until they abate. Gastrointestinal adverse effects can be alleviated by taking PrEP medications with food or antidiarrheal agents, anti-gas medications, and antiemetics. In the iPrEx and Partners trials of TDF/FTC as PrEP, rash was not reported as a common adverse effect [Mujugira, et al. 2016; Grant, et al. 2014; Grant, et al. 2010]. Assess individuals who develop a rash while taking TDF/FTC or TAF/FTC as PrEP for syphilis and acute HIV [Apoola, et al. 2002].

# Alternative Oral Dosing: On-Demand PrEP

On-demand (also called intermittent or event-driven) PrEP, taking medication before and after sex instead of daily, is not FDA-approved, but strong evidence for the efficacy of on-demand dosing in cisgender MSM is based on results of the IPERGAY and Prevenir studies.

**Background:** The IPERGAY and Prevenir studies found that 2-1-1 dosing effectively prevented HIV acquisition in MSM [Molina, et al. 2022; Molina, et al. 2015]. Successful on-demand PrEP requires planning ahead for sex by at least 2 hours. Data on daily dosing of TDF/FTC are more robust than for on-demand dosing, with longer follow-up. However, the preferred dosing strategy is that which fits best into the individual's lifestyle. Clinicians should review the individual's usual sex planning practices and ensure they understand the complex on-demand dosing schedule. Switching between daily and on-demand PrEP as sexual activity changes is an appealing, evidence-based option for some individuals [Molina, et al. 2022; Hoornenborg(b), et al. 2017]. On-demand dosing of TDF/FTC is not recommended for blood exposures through injection drug use or in individuals with HBV.

Earlier studies have shown that estrogen use may lower tenofovir levels in the plasma of transgender women compared with cisgender men, but more recent studies call these findings into question (see Appendix B: Studies That Support the Use of PrEP in Different Populations > Transgender women). The PREVENIR and IPERGAY studies included too few transgender women who have sex with men to prove effectiveness in this population [Molina, et al. 2022; Molina, et al. 2015]. However, the lack of drug interactions with gender-affirming hormone therapy supports the use of on-demand PrEP in transgender women.

There are no studies of on-demand PrEP for receptive vaginal sex. Modeling data suggest that although tenofovir levels are lower in the female genital tract than in rectal tissue, FTC levels are high enough to offer significant protection at the tissue level within 2 hours of dosing. Tenofovir levels decrease in the female genital tract faster than in rectal tissues, but the addition of 1 more day of TDF/FTC increases protection from 85% to an estimated 93% to 98% [Engel, et al. 2025]. Systemic drug levels of TDF/FTC measured in PBMCs reflect intracellular concentrations necessary to inhibit HIV replication, regardless of tissue concentrations in the female genital tract. If individuals who are at risk of HIV exposure through receptive vaginal sex prefer an on-demand option instead of daily oral or injectable PrEP, it is reasonable to engage them in shared decision-making about on-demand PrEP (with an additional day of dosing) while awaiting clinical trial data.

**Dosing strategies:**

- **On-demand dosing for rectal and penile exposures:** TDF/FTC is taken as a "2-1-1" regimen:
  - 2 to 24 hours *before* sex: **Take 2** TDF/FTC tablets (closer to 24 hours is preferred), followed by
  - 24 hours *after* sex: **Take 1** TDF/FTC tablet, then
  - 48 hours *after* sex: **Take 1** TDF/FTC tablet
  - If sex occurs again: **Take 1** TDF/FTC tablet daily until 48 hours after the last sex act, effectively becoming daily PrEP for as long as sex continues.
- **On-demand dosing for receptive vaginal exposures:** TDF/FTC is taken as a "2-1-1-1" regimen:
  - 2 to 24 hours *before* sex: **Take 2** TDF/FTC tablets (closer to 24 hours is preferred), followed by
  - 24 hours *after* sex: **Take 1** TDF/FTC tablet, then
  - 48 hours *after* sex: **Take 1** TDF/FTC tablet
  - 72 hours *after* sex: **Take 1** TDF/FTC tablet
  - If sex occurs again: **Take 1** TDF/FTC tablet daily until 72 hours after the last sex act, effectively becoming daily PrEP for as long as sex continues.
- On-demand dosing cannot be recommended for protection against blood exposures.

There are no data to guide decisions on the use of on-demand PrEP for neovaginal or neopenile HIV exposures.

**→ KEY POINTS**

- On-demand PrEP with TDF/FTC is an alternative oral dosing option for sexual exposures. The number of days patients take a dose differs depending on the site of exposure.
- On-demand dosing of TAF/FTC as PrEP has not been studied in clinical trials; TAF/FTC should not be dosed in this way.
- On-demand PrEP is not recommended for individuals who use injection drugs or have HBV infection.
- When risk is episodic, use of PrEP only during discrete periods is a reasonable alternative to ongoing daily PrEP.

# Injectable Regimen: CAB LA Every 2 Months

**When CAB LA is preferred:** Because of its statistically superior efficacy to oral PrEP regimens and its protection against HIV through all types of sexual exposure, CAB LA is a preferred PrEP agent for all adults and adolescents weighing ≥35 kg who are open to injectable PrEP. CAB LA is an advantageous option when oral medication poses a challenge to PrEP use. TDF/FTC (or TAF/FTC if available same day) can be used as an alternative therapy for same-day initiation when oral CAB or CAB LA is not immediately available because of insurance or logistics issues. Overlapping 7 days of oral TDF/FTC or TAF/FTC with CAB initiation can be used to maintain protection against HIV while CAB levels are attaining steady-state.

**Oral CAB lead-in:** In clinical trials of CAB LA, a 5-week oral CAB lead-in was administered to rule out adverse effects before individuals received a long-acting injection [Delany-Moretlwe, et al. 2022; Landovitz, et al. 2021]. Although there are no data on the safety or efficacy of CAB LA when used for PrEP without an oral lead-in, in clinical trials of long-acting injectable CAB plus rilpivirine (CAB/RPV LA) for HIV treatment, omission of the oral lead-in was safe and did not interfere with achievement of adequate plasma CAB levels when injections were initiated [Orkin, et al. 2021]. There were no CAB safety concerns identified during the oral lead-in phase in trials of CAB/RPV LA as HIV treatment [Rizzardini, et al. 2020] or in trials of CAB LA as PrEP [Delany-Moretlwe, et al. 2022; Landovitz, et al. 2021]. As a result, the oral lead-in phase for CAB LA as PrEP is now optional.

Some care providers or individuals initiating PrEP who are concerned about tolerability may prefer an oral CAB lead-in. An important consideration in such cases is the potential risk of HIV acquisition for individuals who may struggle with adherence to daily oral medication. Of note, 3 of the 12 incident HIV infections in individuals using CAB as PrEP in the HPTN 083 study were acquired during the oral lead-in phase [Marzinke(a), et al. 2021]. Ongoing daily oral CAB is not FDA-approved or recommended as PrEP.

**CAB LA injections:** See Box 2, below, for details on the dosing, preparation, and administration of CAB LA as PrEP.

**Box 2: Dosing, Preparation, and Administration of Long-Acting Injectable Cabotegravir as Pre-Exposure Prophylaxis [a]**

**Initiation and continuation doses:**

- Long-acting injectable cabotegravir (CAB LA) as pre-exposure prophylaxis is given as a 600 mg (3 mL) deep intramuscular (IM) gluteal injection. After the first injection, a second injection is administered 4 weeks later, after which injections are administered every 8 weeks (within 1 week before or after the next planned dose).
- If a planned injection is missed by 4 weeks or more (i.e., 12 weeks after the previous dose), then the next 2 injections should be administered 4 weeks apart before returning to a bimonthly injection schedule.

**Preparation and administration:**

- For aspiration, use a vial adaptor or general-use syringe with a sterile 21-gauge x 1 ½ inch hypodermic needle (adjust needle length based on body mass index).
- Shake the vial vigorously before aspiration.
- Once CAB LA has been drawn up into the syringe, it must be administered within 2 hours.
- This deep IM injection is not appropriate for self-injection, and the only site currently recommended for injection is the gluteus.
- Inject into the gluteus medius muscle at a 90-degree angle using a Z-track method, ventrogluteal (preferred) or dorsogluteal (upper-outer quadrant of the buttock), with care that the compound is not injected into a vein.

**Note:**

a. See prescribing information.

**Adverse effects:** In the clinical trials noted above, CAB LA as PrEP was well tolerated. Adverse reactions observed in at least 1% of participants included injection site reactions, diarrhea, headache, pyrexia, fatigue, sleep disorders, nausea, dizziness, flatulence, abdominal pain, vomiting, myalgias, rash, decreased appetite, somnolence, back pain, and upper respiratory tract infection; however, almost all were grade 1–level effects [Delany-Moretlwe, et al. 2022; Landovitz, et al. 2021]. The most common adverse effects were injection site reactions in 81% of HPTN 083 study participants and 32% of HPTN 084 study participants. Reactions were mostly mild or moderate in intensity and decreased in frequency and intensity over time. Median onset was 1 day after injection in the HPTN 083 trial and lasted a median of 3 days. Discontinuations due to injection site reactions were rare and occurred at a rate of 2.4% in the HPTN 083 trial and 0.0% in the HPTN 084 trial. Other studies

have reported a strong preference for long-acting injectable medications despite injection site reactions [Tolley, et al. 2020; Murray, et al. 2018].

**Drug-drug interactions:** Strong inducers of cytochrome 450 (CYP), uridine diphosphate glucuronosyltransferase (UGT)1A and P-glycoprotein (P-gp) can significantly decrease CAB levels. Although the risk of drug-drug interactions when combining CAB LA with most medications used in primary care is low, there is a risk of reduced CAB drug concentrations when used concurrently with certain antiseizure drugs such as carbamazepine, oxcarbazepine, phenobarbital (and primidone), phenytoin, as well as with rifamycins. For guidance in managing CAB LA drug-drug interactions, consult the following resources:

- NYSDOH AI Drug-Drug Interaction Guide: From HIV Prevention to Treatment
- University of Liverpool HIV Drug Interactions

**Metabolic effects:** Mild weight gain was observed in MSM and transgender women receiving CAB LA as PrEP compared with TDF/FTC, but there was no significant difference in weight between the 2 study arms in cisgender women, and there was no significant effect on lipid levels [Delany-Moretlwe, et al. 2022; Landovitz, et al. 2021].

**Oral CAB as bridge therapy:** Oral CAB can be used as bridge therapy when it is anticipated that a CAB LA injection will be missed. Oral CAB is currently only available from a central pharmacy in collaboration with ViiV Healthcare. TDF/FTC (or TAF/FTC if appropriate) can also be used as bridge therapy when logistics impede timely access to oral CAB.

**Alternative sites of injection:** Data on alternative sites of injection are insufficient. Thigh injections into the vastus lateralis muscle were associated with a 10% decrease in bioavailability and more rapid decline in drug levels [Han(b), et al. 2024].

**Managing missed injections:** As mentioned above, CAB LA is given every 2 months, with a window period of 1 week before or after the prior injection. Missed injections are bridged with oral PrEP.

- **Planned missed injection (>5 weeks since initiation injection or >9 weeks since last continuation injection):** If an individual misses their CAB LA injection for a planned reason, initiate oral PrEP (oral CAB, TDF/FTC, or TAF/FTC) beginning when the injection is due and continuing until CAB LA can be administered. If it has been more than 12 weeks since their last injection, the individual can stay on oral PrEP or restart CAB LA injections with the 4-week loading dose.
- **Unplanned missed injections:** If an individual misses their CAB LA for an unplanned reason, determine why the individual is unable to return and refer them for appropriate services as needed. Offer the individual oral PrEP until injections can be resumed (if appropriate) and guidance as noted above for planned missed injections.

**Discontinuing CAB LA:** CAB levels begin to decline in the body 2 months after the last injection but persist and slowly decline over a median of 43.7 weeks for men and 67.3 weeks for women [Landovitz, et al. 2020]. During this time there are increasingly lower CAB levels that will not protect from HIV infection. Educate individuals receiving CAB LA as PrEP on the medication "tail" and provide individualized guidance on alternative PrEP options and prevention planning if HIV risk continues. If risk is ongoing, oral PrEP should be continued for at least 1 year to prevent the acquisition of INSTI-resistant HIV. However, it is reassuring that none of the individuals in the HPTN 083 study who acquired HIV during the tail phase had INSTI resistance-associated mutations [Landovitz, et al. 2021].

**Diagnosing HIV in individuals receiving CAB LA:** Diagnosing HIV seroconversion in individuals receiving CAB LA can be challenging. For discussion of long-acting early viral inhibition (LEVI) syndrome with potential delayed HIV positivity, altered presentation of acute HIV, and altered testing algorithms while using CAB LA as PrEP, see guideline section Managing a Positive HIV Test Result > Ambiguous HIV Test Results > LEVI syndrome.

## Injectable Regimen: SC LEN Every 6 Months

**When SC LEN is preferred:** Because of its statistically superior efficacy to oral PrEP regimens and its protection against HIV through all types of sexual exposure, SC LEN is a preferred PrEP agent for all adults and adolescents weighing ≥35 kg who are open to injectable PrEP.

**Dosing:** See Box 3, below, for details on the dosing, preparation, and administration of SC LEN as PrEP.

**Box 3: Dosing, Preparation, and Administration of Subcutaneous Lenacapavir as Pre-Exposure Prophylaxis [a]**

**How supplied:**

- Injection: 463.5 mg/1.5 mL (309 mg/mL) in 2 single-dose vials, 2 vial access devices, 2 disposable syringes, and 2 injection safety needles for subcutaneous (SC) injection (22 gauge, ½ inch)
- Tablets: 300 mg x 4 tablets
- Oral lenacapavir (LEN) tablets should be stored at room temperature, between 68° and 77° F, in their original packaging.
- SC LEN vials should be stored at room temperature, between 68° and 77° F, with excursions permitted at 59° to 86° F. Vials should be kept in their original carton until just before use to protect from light. Do not shake the vial before injection.

**Initiation dose:**

- Day 1: 927 mg (3 mL) LEN by SC injection (two 1.5 mL injections in separate areas) plus 600 mg LEN orally (two 300 mg tablets)
- Day 2: 600 mg LEN orally (two 300 mg tablets)

**Continuation dose:**

- Every 6 months (26 weeks), plus or minus 2 weeks, from the date of the last injection: 927 mg (3 mL) LEN by SC injection (two 1.5 mL injections in separate areas)

**Preparation and administration:**

- Use of ice packs before and after and analgesics after injections significantly decreases discomfort from injection site reactions (ISRs).
- Once the solution has been drawn into the syringes, administer as soon as possible. Discard solution if not used within 4 hours.
- SC LEN injections are administered at a 90° angle to decrease the risk of ISRs, placing the 2 injections on the opposite side of the body. The U.S. Food and Drug Administration lists the preferred site of administration as the abdomen, but the lateral thigh, upper arm, and buttocks are also acceptable sites based on patient preference.
- SC LEN is not appropriate for self-injection and should be administered by a healthcare professional.

**Note:**

a. See prescribing information.

**Adverse effects:** The most common and expected adverse effects associated with SC LEN are injection site reactions (ISRs), which may include pain, erythema, swelling, nodules, induration, and pruritus. Individuals receiving SC LEN as PrEP should be counseled to expect potential discomfort, induration, and subcutaneous nodules in the first week after the injection. SC LEN injections commonly create persistent subcutaneous nodules, which in the PURPOSE-2 study lasted a median of 183 days [Kelley, et al. 2025]. Although they are generally painless, the nodules can be palpated and sometimes visible depending on the physique of the individual. ISRs rarely led to discontinuation [Kelley, et al. 2025; Bekker, et al. 2024]. Proper injection technique (using ice packs at the site before injection and injecting at a 90° angle) can significantly decrease the incidence and intensity of ISRs [FDA(d) 2025; Kelley, et al. 2025].

**Where to inject:** The FDA label lists the preferred site of administration as the abdomen, with the thigh an accepted alternate site. However, pharmacokinetic data show similar or higher LEN levels for upper arm and thigh injections [Lat, et al. 2023] and safety data show similar or lower rates of ISRs with thigh, upper arm, and gluteal region injections [Saunders, et al. 2024], compared with abdomen injections. These data support using alternate injection sites based on patient preference.

**Drug-drug interactions:** Because LEN is a substrate and moderate inhibitor of CYP3A4 and a substrate of P-gp, the potential for drug-drug interactions associated with the use of SC LEN as PrEP should be carefully considered. Although the risk of drug-drug interactions when combining LEN with most medications used in primary care is low, there is a risk of reduced LEN drug concentrations when used concurrently with CYP3A4 or P-gp inducers. Examples of common CYP3A4 inducers can be remembered with the mnemonic COPPER: **C**arbamazepine, **O**xcarbazepine, **P**henobarbital (and primidone), **P**henytoin, **E**nzalutamide, and **R**ifampin (also rifabutin and rifapentine). Although not a complete list, these are the most common CYP3A4 inducers used in clinical practice.

LEN increases drug concentrations of gamma-hydroxybutyrate (GHB), ketamine, benzodiazepines, fentanyl, and nitazenes, making adverse effects and overdose of these drugs when used concurrently with SC LEN a concern. LEN also increases drug concentrations of PDE5 inhibitors, which are used to treat erectile dysfunction. Taking amyl nitrates ("poppers") with PDE5 inhibitors is contraindicated because of the risk of a severe drop in blood pressure, which would be more likely with concomitant SC LEN use. It is important that clinicians discuss the risk of and effects of drug-drug interactions with individuals receiving SC LEN.

**Dosing of SC LEN with concomitant strong or moderate CYP3A4 inducers:** Current FDA prescribing information for SC LEN for HIV prevention provides recommendations for supplemental dosing with LEN injections and/or oral tablets to offset potential interactions; these recommendations vary depending on whether a strong or a moderate CYP3A4 inducer is being added to LEN. For guidance in determining the degree of induction from CYP3A4 (and other isoenzymes of CYP450) when managing drug-drug interactions, consult the following resources:

- NYSDOH AI Drug-Drug Interaction Guide: From HIV Prevention to Treatment
- FDA Drug Development and Drug Interactions, Table of Substrates, Inhibitors and Inducers (may not contain all medications identified as CYP3A4 inducers)
- U.S. Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV > Drug-Drug Interactions
- University of Liverpool HIV Drug Interactions

Note that FDA recommendations for managing concurrent use of CYP3A4 inducers differ greatly in the prescribing information for LEN used as HIV prevention (Yeztugo) and LEN used for HIV treatment (Sunlenca).

**→ KEY POINTS**

- Apply ice packs to the planned injection sites for 10 minutes before injection and use analgesics as needed to decrease discomfort from ISRs.
- Administer SC LEN injections at a 90° angle to decrease the risk of ISRs.
- The day 2 dose of oral LEN is necessary to assure adequate LEN levels during initiation.
- Supplemental doses of SC LEN are recommended for individuals initiating either strong or moderate CYP3A inducers.

**Managing missed injections:** As mentioned above, SC LEN is given every 6 months, with a window period of 2 weeks before or after the prior injection. Missed injections are bridged with oral LEN or another oral PrEP regimen if oral LEN is not available. For both planned and unplanned missed injections, if oral LEN is not initiated for bridging and more than 28 weeks have lapsed since the prior injection, reinitiation with oral LEN 600 mg daily for 2 days is needed in addition to LEN injections.

- **Planned missed injection >14 days late (>28 weeks since the last injection):** If an individual misses their LEN injection for a planned reason, initiate oral LEN 300 mg once every 7 days (beginning when the injection is due) and continue until SC LEN can be administered, up to a maximum of 6 months (26 weeks). If the injection is missed beyond 6 months (i.e., more than 52 weeks since the last injection), transition the individual to another PrEP regimen if they plan to continue PrEP (see Discontinuing SC LEN, below). If oral LEN is unavailable for bridging, prescribe another oral PrEP regimen.
- **Unplanned missed injection >14 days late (>28 weeks since the last injection):** If an individual misses their SC LEN injection for an unplanned reason, determine why the individual is unable to return and refer them for appropriate services as needed. Offer the individual oral LEN or another oral PrEP regimen as noted above for planned missed injections.

**Discontinuing SC LEN:** Levels of SC LEN begin to decline in the body 6 months after the last injection and continue to decline over the following 6 months (the medication "tail"). During this time there are increasingly lower levels of SC LEN that will not protect from HIV infection. Individuals receiving SC LEN as PrEP should be educated on the medication "tail" and provided individualized guidance on alternative PrEP options and prevention planning if HIV risk continues.

**Managing a positive HIV test result:** See guideline section Managing a Positive HIV Test Result. In the 2 seroconversions seen in the PURPOSE 2 study, no delay was observed in HIV antigen/antibody positivity, and viral load results were 14,100 and 934,000 copies/mL, respectively [Kelley, et al. 2025]. For individuals who have a positive HIV test result while receiving SC LEN as PrEP, an initial INSTI-based antiretroviral therapy (ART) regimen should be initiated (see the NYSDOH AI guideline Selecting an Initial ART Regimen).

**→ KEY POINT**

- The logistics of implementing CAB LA and SC LEN in PrEP programs may be challenging and require institutional, clinician, and individual preparations. Procedures for obtaining prior authorizations, medication storage, scheduling and reminders, tracking systems, staff education, and staffing levels must be addressed with implementation plans appropriate to each setting. See Checklist 3: Implementation Strategies for Long-Acting Injectable PrEP Regimens.

# PrEP During Pregnancy

PrEP should be offered to pregnant individuals with ongoing HIV exposure, as HIV acquisition risk is higher during pregnancy and highest in the late pregnancy and early postpartum periods [Thomson, et al. 2018]. Risk of perinatal transmission is also significantly higher during pregnancy and breast/chestfeeding in cases of acute seroconversion [Drake, et al. 2014; Singh, et al. 2012], and this committee recommends PrEP in individuals at risk while they are breast/chestfeeding. Encourage pregnant individuals to inform their obstetric and pediatric care providers when using PrEP medications or any other prescription or over-the-counter medications. Prospectively report pregnancies in individuals on PrEP to the Antiretroviral Pregnancy Registry.

**TDF/FTC:** TDF/FTC is considered safe to use during pregnancy [FDA 2024]. Available data suggest that TDF/FTC as PrEP does not increase the risk of congenital anomalies. Conflicting results have been observed in studies of bone mineral density in infants born to women taking TDF as a component of ART for HIV [Siberry, et al. 2015; Vigano, et al. 2011]. However, more recent studies of infants exposed to TDF in utero, 1 due to maternal HIV [Reddy, et al. 2024] and 2 for HBV transmission prevention [Wen, et al. 2020; Salvadori, et al. 2019], showed comparable bone mineral composition in exposed versus unexposed infants aged 1 to 7 years.

Infant exposure to TDF/FTC through breast milk is much lower than TDF exposure in utero; evidence to date suggests that TDF is safe during breastfeeding [Liotta, et al. 2016; Ehrhardt, et al. 2015]. Although data on breastfeeding effects are limited, TDF/FTC is commonly prescribed as part of an ART regimen before, during, and after pregnancy, and the benefit of preventing HIV infection and subsequent perinatal transmission among individuals at increased risk outweighs the theoretical concerns associated with prescribing TDF/FTC as PrEP during breastfeeding, pending further data.

**TAF/FTC:** Clinical trials, observational studies, and data from the Antiretroviral Pregnancy Registry support the use of TAF/FTC in pregnancy [Zeng, et al. 2025]. Further, the Society for Maternal-Fetal Medicine states that TAF/FTC has a similar safety profile to TDF/FTC for PrEP [Badell, et al. 2024]. TAF/FTC has been shown to be well tolerated and there have been no increased adverse pregnancy or infant outcomes in those taking TDF as PrEP or treatment for chronic HBV infection during pregnancy [Heffron, et al. 2018].

**CAB LA:** No significant differences in maternal adverse events or pregnancy outcomes were observed between CAB LA and TDF/FTC in the HPTN 084 trial [Delany-Moretlwe, et al. 2025]. HPTN 084 researchers presented updated pharmacokinetic data for CAB LA as PrEP used before and during pregnancy. CAB LA was generally well tolerated. CAB LA levels declined in each trimester of pregnancy but remained above specific target levels. These findings suggest that no dose changes are needed when using CAB LA during pregnancy, although more human data are needed. None of the women who became pregnant while receiving CAB LA acquired HIV during their pregnancy. Use of CAB LA as PrEP appears to be safe during pregnancy, but data are limited. Use shared decision-making when considering whether to initiate or switch from CAB LA as PrEP for individuals who are pregnant or planning to conceive.

**SC LEN:** In the PURPOSE 1 study, there were 208 pregnancies and 132 live births in the SC LEN group, there were no pregnancy complications found to be related to SC LEN use, and the infant mortality rate was similar to background rates in the study region and to tenofovir-based PrEP [FDA(d) 2025; Bekker, et al. 2024]. No adverse effects related to SC LEN during breast/chestfeeding have been observed. Discuss potential risks and benefits and engage individuals who are or may become pregnant in shared decision-making when considering SC LEN as PrEP.

# Initiating PrEP

## ☑ RECOMMENDATIONS

**Preinitiation Assessment**

- Before prescribing PrEP, clinicians should assess all candidates for:
  - Symptoms or signs of acute HIV, including febrile, flu-like, or mono-like illness in the previous 6 weeks (A3)
  - Risk encounters within the previous 72 hours that require PEP before PrEP (A3)
  - Reproductive plans (A3)
  - Potential drug-drug interactions or increased risk of nephrotoxicity with concomitant medications (A3)

**Baseline Laboratory Testing**

- Clinicians should perform baseline laboratory testing as recommended in Table 3: Recommended Laboratory Tests for All Individuals Within 1 Week Before Initiating PrEP.

**Same-Day Initiation**

- Clinicians should recommend same-day PrEP initiation while laboratory results are pending in candidates for whom there are no signs or symptoms of acute HIV infection, no history of renal disease, and no concern for HIV exposure in the previous 72 hours requiring PEP. (A2)
- For same-day initiation of PrEP, clinicians should obtain a rapid HIV test and order a laboratory-based HIV-1/2 Ag/Ab combination immunoassay and an HIV RNA test for all candidates unless there are laboratory-based HIV test results in the past 7 days (A3) and ensure that HIV test results are available and acted upon within 7 days of initiation. (A3)
  - See the NYSDOH AI guideline HIV Testing.
- If a patient has a positive baseline HIV test result after oral PrEP initiation, the clinician should intensify the PrEP regimen to fully suppressive ART and refer the patient to an experienced HIV care provider for ongoing care. (A3)
- If a long-acting injectable PrEP regimen is chosen but same-day initiation is not possible, the clinician should initiate oral PrEP until injectable PrEP is available unless the individual declines. (A3)
- If same-day initiation is not possible, clinicians should repeat laboratory-based HIV-1/2 Ag/Ab and HIV RNA testing if more than 1 week has lapsed since HIV testing was performed (A3) and ensure that HIV test results are available and acted upon within 7 days of initiation. (A3)
- If an individual has been exposed to HIV within the previous 72 hours, the clinician should recommend PEP before PrEP. (A1)

**Initiating PrEP During the HIV Testing Window Following Exposure**

- Clinicians should not wait to initiate PrEP in individuals who have had a potential exposure to HIV and are no longer eligible for PEP (>72 hours) but are still in the window period for seroconversion when an HIV test cannot detect infection; doing so risks additional exposures and significant delays in PrEP. (A*)
- Clinicians should repeat HIV testing 1 month after PrEP initiation in individuals who report a risk exposure in the 30 days before PrEP initiation. (A2†)
- If a patient has a positive HIV test result after receiving the first CAB LA injection, the clinician should consult with an experienced HIV care provider to identify the best strategy for ART intensification. (A3) To consult an expert, call the NYSDOH AI CEI Line at 1-866-637-2342.
- If a patient has a positive HIV test result after receiving the first dose of SC LEN, clinicians should initiate any preferred ART regimen, or alternative ART regimen based on individual patient need, and refer the patient to an experienced HIV care provider for ongoing care. (A3)

**Resources:** Checklist 2: Assessment and Counseling Before PrEP Initiation; Checklist 4: PrEP Initiation

**Abbreviations:** Ag/Ab, antigen/antibody; ART, antiretroviral therapy; CAB LA, long-acting injectable cabotegravir (Apretude); CEI, Clinical Education Initiative; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis.

# Before Initiating PrEP

**Assess for acute HIV infection:** Before initiating PrEP, all individuals should be evaluated for potential HIV exposure in the prior 6 weeks and assessed for the flu-like symptoms of acute HIV. Both an HIV-1/2 Ag/Ab combination immunoassay and an HIV RNA test should be performed within 1 week before PrEP initiation. HIV RNA (viral load) testing is recommended at baseline to rule out acute HIV infection regardless of reported risk, as individuals may be reluctant to disclose a recent potential risk exposure. If a confirmed negative result is not available at the time of the patient's initial visit, a rapid HIV-1/2 test should be performed for same-day PrEP initiation.

Drug-resistant virus has been found in individuals with undiagnosed HIV who initiated PrEP with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), tenofovir alafenamide/emtricitabine (TAF/FTC), CAB LA and subcutaneous lenacapavir (SC LEN) [Kelley, et al. 2025; Molina, et al. 2022; Landovitz, et al. 2021; Cox, et al. 2020; Lehman, et al. 2015].

**Perform recommended laboratory testing:** Table 3, below, lists the baseline laboratory tests that should be performed before PrEP initiation. When an individual is engaged in PrEP care, primary healthcare may also be offered as indicated, including vaccinations against hepatitis A and B viruses, human papillomavirus, meningococcus, mpox, influenza, and COVID-19 (see the NYSDOH AI guidelines Primary Care for Adults With HIV and Immunizations for Adults With HIV).

**Table 3: Recommended Laboratory Tests for All individuals Within 1 Week Before Initiating PrEP [a]**

| Purpose (rating) | Test | Comments |
|---|---|---|
| HIV status (A*) | • Baseline HIV-1/2 Ag/Ab combination immunoassay [b]<br>• HIV RNA assay | • A laboratory-based HIV Ag/Ab within the past 7 days. For same-day initiation, a rapid HIV test plus a laboratory-based test is required.<br>• A negative HIV RNA assay more confidently rules out acute HIV infection, as individuals may be reluctant to disclose risk behavior.<br>• HIV RNA testing is not required at initiation if switching PrEP regimens. |
| Renal function (A*) | Serum creatinine and calculated CrCl | • **TDF/FTC:** Do not initiate in individuals with confirmed CrCl <60 mL/min.<br>• **TAF/FTC:** Do not initiate in individuals with confirmed CrCl <30 mL/min.<br>• **CAB LA:** Increase monitoring for adverse effects in individuals with CrCl <30 mL/min.<br>• **SC LEN:** Increase monitoring for adverse effects in individuals with CrCl <15 mL/min. |
| Pregnancy status (A3) | Pregnancy test for all individuals of childbearing potential | • Discuss the importance of preventing HIV during pregnancy with anyone who is or may become pregnant while using PrEP.<br>• **TDF/FTC, TAF/FTC, CAB LA, and SC LEN:** Discuss risks, benefits, and available data suggesting no increased risk of pregnancy complications or negative birth outcomes. |
| HBV infection status (A2†) | HBV serologies: HBsAg, anti-HBs, and anti-HBc (IgG or total) | • Vaccinate nonimmune individuals (A2).<br>• **Chronic HBV:** Treat and monitor HBV [c] or refer to an HBV specialist. |
| Syphilis screening (A2†) | All individuals: Syphilis testing [d] | Screen for syphilis according to the laboratory's testing algorithm. |

| Table 3: Recommended Laboratory Tests for All individuals Within 1 Week Before Initiating PrEP [a] | | |
|---|---|---|
| **Purpose (rating)** | **Test** | **Comments** |
| Gonorrhea and chlamydia screening (A2†) | • All individuals, all potential exposure sites: NAAT [d]<br>• MSM and transgender women: Routine 3-site testing (genital, rectal, and pharyngeal) regardless of reported exposure sites, unless declined | • **Detecting urethral infection:** Urine specimens are preferred over urethral specimens.<br>• **Vaginal and cervical testing:** Vaginal swabs are preferred over urine-based testing.<br>• **Transgender women with a neovagina:** Data are insufficient to support a recommendation regarding urine-based testing vs. vaginal swab [e].<br>• Self-collected swabs from the pharynx, vagina, and rectum are reasonable and noninferior options for individuals who may prefer them over clinician-obtained swabs. |
| HCV infection status (A3) | HCV serology with reflex to RNA | Inform individuals with HCV about transmission risk and offer or refer for treatment [f]. |
| HAV infection status (good practice) | HAV serology for MSM and individuals at high risk of HAV infection [g] | Vaccinate nonimmune individuals. |
| Hepatic function (good practice) | Serum liver enzymes | Increased serum liver enzymes may indicate acute or chronic viral hepatitis infection and require further evaluation. |
| Assess for preexisting renal disease, proteinuria, and glycosuria (good practice) | Urinalysis | Only calculated CrCl is used to guide decisions regarding the use of TDF/FTC and TAF/FTC as PrEP based on renal function; however, baseline urinalysis abnormalities may indicate an increased risk of renal tenofovir toxicity. |

**Abbreviations:** Ab, antibody; Ag, antigen; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; CAB LA, long-acting injectable cabotegravir (Apretude); CDC, Centers for Disease Control and Prevention; CrCl, creatinine clearance; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgG, immunoglobulin G; SC LEN, subcutaneous lenacapavir (Yeztugo); MSM, men who have sex with men; NAAT, nucleic acid amplification test; TAF/FTC, tenofovir alafenamide/emtricitabine (Descovy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (Truvada); UCSF, University of California San Francisco.

**Notes:**

a. Initiate PrEP while the result is pending in the absence of potential contraindications.
b. See NYSDOH AI guideline HIV Testing.
c. See CDC Recommendations for Routine Testing and Follow-up for Chronic HBV Infection.
d. See CDC Sexually Transmitted Infections Treatment Guidelines, 2021.
e. See UCSF Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People.
f. See NYSDOH AI guideline Hepatitis C Virus Screening, Testing, and Diagnosis in Adults.
g. Risk factors for HAV infection include chronic liver disease or conditions that can lead to chronic liver disease (e.g., chronic HBV, chronic HCV, alcohol use, or genetic liver diseases), travel to or from countries with high or intermediate HAV endemicity, injection drug use, unstable housing or homelessness, exposure through a health department–confirmed HAV outbreak, clotting-factor disorders, and occupational risk without HAV vaccination.

# Assessment and Counseling Before PrEP Initiation

**Engagement in primary care:** PrEP is an integral part of sexual health and well-being. Developing an HIV prevention plan that includes PrEP is an opportunity to engage individuals in primary care. Clinicians can encourage age-appropriate health screenings, substance use screening and interventions, linkage to specialty services, and other health maintenance activities such as immunizations (see the NYSDOH AI guideline Immunizations for Adults With HIV). For additional information, see Centers for Disease Control and Prevention Recommended Adult Immunization Schedule for Ages 19 Years or Older, United States, 2025 and ACIP Recommendations: COVID-19 Vaccine and NYSDOH Health Advisory: NYSDOH Meningococcal Vaccine Recommendations for HIV-Infected Individuals and Those at High Risk of HIV Infection.

**Patient education:** Patient education is vital to shared decision-making and the success of PrEP as part of a comprehensive HIV prevention plan. Educate PrEP candidates about its risks and benefits and the choice of oral versus injectable PrEP. Discuss individual preferences, needs, and circumstances. Adherence and persistence improve when individuals participate in medication-related decisions and are informed about the strong efficacy of PrEP when taken as directed [Grinsztejn, et al. 2025] (see guideline section Adherence, below). Education provided in the individual's native or preferred language and tailored to the individual's level of comprehension and health literacy will help ensure understanding of the benefits and potential adverse effects, the need for adherence, regular monitoring, the process of obtaining refills for oral PrEP, payment and payment assistance, and how safer sex or drug injection practices decrease the risk of pregnancy or of acquiring HIV and other sexually transmitted infections (STIs) (see Be in the KNOW > Sex and HIV and NYSDOH Syringe Access and Disposal).

**Sex and drug use histories:** A detailed HIV risk assessment includes obtaining a patient's sexual history and drug use history and having a frank, open, and nonjudgmental discussion of risk-related behaviors. As indicated, this discussion may also include offering further counseling and referrals, such as for substance use treatment (see NYSDOH Office of Addiction Services and Supports > Treatment and guidelines on Substance Use Care).

**Viral load status of sex partner(s) with HIV:** The antiretroviral therapy (ART) and viral load status of a sex partner with HIV may inform the discussion of risk. Sexual transmission of HIV does not occur when an individual with HIV has a persistently undetectable HIV viral load; nonetheless, an individual without HIV in a serodifferent partnership who does not have HIV may still elect to use PrEP [Rodger, et al. 2016] (see discussion below). If the patient's partner has detectable virus and genotypic test results are unavailable, knowledge of the partner's ART regimen may be helpful. HIV acquisition risk is increased when an individual is exposed to HIV that is resistant to the components of their PrEP regimen [Gibas, et al. 2019; Knox, et al. 2017]. The potential for drug resistance is an important consideration when choosing a PrEP regimen. If there is a risk for drug resistance in a sex partner with HIV, choose a PrEP option to which said partner is not known to be resistant.

**HIV-serodifferent couples:** As mentioned above, in an HIV-serodifferent partnership the partner who does not have HIV may decide to use PrEP even if the partner with HIV has achieved an undetectable viral load with ART. Although this supplemental protection is likely unnecessary in light of the finding that undetectable = untransmittable (U=U), PrEP can be discussed as an additional option for HIV prevention. The partner without HIV may choose to take PrEP for other reasons, including if they have additional sex partners, are unsure of a sex partner's viral load or ability to maintain viral suppression, or feel more secure about and in control of their sexual health with the added protection of PrEP. In September 2017, the NYSDOH endorsed the U=U consensus statement from the Prevention Access Campaign. For more information, see Appendix B: Studies That Support the Use of PrEP in Different Populations > HIV-serodifferent couples and NYSDOH AI U=U Guidance for Implementation in Clinical Settings.

**Reproductive counseling:** Inquire about the individual's reproductive plans and provide preconception counseling when indicated. Determine whether they or their partner is pregnant or breast/chestfeeding, intends to conceive, or is currently using hormonal or other contraception in addition to condoms [Bujan and Pasquier 2016; Lampe, et al. 2011; Vernazza, et al. 2011]. Counsel HIV-serodifferent couples who are considering the use of PrEP during attempts to conceive about the utility, safety, and possible risks of the medication (see guideline section Choosing and Prescribing a PrEP Regimen > PrEP During Pregnancy).

**Psychosocial assessment:** Assessments of psychosocial needs, strengths, challenges, mental health, and substance use are integral to good general medical practice. In the case of someone prescribed PrEP, such assessments enable clinicians to identify modifiable barriers to adherence and provide services and referrals to support adherence and retention in care.

**PrEP after PEP:** Individuals who remain at increased risk of HIV exposure after completing a course of non-occupational post-exposure prophylaxis (nPEP) and are negative for HIV at the 4-week test should be offered PrEP to begin immediately after the last dose of nPEP. Giving a prescription for the first month of PrEP at the time PEP is prescribed can significantly increase access to and uptake of PrEP [Cockbain, et al. 2022].

**→ KEY POINTS**

- Individualize the decision of which PrEP regimen to initiate by weighing patient preferences and the benefit of reducing their risk of acquiring HIV against the potential adverse effects of PrEP medications.
- Psychosocial assessments allow clinicians to identify modifiable barriers to adherence and provide services and referrals to support adherence and retention in care.
- Developing an HIV prevention plan that includes PrEP offers care providers the opportunity to engage individuals in primary care.
- See Checklist 2: Assessment and Counseling Before PrEP Initiation.

## Same-Day PrEP Initiation

Once laboratory specimens are obtained (see Table 3, above) PrEP may be initiated while test results are pending as long as results will be available and addressed within 7 days and a rapid HIV test result is negative and if the individual has not had symptoms or signs of acute HIV in the prior 6 weeks, has no history of renal disease, and no risk exposures in the past 72 hours requiring PEP. Same-day PrEP initiation has been shown to be safe, and delayed PrEP initiation has been associated with a significant rate of loss to follow-up [Kamis, et al. 2019; Mikati, et al. 2019]. Same-day PrEP initiation may engage individuals more fully in care and reduce HIV exposures while test results are pending and encourages immediate attention to insurance coverage for PrEP or identification of other options for payment if needed.

Same-day PrEP initiation also risks starting a nonsuppressive ART regimen in someone with HIV. However, if laboratory results are available promptly, the PrEP regimen for an individual who tests positive for HIV can be intensified to a fully suppressive ART regimen and a referral for HIV care can be made. If the baseline HIV testing result is positive after the individual has received the first CAB LA injection, the clinician should consult with an experienced HIV care provider regarding the best way to intensify the PrEP regimen to a fully suppressive ART regimen (see guideline section Managing a Positive HIV Test Result). If a patient has a positive HIV test result after receiving the first dose of SC LEN, they should be placed on any preferred regimen as per HIV treatment guidelines.

TAF/FTC may require a prior authorization, which can make same-day initiation a challenge, but generic TDF/FTC is usually available for same-day initiation. If prior insurance authorization is required, same-day CAB initiation (oral or injection) and SC LEN may not be possible. Implementation challenges such as stocking and storing injectable medications in advance may also be prohibitive. If same-day initiation of CAB LA or SC LEN is not possible, an oral PrEP regimen can be an interim option while barriers to accessing injectable PrEP are addressed.

Although delays such as insurance barriers may impede PrEP initiation, the overall goal should be same-day initiation in individuals without renal disease, need for PEP, or signs or symptoms of acute HIV.

**Initiating PrEP during the HIV testing window period:** The window period is the time between when an individual has acquired HIV and when a diagnostic test can detect infection. The median time to positivity is 12 days for an HIV viral load test and 18 days for a laboratory-based HIV-1/2 Ag/Ab combination immunoassay; however, the 99th percentile for a positive test is 33 days for an HIV viral load test and 42 days for a laboratory-based HIV-1/2 Ag/Ab combination immunoassay [Delaney, et al. 2017]. Clinicians should not defer initiation of PrEP in candidates who, based on their reported sexual and drug use exposures, may be in the window period for seroconversion; doing so risks additional exposures and significant delays in PrEP initiation. Repeat HIV testing 1 month after PrEP initiation to help identify potentially positive individuals in a timely manner (see guideline section Ongoing Laboratory Testing).

**→ KEY POINTS**

- Same-day initiation of PrEP is the goal whenever possible.
- Do not delay PrEP initiation if a patient has an HIV exposure too recent to be detected on testing.

## Adherence

**Challenges:** Adherence remains a critical factor for oral PrEP effectiveness and is difficult for some individuals because of a range of intersecting factors, including pill size, tolerability, privacy concerns, PrEP-related stigma, neurocognitive impairment, mental health conditions, substance use, history of trauma, personal beliefs, travel, occupational demands, and health literacy. Although once-daily and on-demand oral PrEP dosing options are available, real-world experience and research continue to show adherence challenges for certain populations. Effective HIV prevention with TDF/FTC requires at least 4 doses per week [Engel, et al. 2025; Grant, et al. 2014], and TAF/FTC effectiveness was found to be similar to TDF/FTC based on adherence [Kiweewa, et al. 2025].

Timely injections are essential for long-acting injectable PrEP, as missed and delayed injections can cause viral breakthrough [Landovitz, et al. 2021].

**Strategies for adherence support:** For oral PrEP, strategies to support and improve adherence include increasing visit frequency or follow-up contact, particularly for populations such as adolescents in whom adherence declined when visits shifted from monthly to quarterly [Hosek, et al. 2017]. Individualizing assessment of adherence barriers and incorporating peer support can also reinforce medication and appointment adherence [Goodreau, et al. 2018; Jenness, et al. 2016].

For those unable or unwilling to maintain adherence to daily oral PrEP despite support efforts, long-acting injectable PrEP is an additional preferred PrEP option. Studies indicate strong interest in injectable PrEP among the general population and key subgroups [Grinsztejn, et al. 2025; Philbin, et al. 2021; Koren, et al. 2020; Rael, et al. 2020]. Injection appointment reminders and ongoing counseling on the importance of on-time injections are crucial to effective injectable PrEP programs.

If injectable PrEP is not desired or is not an option, alternative options should be considered, including on-demand PrEP or intermittent use (e.g., during periods of higher risk). If these options are not feasible, clinicians may consider discussing PrEP discontinuation alongside other HIV prevention strategies that align better with the patient's needs and preferences.

**→ KEY POINTS**

- The minimum degree of adherence to oral PrEP required for protection against HIV is 4 or more doses per week.
- Long-acting injectable PrEP is a preferred PrEP option and is the preferred option when adherence to oral PrEP is a challenge.

# Ongoing Laboratory Testing

**☑ RECOMMENDATIONS**

**Ongoing Laboratory Testing**

- Clinicians should perform ongoing laboratory testing as recommended in Table 4: Recommended Routine Laboratory Testing for Individuals Using PrEP.

**HIV Testing**

- For any individual who reports an HIV exposure that occurred in the 30 days before PrEP initiation, clinicians should repeat HIV testing 30 days after initiation. (A2†)
- Clinicians should perform an FDA-approved plasma or serum HIV-1/2 Ag/Ab combination immunoassay every 3 months in individuals taking oral PrEP. (A3)
- Clinicians should perform an FDA-approved plasma or serum HIV-1/2 Ag/Ab combination immunoassay at each injection visit for patients receiving SC LEN or CAB LA as PrEP. (A3)
- Clinicians should perform an HIV-1/2 Ag/Ab combination immunoassay and HIV RNA test in individuals who present with or report symptoms or signs of acute HIV infection. (A2)
- Clinicians should perform an HIV-1/2 Ag/Ab combination immunoassay and HIV RNA test in individuals who report inconsistent adherence to or an interruption of oral PrEP of more than 1 week or delays in injectable PrEP administration (without oral bridging) during times of sexual activity and possible HIV exposure. (A3)

**Renal Function Testing**

- Clinicians should discontinue daily TDF/FTC as PrEP if an individual develops a confirmed CrCl <50 mL/min and consider alternative options. (A3)
- Clinicians should discontinue TAF/FTC as PrEP if an individual develops a confirmed calculated CrCl <30 mL/min. (A3)
- Clinicians should perform urinalysis at baseline and annually to assess urine glucose and protein in individuals taking TDF/FTC or TAF/FTC as PrEP. (B3)

**STI Screening**

- At every visit, a care team member should assess individuals for signs and symptoms of STIs, including syphilis and gonococcal and chlamydial infections, as part of a sexual history, perform testing as indicated, and treat STIs empirically based on symptoms while test results are pending. (A2†)
- Clinicians should perform routine STI screening as recommended in Table 4: Recommended Routine Laboratory Testing for Individuals Using PrEP.

**HCV Screening**

- Clinicians should perform HCV testing at least annually for at-risk individuals. (A3)

## ☑ RECOMMENDATIONS

**Pregnancy Screening**

- At every visit, clinicians should assess the possibility of pregnancy in individuals of childbearing potential. (A3)

**Resource:** Checklist 5: PrEP Follow-Up

**Abbreviations:** Ag/Ab, antigen/antibody; CrCl, creatinine clearance; FDA, U.S. Food and Drug Administration; HCV, hepatitis C virus; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide/emtricitabine (Descovy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (Truvada).

Services for follow-up and monitoring of individuals receiving PrEP are part of a comprehensive HIV prevention plan: routine HIV testing; risk-reduction counseling; access to condoms and syringes; STI, mental health, and substance use screening; and referral for treatment when indicated.

Table 4, below, lists the laboratory tests that should be performed for individuals using oral or injectable PrEP.

**Table 4: Recommended Routine Laboratory Testing for Individuals Using PrEP**

| Test | Laboratory Testing Indications | | |
|---|---|---|---|
| | **All PrEP Regimens** | **Oral PrEP: TDF/FTC or TAF/FTC** | **Injectable PrEP: CAB LA or SC LEN** |
| HIV-1/2 Ag/Ab combination immunoassay [a] | • When a patient has symptoms of acute HIV infection [b] (A2)<br>• 1 month after PrEP initiation if an HIV exposure occurred ≤1 month before the start of PrEP (A2†) | • Every 3 months (A3)<br>• When PrEP has been interrupted for >1 week in the past month and a potential exposure occurred (A3)<br>• When an individual reports inconsistent adherence during times of sexual activity and possible HIV exposure (A3) | • At the end of the oral CAB lead-in (if used) (A2)<br>• Every injection visit (A3)<br>• Consider interim 3-month HIV testing for high-risk individuals receiving SC LEN every 6 months |
| HIV RNA assay [a] | When a patient has symptoms of acute HIV [b] (A2) | • When PrEP has been interrupted for >1 week in the past month and a potential exposure occurred (A3)<br>• When an individual reports inconsistent adherence during times of sexual activity and possible HIV exposure (A2) | • At the end of the oral CAB lead-in, if implemented (A2)<br>• At injection visit if injection was delayed without use of oral bridging |
| Serum creatinine and calculated CrCl | — | • 3 months after initiation (B3)<br>• Every 6-12 months thereafter (A3)<br>• Consider more frequent screening in those at high risk, e.g., aged >40 years or with comorbidities (A3) | At least annually (A3) |

| Table 4: Recommended Routine Laboratory Testing for Individuals Using PrEP | | | |
|---|---|---|---|
| | Laboratory Testing Indications | | |
| **Test** | **All PrEP Regimens** | **Oral PrEP: TDF/FTC or TAF/FTC** | **Injectable PrEP: CAB LA or SC LEN** |
| STI (gonorrhea, chlamydia, and syphilis) screening (A2†) Note: Screening can be less frequent in those at lower risk | Ask about symptoms at every visit; if present, perform diagnostic testing and treat as indicated | Every 3-6 months based on reported risk | • CAB LA: Every 2-6 months based on reported risk<br>• SC LEN: every 3-6 months based on reported risk |
| HCV serology [d] | At least annually if at risk (A3) | — | — |
| Pregnancy test in individuals of childbearing potential | • At every visit, assess for the possibility of pregnancy (A3)<br>• Test for pregnancy when appropriate and on patient request (A3)<br>• Offer contraception when requested or indicated (A3) | — | — |
| Urinalysis | — | Annually (B3) | — |

**Abbreviations:** Ab, antibody; Ag, antigen; CAB LA, long-acting injectable cabotegravir (Apretude); CrCl, creatinine clearance; HCV, hepatitis C virus; SC LEN, subcutaneous lenacapavir (Yeztugo); oral CAB, oral cabotegravir (Vocabria); PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide/emtricitabine (Descovy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (Truvada).

**Notes:**

a. See NYSDOH AI guideline HIV Testing.
b. See NYSDOH AI guideline Diagnosis and Management of Acute HIV Infection.
c. To detect urethral infection, urine specimens are preferred over urethral specimens. For vaginal/cervical testing, vaginal swabs are preferred over urine-based testing. For transgender women with a neovagina, data are insufficient to make a recommendation regarding urine-based testing vs. vaginal swab. Self-collected swabs from the pharynx, vagina, and rectum are reasonable options for individuals who prefer them over clinician-obtained swabs. See NYSDOH Sexually Transmitted Infection Self-Collection Outside of a Clinic Setting in New York State: Frequently Asked Questions.
d. See NYSDOH AI guideline Hepatitis C Virus Screening, Testing, and Diagnosis in Adults.

# HIV Testing

For individuals using PrEP, routine HIV testing is recommended for early detection of PrEP failure. None of the available regimens are adequate for treating acute or chronic HIV infection. Continued use of only TDF/FTC, TAF/FTC, long-acting injectable cabotegravir (CAB LA), or subcutaneous lenacapavir (SC LEN) in the presence of HIV infection may lead to viral resistance to these drugs.

**Routine HIV testing with oral PrEP:** A quarterly (every 3 months) HIV-1/2 Ag/Ab combination immunoassay is recommended for individuals taking TDF/FTC or TAF/FTC as PrEP. Quarterly HIV RNA testing is not needed for individuals who report consistent adherence to oral PrEP.

Breakthrough HIV infections among individuals adherent to oral PrEP are rare. When failure of an oral PrEP regimen occurs, it is usually associated with poor adherence and is infrequently associated with the development of resistance. When drug resistance develops, it is typically an M184V/I resistance mutation, which has little or no effect on subsequent response to HIV treatment. The development of the K65R resistance mutation (associated with tenofovir) has rarely been reported [van de Vijver, et al. 2021; Gibas, et al. 2019]. Unrecognized acute HIV infection at the time of PrEP initiation carries the highest risk for developing resistance mutations [van de Vijver, et al. 2021; Gibas, et al. 2019]. For this reason, this committee recommends that clinicians perform baseline HIV RNA testing for all individuals before initiating PrEP.

In the HPTN 083 study, there was less delay in detection of new HIV infections with seroconversion for participants receiving TDF/FTC than for those receiving CAB LA. There were a median of 34 days and 31 days of unrecognized baseline and incident HIV infections, respectively, in the TDF/FTC arm, compared with 62 days and 98 days, respectively, in the CAB LA arm [Marzinke(a), et al. 2021].

HIV RNA testing is recommended for individuals who report an interruption in PrEP of more than 1 week or report missing doses of PrEP during a time of sexual activity since the preceding visit.

**→ KEY POINT**

- Routine HIV RNA testing is not recommended for individuals who are adherent to TDF/FTC or TAF/FTC as PrEP, for the following reasons:
  - Breakthrough infections are rare with adherence to these regimens.
  - The use of an HIV-1/2 Ag/Ab combination immunoassay alone does not significantly delay detection of new infections.
  - Failure of these regimens infrequently leads to resistance.
  - The M184V/I mutation has little impact on response to initial HIV treatment.

Testing for HIV every 3 months is based on good practice rather than evidence. If HIV testing is missed, every effort should be made to avoid interruption of PrEP, as the potential harm of discontinuing PrEP outweighs the theoretical risk of delaying HIV testing in a stable individual. It is reasonable to provide an additional month of PrEP and plan for HIV testing as soon as possible.

In-office visits are not a requirement for ongoing prescription of PrEP. Individuals established on oral PrEP can be tested for HIV every 3 months, either on site or at an outside laboratory, and see their care providers every 6 to 12 months. Requiring in-office visits may create a barrier to PrEP access for some individuals. Alternative monitoring models, such as at-home testing and telehealth visits, can decrease barriers to PrEP access and monitoring.

**Routine HIV testing with CAB LA:** CAB LA injections are administered by clinic staff every 2 months. HIV Ag/Ab testing should be performed at the end of the oral CAB lead-in (if implemented) and at every injection visit. Breakthrough HIV infections were observed in 4 individuals who received on-time CAB LA injections in the HPTN 083 study, and were also observed during the oral CAB lead-in phase and during treatment interruptions [Marzinke(a), et al. 2021]. Adherence to the CAB LA injection schedule is not a guarantee of protection against HIV acquisition.

HIV RNA tests were initially recommended at all injection visits due to the long delay in HIV Ag/Ab conversion while on CAB LA PrEP (98 days for incident infections) [Eshleman, et al. 2022; Marzinke(a), et al. 2021] (see guideline section Managing a Positive HIV Test Result > Ambiguous HIV Test Results > LEVI syndrome). However, when viral load tests were added to HIV Ag/Ab testing at all CAB LA injection visits in the HPTN 083 open-label extension study, there was a 75% rate of false-positive viral load test results, especially after 6 months of CAB LA use [Landovitz(b), et al. 2024]. Therefore, the use of routine viral load monitoring in individuals using CAB LA as PrEP is no longer recommended. In the HPTN 083 and 084 studies, false-positive viral load test results led to interruptions in PrEP use while negative results were confirmed.

**Routine HIV testing with SC LEN:** SC LEN injections are administered by clinic staff every 6 months. HIV Ag/Ab testing should be performed at the initial injection visit and every continuation injection visit. Two breakthrough infections with on-time injections were observed in the PURPOSE 2 study, 1 of which was found at an interim 3-month visit [Kelley, et al. 2025]. Adherence to the SC LEN injection schedule is not a guarantee of protection against HIV acquisition, and it is reasonable to perform interim 3-month HIV testing along with interim STI screenings for individuals at high risk. HIV RNA testing is not necessary after the initial injection visit unless there has been a delay in the injection schedule without oral bridging medication.

**HIV testing if exposure is suspected:** For individuals who present for PrEP initiation but have had a potential HIV exposure within the past 30 days, initial HIV testing may not detect early infection. Therefore, repeat HIV testing 1 month after initiation is recommended to rule out early HIV infection. For individuals who report an interruption in PrEP during a time of sexual activity, an HIV-1/2 Ag/Ab combination immunoassay and HIV RNA test are recommended when reinitiating PrEP.

**HIV testing if acute HIV is suspected:** Vigilance for signs and symptoms of potential HIV seroconversion in individuals using PrEP is crucial. If acute HIV is suspected, the clinician should perform an HIV-1/2 Ag/Ab combination immunoassay and a quantitative HIV RNA test [Chin, et al. 2013; Apoola, et al. 2002]. When testing for acute HIV infection is indicated, any use of a rapid HIV-1/2 Ag/Ab test should be followed with a laboratory-based HIV-1/2 Ag/Ab combination immunoassay. Detection

of HIV RNA or Ag in the absence of serologic evidence of HIV should be considered a preliminary positive result (see guideline section Managing a Positive HIV Test Result).

For more detailed recommendations on testing for acute HIV, see the NYSDOH AI guidelines Diagnosis and Management of Acute HIV Infection and HIV Testing.

**→ KEY POINTS**

- Routine HIV testing is an integral component of safe PrEP use.
- If an individual taking oral PrEP misses a scheduled testing appointment, do not interrupt PrEP. Instead, encourage the continuation of PrEP and work with the individual to reschedule any necessary visits or laboratory testing.
- Frequent screening for HIV infection is performed to prevent the development of drug-resistant virus and protect against HIV transmission if seroconversion has occurred.
- Alternative monitoring models, such as at-home testing and telehealth visits, can decrease barriers to PrEP access and monitoring.

# Routine Laboratory Testing

**Renal function testing:** One sign of tenofovir toxicity is the development of proteinuria and glucosuria. A baseline urinalysis along with serum creatinine levels help identify preexisting abnormalities before PrEP initiation. Periodic renal function monitoring is also important while a patient is taking TDF/FTC or TAF/FTC as PrEP. An elevated creatinine level should prompt an assessment for causes of renal dysfunction other than tenofovir, such as the use of nonsteroidal anti-inflammatory drugs, and an assessment for possible spurious elevation caused by use of creatine supplements.

After initiation of TDF/FTC or TAF/FTC as PrEP in adults younger than 40 years with no evidence of current or ongoing risks for renal dysfunction, creatinine screening can be done every 6 to 12 months. More frequent creatinine screening may be appropriate in individuals older than 40 years because renal toxicity is more likely to occur in this population [Gandhi, et al. 2016]. More frequent screening may also be appropriate for individuals with comorbidities, such as diabetes or hypertension, and those taking concomitant nephrotoxic drugs that might increase the risk of renal dysfunction.

CAB LA and SC LEN are not known to cause renal dysfunction, but caution and increased monitoring for adverse effects is recommended when CrCl is <30 mL/min for CAB LA and <15 mL/min for SC LEN. Baseline testing and annual monitoring of renal function are recommended.

**STI screening:** High baseline STI rates are seen among PrEP users. Starting PrEP offers a valuable entry point for routine STI screening and treatment, especially for asymptomatic infections. Relying solely on symptom-based screening misses many infections. Frequent testing allows early diagnosis and treatment, preventing complications such as neurosyphilis and pelvic inflammatory disease and reducing onward transmission [Tang, et al. 2020; Golub, et al. 2016; Liu, et al. 2016]. Modeling data indicate that wider PrEP use combined with regular STI screening and treatment reduces overall STI incidence even if condom use declines, by identifying and treating asymptomatic infections [Jenness, et al. 2017]. There is currently international debate as to whether the benefits of screening for asymptomatic gonorrhea and chlamydia in cisgender men and transgender women who exclusively have sex with men outweigh the risks, given the lack of significant long-term adverse outcomes from these infections in these populations. Treating asymptomatic gonorrhea and chlamydia have not driven down STI rates as expected, and there is increasing concern about rising antibiotic resistance [Williams, et al. 2023]. However, until there is further evidence and consensus on this subject, this committee continues to endorse routine screening.

**Recommended testing and intervals:** Testing intervals are set to align with visit frequency. See Table 4: Recommended Routine Laboratory Testing for Individuals Using PrEP, above.

Perform syphilis serologic testing routinely. Screen for gonorrhea and chlamydia based on reported sites of exposure, using nucleic acid amplification tests (NAATs) because of their higher sensitivity compared with culture. The FDA has approved diagnostic extragenital gonorrhea and chlamydia tests [FDA 2019], making access to testing more readily available.

For men who have sex with men (MSM) and transgender women, default to 3-site testing (urethral/genital, rectal, and pharyngeal) unless declined, as extragenital infections are common and often missed by urine-only testing [Pitasi, et al. 2019; Patton, et al. 2014]. Studies have reported high rates of extragenital gonococcal and chlamydial infections in transgender men attending STI clinics [Pitasi, et al. 2019]; therefore, risk for extragenital STIs should be considered in this population. Vaginal swabs are preferred for cervical infections because of their higher sensitivity, urine samples are recommended for urethral infections because of comfort. For transgender women with a neovagina, data are lacking regarding optimal

specimen type (neovaginal swab vs. urine-based testing). There are some reports of gonococcal infections detected via testing obtained from the neovagina [van der Sluis, et al. 2015]. Self-collected swabs for vaginal, rectal, and pharyngeal specimen types have performed well in many studies and are preferred by many individuals (see NYSDOH Sexually Transmitted Infection Self-Collection Outside of a Clinic Setting in New York State: Frequently Asked Questions) [Dize, et al. 2016; Lunny, et al. 2015; Workowski and Bolan 2015; Taylor, et al. 2013].

**Doxycycline post-exposure prophylaxis (doxy-PEP):** Clinicians should offer doxy-PEP for STI prevention to cisgender MSM and transgender women who engage in condomless sex with partner(s) assigned male sex at birth, and who have had a bacterial STI diagnosed in the past year, or who have ongoing risk of STI exposure. See the NYSDOH AI guideline Doxycycline Post-Exposure Prophylaxis to Prevent Bacterial Sexually Transmitted Infections for more information. Doxy-PEP was not effective for receptive vaginal sex [Stewart, et al. 2023], but the result may have been due to low adherence. Additional trials are underway to reassess use in this population. Clinicians should engage in shared decision-making with cisgender men who are at ongoing risk of STI exposure and engage in condomless sex with multiple partners assigned female sex at birth, offering doxy-PEP on a case-by-case basis.

**→ KEY POINTS**

- STI testing at close intervals, including extragenital testing for gonorrhea and chlamydia, and prompt treatment of STIs are integral components of PrEP management.
- Offer doxy-PEP to MSM and transgender women with ongoing risk of STI exposure.
- Engage in shared decision-making about doxy-PEP with cisgender men who have sex with individuals assigned female sex at birth.

**Annual HCV screening:** MSM, particularly those living with HIV, are at increased risk for acquiring HCV [Fierer and Factor 2015; Bradshaw, et al. 2013] and data show elevated risk among MSM using PrEP as well [Price, et al. 2019; Hoornenborg(b), et al. 2017]. A case-control study identified risk factors for HCV acquisition in MSM with HIV, including recent ulcerative STIs, condomless receptive anal intercourse, sharing sex toys, unprotected fisting, injection drug use, and sharing straws for intranasal drug use [Vanhommerig, et al. 2015]. These behaviors may also elevate HCV risk in MSM without HIV and in the broader population. Annual HCV screening is recommended for MSM, transgender women who have sex with men, and individuals who inject drugs while using PrEP. More frequent testing should be considered for individuals at highest risk or with abnormal liver function test results.

**Pregnancy screening:** In individuals of childbearing potential using PrEP, routine assessment for the possibility of pregnancy and testing as appropriate can decrease potential concerns associated with unplanned pregnancies. Individuals of childbearing potential who are using PrEP and wish to avoid pregnancy should be offered contraception.

# Managing a Positive HIV Test Result

**☑ RECOMMENDATIONS**

**Suspected Acute HIV**

- For individuals with any symptoms of acute retroviral illness and for whom acute HIV is suspected, clinicians should perform a plasma HIV RNA test in conjunction with a laboratory-based HIV-1/2 Ag/Ab combination immunoassay. (A2)
  - See the NYSDOH AI guidelines HIV Testing and Diagnosis and Management of Acute HIV Infection.
- In the case of a reactive HIV-1/2 Ag/Ab combination immunoassay result and an HIV RNA test result that indicates the virus at any level, a diagnosis of HIV can be made and the clinician should initiate treatment. (A1)
- In the case of a nonreactive HIV-1/2 Ag/Ab combination immunoassay result and an HIV RNA level ≥200 copies/mL, the clinician can make a presumptive diagnosis of acute HIV infection and should proceed with treatment as outlined below. (A3)
- Clinicians should inform individuals with suspected acute HIV about the increased risk of transmitting HIV during acute HIV infection and advise them to refrain from sexual activity or use condoms to minimize transmission risk until acute infection is ruled out. (A2)

**☑ RECOMMENDATIONS**

**Reactive HIV Screening Test Result While Using PrEP**

- Clinicians should assess for dosing interruption of any duration and identify any access or adherence barriers (A3); potential risk exposures since the previous HIV test (A*); and signs and symptoms of acute HIV since the last visit (A2).
- Clinicians should perform supplemental diagnostic testing as soon as possible according to the standard HIV laboratory testing algorithm. (A1)
- If supplemental laboratory testing confirms HIV, the clinician should perform quantitative HIV RNA testing (if not already obtained) to measure viral load, order ART initiation laboratory testing, perform genotypic resistance testing, and initiate ART as outlined below. (A2)

**Ambiguous HIV Test Results**

- Clinicians should consider a reactive HIV-1/2 Ag/Ab combination immunoassay result with a positive HIV-1/2 differentiation and/or a qualitative HIV RNA or a quantitative HIV RNA of any level as a positive HIV test result. (A2)
- In the case of an ambiguous HIV test result (a reactive HIV-1/2 Ag/Ab combination immunoassay result with negative HIV-1/2 differentiation test and a negative HIV RNA test result, or a nonreactive HIV-1/2 Ag/Ab combination immunoassay result and an HIV RNA level <200 copies/mL), the clinician should repeat HIV diagnostic testing to either exclude a false-positive result or identify a true-positive result with a blunted viral response due to the presence of antiretroviral agents used as PrEP. (A3)
- In the case of continued ambiguous HIV test results, the clinician should continue PrEP or intensify to a fully suppressive ART regimen and consult with an experienced HIV and PrEP care provider for guidance on appropriate next steps. (A3) To consult an expert, call the NYSDOH AI CEI Line at 1-866-637-2342.

**ART Selection for a Positive HIV Test Result or When Choosing to Intensify ART for an Ambiguous HIV Test Result**

- For individuals taking TDF/FTC or TAF/FTC as PrEP, clinicians should intensify with DTG or BIC. (A3)
- For individuals receiving SC LEN as PrEP, clinicians should initiate any preferred ART regimen. (A3)
- For individuals receiving CAB LA as PrEP, clinicians should initiate a PI-based ART regimen while awaiting resistance test results. (A2)

**Abbreviations:** Ag/Ab, antigen/antibody; APHL, Association of Public Health Laboratories; ART, antiretroviral therapy; CAB LA, long-acting injectable cabotegravir (Apretude); CDC, Centers for Disease Control and Prevention; CEI, Clinical Education Initiative; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; PrEP, pre-exposure prophylaxis; SC LEN, long-acting injectable lenacapavir (Yeztugo); TAF/FTC, tenofovir alafenamide/emtricitabine (Descovy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (Truvada).

# PrEP Failure

PrEP failure is rare, and HIV acquisition is almost always caused by lack of adherence to oral medication or injection schedules.

**Oral PrEP:** HIV acquisition while taking oral PrEP is related to suboptimal adherence in all but a small number of cases, and in most cases of acquisition while adherent to PrEP there was unrecognized HIV infection at the time of PrEP initiation. Other potential causes include exposure to resistant virus, exposure to an extremely high viral inoculum, or pharmacokinetic variability.

**CAB LA:** PrEP failures with CAB LA are rare. In studies, failure mainly occurs during the optional oral lead-in before the first injection, a missed or late injection, or during the tail phase after treatment discontinuation. In the HPTN 083 study, 6 individuals acquired HIV despite on-time CAB LA injections [Landovitz, et al. 2022; Landovitz, et al. 2021]. In at least 3 of these failures CAB LA was absorbed more quickly and/or levels declined more rapidly than the mean [Marzinke, et al. 2023].

Integrase resistance mutations were found in 5 of 9 participants with a resistance test result in the HPTN 083 study [Marzinke(a), et al. 2021]. There were 4 PrEP failures with CAB LA in the HPTN 084 study, with 1 infection occurring in an individual who received on-time injections; no integrase resistance was found among these participants [Marzinke(b), et al. 2021]. With long-acting injectable medications there is concern about the slow decay in drug levels over time once the medication is stopped and that individuals who acquire HIV during the CAB LA tail phase might develop integrase resistance. It is reassuring that in the HPTN 083 study, none of the individuals who acquired HIV during the tail phase had integrase resistance mutations.

**SC LEN:** The PURPOSE 1 study had no PrEP failures in participants receiving SC LEN [Bekker, et al. 2024]. In the PURPOSE 2 study there were 2 seroconversions with capsid inhibitor resistance despite on-time injections [Kelley, et al. 2025]. The cause of these 2 PrEP failures is unclear and currently under investigation.

## Suspected Acute HIV

Vigilance for signs and symptoms of potential HIV seroconversion in individuals receiving PrEP is crucial. TDF/FTC, TAF/FTC, CAB LA, or SC LEN as PrEP are inadequate treatments for acute or chronic HIV infection, and continued use in individuals with HIV may lead to the emergence of viral resistance to these drugs.

The mean time from HIV exposure to onset of symptoms in acute HIV infection is generally 2 to 4 weeks, with a range of 5 to 29 days; however, some individuals are asymptomatic and some have presented with symptoms up to 3 months after exposure [Apoola, et al. 2002]. This time course may be prolonged in individuals who acquire HIV while using PrEP, and symptoms of acute HIV infection may be blunted by TDF/FTC, TAF/FTC, SC LEN, and, particularly, CAB LA use (see Ambiguous HIV Test Results, below). While evaluating individuals for possible acute HIV infection, advise them to refrain from sexual activity or use condoms to minimize the risk of transmitting HIV to a partner without HIV.

For individuals with symptoms consistent with acute HIV infection who have a nonreactive HIV test result but have a plasma HIV RNA level ≥200 copies/mL, a clinician can make a presumptive diagnosis of acute HIV, perform HIV genotype testing, obtain routine initial HIV laboratory tests, and recommend immediate ART initiation.

For individuals who have a nonreactive HIV test result but have an HIV RNA level <200 copies/mL, clinicians should repeat HIV RNA testing and HIV diagnostic testing according to the standard HIV laboratory testing algorithm to exclude a false-positive test result versus a true-positive test result with a blunted viral response due to the use of antiretroviral drugs. Unless suspicion for acute HIV is low, initiate ART while seeking a definitive diagnosis.

## Confirmed Reactive HIV Screening Test Result

A complete HIV treatment regimen should be initiated immediately upon confirmation of HIV infection while awaiting further test results, including resistance testing.

**Oral PrEP:** Because HIV acquisition in individuals taking oral PrEP is most often due to nonadherence, most HIV infections in these individuals are with wild-type virus (virus without resistance mutations). When resistance does occur, FTC-associated resistance due to the emergence of the M184V/I mutation is the usual finding, and tenofovir-associated resistance with the K65R mutation is rare [Girometti, et al. 2022; Mayer, et al. 2020; Lehman, et al. 2015]. Therefore, in individuals taking oral PrEP who have a positive HIV test result, it is reasonable to initiate a 3-drug INSTI-based ART regimen while awaiting resistance test results.

**Injectable PrEP:** For individuals who have a positive HIV test result while receiving CAB LA as PrEP, a PI-based ART regimen should be initiated while awaiting confirmation of HIV infection and resistance test results. If no INSTI resistance is found, the patient can be switched to an INSTI-based ART regimen if desired. For individuals who have a positive HIV test result while receiving SC LEN as PrEP, an INSTI-based ART regimen should be initiated while awaiting confirmatory test results. For more information, see the NYSDOH AI guidelines Rapid ART Initiation and Selecting an Initial ART Regimen.

## Ambiguous HIV Test Results

Antiretroviral medications used as PrEP can blunt viral load response or cause an undetectable viral load and delay or change the antibody response to an acute infection. Interpreting HIV test results may be complicated by the effect of PrEP on viral and immune markers when the current CDC/APHL testing algorithm is followed [Landovitz(a), et al. 2024; Zucker, et al. 2018; Hoornenborg(a), et al. 2017; Knox, et al. 2017; Markowitz, et al. 2017]. If an HIV test result is indeterminate or ambiguous, a decision must be made as to the likelihood of the result being a false positive or a true positive with an altered timeframe or testing algorithm due to the use of antiretroviral medications as PrEP. Assessing adherence can assist with PrEP management while further testing or expert consultation is pending. Because HIV acquisition is rare in someone who is fully adherent to oral or injectable PrEP, a positive HIV test result is more likely to be a false positive in such an individual. There is an increased possibility of a true-positive test result when an individual reports gaps in adherence or access to oral PrEP medications, a delayed injection visit for injectable PrEP without oral bridging medication, or symptoms consistent with acute HIV since their last HIV test.

**Oral PrEP:** There are no commercially available tests of medication concentrations to confirm longer-term adherence to current oral PrEP regimen. Hair samples and dried blood spots are used in research only. Because false-positive HIV-1/2 Ag/Ab combination immunoassay results occur and there is a risk of HIV exposure if PrEP is discontinued, PrEP should be continued while awaiting confirmation. Clinicians should decide whether to continue PrEP or intensify to a fully suppressive ART regimen (see section above) while awaiting confirmatory test results, based on the degree of suspicion for a false-positive or true-positive HIV test result. Clinicians should perform supplemental diagnostic testing as soon as possible according to the standard HIV laboratory testing algorithm. Multiple tests over time may be needed. See A Strategy for PrEP Clinicians to Manage Ambiguous HIV Test Results During Follow-Up Visits for a thorough review of this topic [Smith, et al. 2018].

**CAB LA:** There were several cases of HIV acquisition during the oral lead-in phase in clinical trials of CAB LA. If an individual has a positive HIV test during or shortly after taking oral CAB, assess for adherence and proceed as described above for oral PrEP. Assessing adherence to the CAB LA injection schedule is straightforward, and a true-positive result is more likely with delayed injections without oral bridging medication; however, there were 6 breakthrough HIV infections with CAB LA despite on-time injections in the HPTN 083 study [Landovitz, et al. 2021]. Interpreting HIV test results can be particularly challenging because of the propensity for CAB LA to affect symptoms and markers of acute HIV infection, leading to long-acting early viral inhibition (LEVI) syndrome.

**LEVI syndrome:** In the HPTN 083 study, a median delay of 98 days (range, 35-185 days) from HIV acquisition to a positive HIV Ag/Ab test result was observed in individuals receiving CAB LA as PrEP [Marzinke(a), et al. 2021]. LEVI syndrome is an altered presentation of acute HIV in individuals using CAB LA as PrEP, is characterized by low or undetectable HIV RNA and diminished or delayed Ab production, and is usually clinically silent [Landovitz(a), et al. 2024]. Because levels of HIV Ag, Ab, RNA, and DNA may be ambiguous and revert from reactive, indeterminate, or positive to nonreactive or negative, confirming HIV infection can be challenging. Confirmatory HIV assay results can remain negative or indeterminate as long as 1 year after HIV diagnosis. Expert consultation is advised to determine the best next steps when someone has an indeterminate HIV test result while using CAB LA as PrEP. Often, repeat testing over time is needed, and a decision should be made on whether to intensify to a fully active ART regimen while awaiting further testing.

**SC LEN:** In the 2 cases of seroconversion in the PURPOSE 2 study, a positive HIV Ag/Ab test result after HIV acquisition did not appear to be delayed [Kelley, et al. 2025].

**Management summary:** In cases of ambiguous HIV test results in individuals using PrEP, repeating HIV testing in a few days may resolve ambiguity if the initial results were due to early infection or technical issues.

If ambiguity persists, continue PrEP, intensify to a full HIV treatment regimen while waiting for additional testing to resolve the ambiguity, or discontinue PrEP and allow viral replication to occur and be measured if the individual does have HIV. However, discontinuing PrEP leaves an individual who does not have HIV at risk, and delaying intensification risks loss of the theoretical virologic and immunologic benefits of early ART in an individual who does have HIV. Given the complexities of this issue, consultation with an experienced HIV care provider is recommended.

**→ KEY POINTS**

- PrEP failure is rare, and HIV acquisition is almost always caused by lack of adherence to oral medication or injection schedules.
- Assessing for signs and symptoms of potential HIV seroconversion in individuals using PrEP is crucial, as PrEP medication is not adequate treatment for acute or chronic HIV infection.
- Empiric HIV treatment should be initiated immediately upon confirmation of HIV infection while awaiting resistance test results.
- PrEP use may alter HIV viral load and immune response and cause ambiguous HIV test results. Consultation with an experienced HIV care provider is recommended when HIV test results are inconclusive.

# Discontinuing PrEP

**☑ RECOMMENDATIONS**

**Discontinuing PrEP**

- Clinicians should discontinue PrEP in any individual with a confirmed positive HIV test result and initiate a fully active HIV regimen (see recommendations in the guideline section Managing a Positive HIV Test Result). (A1)
- Clinicians should discontinue oral PrEP if an individual does not adhere to HIV testing requirements despite repeated efforts at engagement in care. (A3)
- Clinicians should discontinue injectable PrEP if there are repeated episodes of late or missed injections without oral bridging medication despite repeated efforts to engage the individual in care. (A3)
- Clinicians should discontinue TDF/FTC as PrEP in individuals who develop a confirmed calculated CrCl <50 mL/min and discontinue TAF/FTC as PrEP in individuals who develop a confirmed CrCl <30 mL/min (A2); switch to an alternate PrEP regimen in those who wish to continue PrEP. (A3)
- Clinicians should closely monitor individuals with chronic HBV for potential viral rebound when PrEP with TDF/FTC or TAF/FTC is discontinued and develop an alternative treatment plan if necessary. (A2)
- For individuals who decide to discontinue PrEP but have a recent HIV exposure, clinicians should advise them to continue PrEP until 48 hours after last rectal exposure (A2†) and 72 hours after last vaginal receptive exposure (A3).
- Clinicians should educate individuals about the "tail" phase of long-acting injectable PrEP medications and the risk of developing drug resistance after HIV acquisition with use of subtherapeutic levels of antiretroviral medications during this period and should provide individualized guidance on alternative PrEP options and prevention planning if HIV risk continues. (A1)
- Clinicians should advise individuals on how to access PrEP in the future should they want to restart it. (A3)

**Abbreviations:** CAB LA, long-acting injectable cabotegravir (Apretude); CrCl, creatinine clearance; HBV, hepatitis B virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; SC LEN, subcutaneous lenacapavir (Yeztugo); TAF/FTC, tenofovir alafenamide/emtricitabine (Descovy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (Truvada).

The 2-drug PrEP regimens of TDF/FTC and TAF/FTC and the single-drug injectable regimens of CAB LA and SC LEN are inadequate for HIV treatment. If HIV infection is confirmed, PrEP should be converted immediately to a fully suppressive HIV treatment regimen (see guideline section Managing a Positive HIV Test Result).

**Renal dysfunction:** Monitor renal function as outlined in the guideline section Ongoing Laboratory Testing. If an increase in serum creatinine or a decrease in calculated CrCl is observed, evaluate potential causes other than TDF or TAF use, such as the use of nonsteroidal anti-inflammatory drugs (NSAIDs), spurious elevations due to creatine supplementation, or recent heavy exercise leading to muscle breakdown, and repeat testing to confirm the finding before considering discontinuation. TDF/FTC as PrEP should be discontinued in individuals who develop a confirmed CrCl <50 mL/min to avoid further toxicity. In 1 study, a majority of participants with a creatinine clearance of <60 mL/min were able to continue TDF/FTC after repeating laboratory testing, discontinuing oral protein supplements 2 days before laboratory testing, and/or addressing substance and NSAID use, and on-demand dosing did not lead to further deterioration of renal function [Liegeon, et al. 2024].

On-demand TDF/FTC is a potential option for those with borderline renal function who do not have access to or interest in alternative PrEP options. Although TDF/FTC for HIV treatment can be adjusted to every-other-day dosing in individuals with a CrCl between 30 mL/min and 49 mL/min, this strategy has not been established for PrEP and should not be used. TAF/FTC is an option for individuals with CrCl ≥30 mL/min. CAB LA and SC LEN are options for all individuals with renal dysfunction who are at risk for HIV infection. Increased monitoring for adverse effects is recommended for those with severe or end-stage renal impairment.

**Change in risk profile:** Individuals may choose to discontinue PrEP when their risk for HIV acquisition is no longer a concern. If an individual decides to stop using PrEP because of the challenges of adhering to medication and visits but is still at risk for HIV acquisition, make attempts to individualize care to maintain access to the protection afforded by PrEP. Individuals who decide to discontinue PrEP and have a recent HIV exposure should continue PrEP until 48 hours after last rectal exposure and 72 hours after last vaginal receptive exposure, based on data regarding on-demand dosing. For individuals who do not adhere to the testing requirements for the safe prescribing of PrEP, PrEP should be discontinued only after repeated attempts have been made to accommodate specific patient needs and engage the patient in ongoing PrEP care.

**HBV infection:** Because discontinuation of TDF/FTC or TAF/FTC in individuals with chronic HBV infection can exacerbate HBV [Buti, et al. 2015; Dore, et al. 2010; Chamorro, et al. 2005], an alternative treatment plan for these individuals is critical. For more information, see Centers for Disease Control and Prevention Recommendations for Routine Testing and Follow-up for Chronic HBV Infection.

**Managing the pharmacokinetic tail of long-acting injectable drugs:** Long-acting injectable drug levels decline after the last injection. Levels of CAB LA begin to decline 2 months after the last injection and continue for at least 1 year. Levels of SC LEN begin to decline 6 months after the last injection and decline over the next 6 months. During this time there are increasingly lower levels of these drugs as PrEP that will not protect from HIV infection and could potentially place the individual at risk of developing drug-resistant HIV if they were to seroconvert with subtherapeutic plasma levels. Individuals should be educated on the medication "tail" and provided individualized guidance on alternative PrEP options and prevention planning if HIV risk continues.

**Planning for PrEP reinitiation:** Individuals may discontinue PrEP for various reasons, including reduced exposure risk, adverse effects, and access challenges. When possible, clinicians should discuss the process of restarting PrEP at the time of discontinuation. Individuals that were taking oral PrEP may still have a supply of PrEP and it is important that these individuals understand how to restart, time to protection, and PrEP initiation laboratory testing requirements, including HIV testing (see guideline section Initiating PrEP).

**→ KEY POINTS**

- PrEP can be discontinued for individuals no longer at risk of HIV acquisition because they have changed behaviors that put them at risk.
- If renal dysfunction develops while an individual is taking TDF/FTC or TAF/FTC as PrEP, address potentially reversible causes before discontinuing.
- CAB LA and SC LEN are PrEP options for individuals with severe or end-stage renal impairment.
- For an individual at ongoing risk because of nonadherence to protocols, make attempts to engage the patient in ongoing care and accommodate individual needs before discontinuing PrEP.

# Appendix A: Checklists for PrEP Regimen Choice, Assessment and Counseling, Implementation, Initiation, and Follow-Up

## CHECKLIST 1: Key Factors in Choice of PrEP Regimen

| Individual Preferences and Regimen Considerations | | SC LEN | CAB LA | TDF/FTC | TAF/FTC |
|---|---|---|---|---|---|
| Individual's potential risk exposures | Rectal | ✔ | ✔ | ✔ | ✔ |
| | Vaginal | ✔ | ✔ | ✔ | ✔ |
| | Penile | ✔ | ✔ | ✔ | ✔ |
| | Blood | | | ✔ | |
| Individual's preferred administration method | Pill | | | ✔ | ✔ |
| | IM injection | | ✔ | | |
| | SC injection | ✔ | | | |
| Individual's preferred dosing schedule | Daily | | | ✔ | ✔ |
| | Before and after sex, 2-1-1 (rectal or penile exposures) or 2-1-1-1 (vaginal exposure) | | | ✔ | |
| | Bimonthly injections (first 2 are 4 weeks apart) | | ✔ | | |
| | Every 6 months | ✔ | | | |
| Required lab testing schedule | At least every 2 months | | ✔ | | |
| | At least every 3 months | | | ✔ | ✔ |
| | At least every 6 months | ✔ | | | |
| Regimen-specific limitations to consider | Renal dysfunction | ✔ | ✔ | | ✔ |
| | Osteoporosis or risk of | ✔ | ✔ | | ✔ |
| | Chronic HBV infection | | | **Daily only** | ✔ |
| | Generic formulation available | | | ✔ | |
| | Using gluteal fillers (e.g., silicone) | ✔ | | ✔ | ✔ |
| | Pregnant, breast/chestfeeding, or planning pregnancy | ✔ | ✔ | ✔ | ✔ |

**Abbreviations:** CAB LA, long-acting injectable cabotegravir (Apretude); HBV, hepatitis B virus; IM, intramuscular; PrEP, pre-exposure prophylaxis; SC LEN, subcutaneous lenacapavir (Yeztugo); TAF/FTC, tenofovir alafenamide/emtricitabine (Descovy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (Truvada).

## CHECKLIST 2: Assessment and Counseling Before PrEP Initiation

- ✔ Assess the patient's health literacy and ensure that the purpose, benefits, and risks of PrEP are understood.
- ✔ Individualize the decision of which medication to initiate for PrEP by weighing the benefit of reducing the patient's risk of acquiring HIV against the potential adverse effects of the medication as well as the patient's preferences.
- ✔ Make clear that PrEP efficacy is highly dependent on adherence, assess for readiness and willingness to adhere to PrEP and recommended follow-up care, and assess for barriers to adherence.
- ✔ Assess interest in and eligibility for injectable PrEP, including the ability to adhere to visits every 2 months for IM injections or every 6 months for SC injections.
- ✔ Assess for relative contraindications for injectable PrEP, including the presence of gluteal fillers for IM injections and for significant medication interactions with SC LEN.
- ✔ Obtain thorough sexual and drug use histories, identify current risk-taking behaviors, and encourage safer sex practices in addition to PrEP and safer drug injection techniques, if applicable.
- ✔ Ask whether the patient has a sex partner (or partners) with known HIV; if yes, ask if the partner's viral load status is known.
- ✔ Discuss with patients in HIV-serodifferent partnerships the benefits and risks of relying on their partner's undetectable viral load achieved with ART versus adding PrEP to prevent sexual transmission of HIV.
- ✔ Counsel HIV-serodifferent couples who are considering using PrEP during attempts to conceive about the utility, safety, and possible risks of the medication and other approaches to safer conception.
- ✔ Perform a psychosocial assessment and refer for appropriate social and psychological support services, as indicated, to minimize HIV risk and support maintenance in care.
- ✔ Partner with other care providers as needed to provide services that may include mental health and substance use treatment, case management, navigation and linkage services, housing assistance, and income/benefits assessments.

**Resources:**

- Tufts Medicine Health Literacy Tool Shed (funded by the National Library of Medicine)
- AHRQ Short Assessment of Health Literacy–Spanish and English
- AHRQ Rapid Estimate of Adult Literacy in Medicine–Short Form
- AHRQ Short Assessment of Health Literacy for Spanish Adults
- NYSDOH AI GOALS Framework for Sexual History Taking in Primary Care and Substance Use Harm Reduction in Medical Care
- NYSDOH Expanded Syringe Access Program (ESAP): Overview of the Law and Regulations and Directory of New York State Syringe Exchange Programs)

**Abbreviations:** AHRQ, Agency for Healthcare Research and Quality; ART, antiretroviral therapy; PrEP, pre-exposure prophylaxis; SC LEN, subcutaneous lenacapavir.

## CHECKLIST 3: Implementation Strategies for Long-Acting Injectable PrEP Regimens

### Institutional and clinician preparations:

- ✔ Assess pharmacy resources and on-site procedures for storage of oral and injectable medications.
- ✔ Develop procedures for obtaining prior authorizations for insurance and third-party coverage.
- ✔ Train medical care providers on the protocols for CAB LA and SC LEN use and monitoring.
- ✔ Train nurses and other medical care providers regarding proper syringe preparation and injection techniques.
- ✔ Establish billing protocols for the procurement and administration of injectable PrEP.
- ✔ Implement an appointment-reminder system and make call-backs after missed doses.
- ✔ Plan for treatment continuation during shutdowns or other catastrophic events.
- ✔ Educate about the use of oral bridging therapy when appropriate.
- ✔ Educate about possible adverse effects of CAB LA and SC LEN and how to manage them.
- ✔ Ensure that individuals know how to reach the care team if needed.
- ✔ Schedule follow-up appointments for administration in advance.

### PrEP recipient preparations:

- ✔ Confirm the ability to maintain required clinic visit schedule for injections, including transportation availability.
- ✔ Advise on the importance of communicating with the team regarding any insurance and coverage changes.

**Abbreviations:** CAB LA, long-acting injectable cabotegravir; PrEP, pre-exposure prophylaxis; SC LEN, subcutaneous lenacapavir.

## CHECKLIST 4: PrEP Initiation

| | |
|---|---|
| Confirm PrEP eligibility | • Discuss HIV risk, including self-reported risk and history of potential exposure, and assess for signs and symptoms of acute HIV infection.<br>• If exposure occurred within ≤72 hours, recommend and initiate PEP before PrEP. |
| Obtain medical history | • Assess for contraindications or factors that may affect PrEP choice: HIV infection, HBV infection, kidney impairment, osteoporosis, potential drug-drug interactions, current or planned pregnancy. |
| Order baseline lab testing and arrange for specimen collection | • HIV 1/2 Ag/Ab combination immunoassay (for same-day initiation, perform rapid and lab-based HIV test; ensure lab results available within 1 week of PrEP start)<br>• HIV RNA assay<br>• Serum creatinine and calculated CrCl<br>• Serum liver enzymes<br>• HBV and HCV serologies<br>• HAV serology (MSM and if at risk)<br>• Urinalysis<br>• Syphilis testing<br>• Gonorrhea and chlamydia NAATs (all potential exposure sites)<br>• Pregnancy test (if of child-bearing capacity) |
| Review PrEP options and assist individual in making informed choice | • Explain purpose, benefits, potential risks (including possible adverse effects), and time to protection.<br>• Discuss available options, including factors that may influence regimen choice.<br>• If CAB LA is chosen, decide whether to use the oral medication lead-in.<br>• If on-demand oral PrEP is chosen, ensure understanding of 2-1-1 or 2-1-1-1 dosing. |
| Provide education | • Explain symptoms of acute HIV infection and recommended response, including who to contact and how.<br>• Outline adherence requirements: dosing, lab testing, visit schedule.<br>• Discuss strategies to address modifiable barriers to access and adherence.<br>• Explain possible adverse effects, suggestions for management, and when and how to request assistance. |
| Counsel on harm reduction | • Discuss STI prevention and access to contraceptives and needle exchange.<br>• Offer doxy-PEP to individuals at risk of bacterial STIs.<br>• Link to support services as needed. |
| Arrange for follow-up | • Obtain and document contact information for remote follow-up (phone, text, email).<br>• Review potential adverse effects and how to manage, including when and how to contact a care provider.<br>• Schedule follow-up appointments, including injection appointments. |

**Abbreviations:** Ag/Ab, antigen/antibody; CAB LA, long-acting injectable cabotegravir; CrCl, creatinine clearance; doxy-PEP, doxycycline post-exposure prophylaxis; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; MSM, men who have sex with men; NAAT, nucleic acid amplification test; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

## CHECKLIST 5: PrEP Follow-up

| | | |
|---|---|---|
| **Injectable PrEP: CAB LA** | If HIV infection is diagnosed | · Contact individual immediately to recommend HIV treatment.<br>· Obtain baseline lab testing, including genotype testing.<br>· Immediately initiate a PI-based ART regimen. |
| | 2 weeks after starting oral CAB lead-in (if used) | · Contact individual to address problems with acquiring or taking medication; assess adherence, tolerance, and adverse effects; and confirm first injection date. |
| | Within 1 week of first injection | · Contact individual to assess tolerability and advise on adverse effect management if needed.<br>· Confirm next injection date. |
| | Every injection visit | · Repeat HIV testing with HIV-1/2 Ag/Ab combination immunoassay.<br>· Ask about STI symptoms.<br>· Offer contraception to individuals of childbearing potential who wish to avoid pregnancy while using PrEP. |
| | STI testing every 2-6 months regardless of symptoms | · Base testing frequency on reported risk.<br>· Perform syphilis screening and NAATs for gonococcal and chlamydial infections at all exposure sites.<br>· For all MSM and transgender women, routine 3-site testing should be performed regardless of symptoms or sites of reported exposure, unless declined. Self-collected specimens are acceptable. |
| | At least annually | · Obtain serum creatinine and calculated CrCl. |
| | If injection is missed | · If delays are anticipated, arrange for oral bridging medication.<br>· If indicated, adjust schedule for next injection. |
| | If PrEP is discontinued | · If risk is ongoing, recommend oral PrEP be started 2 months after the last injection and continued for ≥1 year to prevent acquisition of INSTI-resistant HIV, and provide risk-reduction counseling and information on accessing emergency PEP.<br>· Discuss option of restarting PrEP in the future. |
| **Injectable PrEP: SC LEN** | If HIV infection is diagnosed | · Contact individual immediately to recommend HIV treatment.<br>· Obtain baseline lab testing, including genotype testing.<br>· Immediately initiate an INSTI-based ART regimen. |
| | Within 1 week of first injection | · Contact individual to assess tolerability and advise on adverse effect management if needed.<br>· Confirm next injection date. |
| | Every injection visit | · Repeat HIV testing with HIV-1/2 Ag/Ab combination immunoassay.<br>· Ask about STI symptoms.<br>· Offer contraception to individuals of childbearing potential who wish to avoid pregnancy while using PrEP. |
| | STI testing every 3-6 months regardless of symptoms | · Base testing frequency on reported risk.<br>· Perform syphilis screening and NAATs for gonococcal and chlamydial infections at all exposure sites.<br>· For all MSM and transgender women, routine 3-site testing should be performed regardless of symptoms or sites of reported exposure, unless declined. Self-collected specimens are acceptable. |
| | At least annually | · Obtain serum creatinine and calculated CrCl. |
| | If injection is missed | · If delays are anticipated, arrange for oral bridging medication.<br>· If indicated, adjust schedule for next injection. |
| | If PrEP is discontinued | · If risk is ongoing, recommend oral PrEP be started 6 months after last injection and continued for another 6 months to prevent acquisition of capsid inhibitor-resistant HIV, and provide risk-reduction counseling and information on accessing emergency PEP.<br>· Discuss option of restarting PrEP in the future. |
| **Oral PrEP: TDF/FTC or TAF/FTC** | If HIV infection is diagnosed | · Order baseline lab testing, including genotype testing.<br>· Intensify PrEP regimen to fully suppressive ART or refer individual to an experienced HIV care provider. |
| | Within 2 weeks of initiation | · Contact individual to address problems with acquiring or taking PrEP medications, assess tolerance and adherence, advise on adverse effect management, and confirm next visit. |
| | 1 month after initiation | · Repeat lab HIV testing if exposure occurred ≤1 month before PrEP initiation.<br>· Ask about adherence, symptoms of acute HIV (repeat HIV testing if reported), STI symptoms (ask at every visit), harm reduction, and pregnancy status (test if indicated or requested). Offer contraception to individuals of childbearing potential who wish to avoid pregnancy while using PrEP.<br>· Arrange for lab testing at month 3: HIV-1/2 Ag/Ab combination immunoassay; syphilis screening and NAATs for gonococcal and chlamydial infections at all exposure sites; and pregnancy testing if indicated or requested (every visit). |
| | 3 months after initiation (and every 6-12 months thereafter) | · Obtain serum creatinine and calculated CrCl. |
| | Every 3 months regardless of symptoms | · Assess adherence.<br>· Ask about symptoms and test for STIs (can decrease frequency based on risk).<br>· For all MSM and transgender women, routine 3-site testing for gonorrhea and chlamydia should be performed regardless of sites of reported exposure, unless declined. Self-collected specimens are acceptable.<br>· Arrange for next lab testing.<br>· Perform pregnancy testing if indicated or requested (every visit). |
| | At least annually | · Obtain urinalysis and HCV serology for those at risk. |
| | If PrEP is interrupted | · Order lab-based HIV testing (HIV-1/2 Ag/Ab combination immunoassay and HIV RNA PCR) whenever individual reports PrEP interruption of >1 week within the past month and possible HIV exposure or reports missing PrEP doses during a time of sexual activity and possible HIV exposure. |
| | If PrEP is discontinued | · If risk is ongoing, provide risk-reduction counseling and information on accessing emergency PEP.<br>· Discuss option of restarting PrEP in the future. |

**Abbreviations:** Ag/Ab, antigen/antibody; ART, antiretroviral therapy; CAB, oral cabotegravir (Vocabria); CAB LA, long-acting injectable cabotegravir (Apretude); CrCl, creatinine clearance; HCV, hepatitis C virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NAAT, nucleic acid amplification test; PI, protease inhibitor; PCR, polymerase chain reaction; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide/emtricitabine (Descovy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (Truvada).

# Appendix B: Studies That Support the Use of PrEP in Different Populations

**Men who have sex with men (MSM):**

- Studies have demonstrated that tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) as pre-exposure prophylaxis (PrEP) is highly effective in MSM [Mayer, et al. 2020; McCormack, et al. 2016; Molina, et al. 2015; Grant, et al. 2014; Grant, et al. 2010].
- Although initial data from the iPrEx study demonstrated only a 44% reduction in the rate of HIV acquisition, there was a 92% reduction in sexual HIV transmission when tenofovir was detectable in the blood, and no seroconversions occurred in individuals with therapeutic plasma concentrations of TDF/FTC [Grant, et al. 2010]. Additionally, based on intracellular concentrations of tenofovir diphosphate, HIV risk-reduction was estimated to be 99% with 7 doses per week, and there were no seroconversions in individuals who took 4 or more doses per week [Anderson, et al. 2012].
- In the PROUD study, TDF/FTC as PrEP had an overall efficacy rate of 86%, and there were no HIV infections in participants who took TDF/FTC as prescribed [McCormack, et al. 2016].
- In the IPERGAY and the PREVENIR studies, on-demand or 2-1-1 dosing of TDF/FTC as PrEP was shown to be effective in cisgender men [Molina, et al. 2022; Molina, et al. 2015].
- The DISCOVER study showed use of both TDF/FTC and tenofovir alafenamide (TAF)/FTC as PrEP to be highly effective in reducing the risk of HIV acquisition in MSM, with a combined total of 22 participants with new HIV infections in 8,756 person-years of follow-up; all except 2 were either infected at baseline or had low tenofovir plasma concentrations at the time of infection [Mayer, et al. 2020].
- In the HPTN 083 study, both TDF/FTC and long-acting injectable cabotegravir (CAB LA) prevented HIV in MSM and transgender women; however, CAB LA was statistically superior, with 14 incident infections among participants receiving CAB LA, compared with 41 incident infections among participants taking TDF/FTC during the blinded phase of the study, mostly driven by poor adherence to TDF/FTC [Landovitz, et al. 2022; Landovitz, et al. 2021].
- In the PURPOSE 2 trial, subcutaneous lenacapavir (SC LEN) was highly effective in preventing HIV in cisgender MSM, transgender women, transgender men, and nonbinary individuals; HIV acquisition was 0.10 per 100 person-years in the SC LEN group and 0.93 per 100 person-years in the TDF/FTC group, and HIV incidence with SC LEN was 96% lower than background (background HIV incidence was 2.37 per 100 person-years) [Kelley, et al. 2025].

**Transgender women:**

- In the iPrEx study, TDF/FTC as PrEP was effective in transgender women who adhered to the regimen. [Deutsch, et al. 2015].
- Multiple studies have shown that TDF/FTC does not alter estrogen levels [Senneker 2024; Yager, et al. 2022; Grant, et al. 2021; Hiransuthikul, et al. 2019; Shieh, et al. 2019].
- Small studies have raised the possibility that estrogen lowers tenofovir levels by approximately 12% in the plasma of transgender women compared with cisgender men, or lowers levels of active metabolite in rectal tissues [Cottrell, et al. 2019; Shieh, et al. 2019]. However, in several subsequent studies, including the iBrEATHe and ImPrEPT studies, there were no significant interactions between hormone therapy and TDF/FTC [Blumenthal, et al. 2022; Grant, et al. 2021].
- The PREVENIR and IPERGAY studies of on-demand PrEP with TDF/FTC included too few transgender women who have sex with men to prove effectiveness in this population [Molina, et al. 2022; Molina, et al. 2015]. However, the lack of drug interactions with gender affirming hormone therapy supports the use of on-demand PrEP in transgender women (see guideline section Preferred Oral Regimen for Daily or On-Demand Dosing: TDF/FTC).
- TAF/FTC was effective as PrEP in transgender women in the DISCOVER study, although transgender women made up only 1% of the study population [Mayer, et al. 2020].
- Studies show that TAF does not alter estrogen levels and estrogen does not alter TAF levels [Hiransuthikul, et al. 2025; Patel, et al. 2024].
- In the HPTN 083 study of CAB LA as PrEP, transgender women made up 12.5% of the study population and CAB LA was effective across all subpopulations [Landovitz, et al. 2021]. Additionally, oral CAB pharmacokinetics were not significantly altered by low-dose hormones used for oral contraceptives in the HPTN 077 study, and CAB LA does not alter estrogen levels [Blair, et al. 2020].
- The PURPOSE 2 study showed SC LEN as PrEP to be highly effective and included a significant number of transgender women [Kelley, et al. 2025].

**Transgender men:**

- Clinical trial data are lacking regarding the efficacy of TDF/FTC, TAF/FTC, and CAB LA as PrEP for transgender men who have sex with either cisgender men or transgender women, despite the increased risk of HIV acquisition in this population [Pitasi, et al. 2019; Scheim, et al. 2017].
- TDF/FTC as PrEP is effective for all sexual exposures, including insertive vaginal sex and receptive anal sex, and is expected to be effective in transgender men.
- There was an 89% reduction in HIV risk among cisgender women who had at least 2 doses of TAF/FTC per week in the PURPOSE 1 trial; therefore, TAF/FTC is expected to be effective in transgender men [Kiweewa, et al. 2025].
- In the iBrEATHe study, TDF/FTC did not lower testosterone levels in transgender men compared with controls, and testosterone did not lower tenofovir levels in transgender men compared with cisgender men [Grant, et al. 2021].
- There are no relevant interactions between CAB and testosterone and no specific reason to suspect that CAB LA as HIV PrEP will be less effective for vaginal or anal exposures in transgender men [FDA(c) 2025].
- The PURPOSE 2 study, which showed SC LEN to be highly effective in preventing HIV infection, was the first to intentionally include transgender men and gender-nonbinary individuals in their protocol [Kelley, et al. 2025].

**Cisgender men and women:**

- Studies have demonstrated that TDF/FTC as PrEP is effective for cisgender men and women [Baeten, et al. 2012; Thigpen, et al. 2012].
- In the Partners PrEP study of TDF/FTC, there was a 67% overall reduction in HIV acquisition in cisgender men and women and a 90% reduction among participants with detectable tenofovir in their blood [Baeten, et al. 2012].
- In the TDF2 study, there was a 62% overall reduction in HIV acquisition, but there were only 2 seroconversions in participants who had detectable drug levels [Thigpen, et al. 2012].
- The FEM-PrEP and VOICE trials did not demonstrate a benefit of TDF/FTC as PrEP for cisgender women; however, subsequent analyses found that this was due to poor adherence [Van Damme, et al. 2012].
- TAF/FTC as PrEP was studied in cisgender adolescent and adult women as part of the PURPOSE 1 trial [Bekker, et al. 2024]. The incidence of new HIV infections among participants taking TAF/FTC or TDF/FTC were not different from background HIV rates, but adherence to both PrEP regimens was low. Participants with medium (4-6 doses per week) or high (7 doses per week) adherence to TAF/FTC had significantly lower odds of acquiring HIV infection than those with low adherence (odds ratio, 0.11).
- Cisgender women who took at least 2 doses of TAF/FTC per week in the PURPOSE 1 trial had an 89% reduction in HIV risk [Kiweewa, et al. 2025], supporting the use of TAF/FTC in this population. In the same trial, SC LEN was 100% effective in preventing HIV infection.
- CAB LA was statistically superior to TDF/FTC as PrEP in the HPTN 084 study among cisgender women, in which there were 34 incident infections in the TDF/FTC arm but only 4 incident infections in the CAB LA arm, a difference driven by lower adherence to oral medication [Delany-Moretlwe, et al. 2022].

**HIV-serodifferent couples:**

- Data from the HPTN 052 study demonstrated a reduction of 93% in HIV transmission risk in HIV-serodifferent heterosexual couples when the partner with HIV was on early versus delayed ART, and there were no phylogenetically linked transmissions at 5-year follow-up when partners were stably suppressed [Cohen, et al. 2016].
- In the Partner [Rodger, et al. 2016], Partner 2 [Rodger, et al. 2019], and Opposites Attract [Bavinton, et al. 2018] studies, there were no sexual transmissions between HIV-serodifferent partners when the partner with HIV had an undetectable viral load.

**People who inject drugs:**

- The Bangkok Tenofovir Study is the only randomized controlled trial of PrEP in people who inject drugs [Choopanya, et al. 2013]. PrEP efficacy with TDF alone, in this study, was 49%, although restricting analysis to participants with detectable TDF levels in their blood increased efficacy to 74%.
- The PURPOSE 4 trial is currently evaluating SC LEN for use in people who inject drugs.
- Given the pharmacokinetic levels of PrEP medications in peripheral blood mononuclear cell (PBMCs), it is reasonable to assume that all current PrEP options would be appropriate for use in people who inject drugs, excluding on-demand dosing.

**Adolescents:**

- Studies have shown the potential for PrEP to be highly effective at reducing HIV incidence among adolescent MSM, directly through use by adolescents and indirectly by reducing HIV prevalence among their sex partners [Hamilton, et al. 2019; Goodreau, et al. 2018]. All current PrEP options have been approved by the U.S. Food and Drug Administration (FDA) for use in adolescents aged 12 and older who weigh at least 35 kg.
- **Oral PrEP:**
  - In May 2018, the FDA approved TDF/FTC as PrEP for adolescents weighing ≥35 kg [FDA 2018]. TDF/FTC as PrEP was safe and effective in adolescents, with no renal events or bone fractures noted [Hosek, et al. 2017]. However, there has been concern about the long-term consequences of TDF/FTC use in younger individuals who have not achieved peak bone mass. Further analysis of the ATN 110 and ATN 113 trials in adolescents during the extension phase showed that the bone loss experienced in participants aged 15 to 19 years did not recover and remained below baseline, unlike that in participants aged 20 to 22 years [Havens, et al. 2020].
  - TAF/FTC is FDA-approved as PrEP for cisgender male and transgender female adults and adolescents weighing ≥35kg [FDA(b) 2025]. Given the potential for irreversible bone loss with TDF/FTC as PrEP, it is reasonable to consider TAF/FTC as a preferred agent in adolescents aged 19 years and younger.
- **CAB LA:** In December 2021, CAB LA was approved by the FDA for use in adolescents ≥12 years old weighing ≥35 kg based on the inclusion of this population in the HPTN 083 and 084 trials [FDA(a) 2025; Delany-Moretlwe, et al. 2022; FDA 2021; Landovitz, et al. 2021].
- **SC LEN:** Both the PURPOSE 1 and PURPOSE 2 trials of SC LEN as PrEP included adolescents aged 16 years and older [Kelley, et al. 2025; Bekker, et al. 2024]. The FDA approved SC LEN in June 2025 for use as PrEP in adolescents weighing ≥35 kg [FDA(d) 2025].

# All Recommendations

## ☑ ALL RECOMMENDATIONS: PrEP TO PREVENT HIV AND PROMOTE SEXUAL HEALTH

**PrEP Candidates**

- Clinicians should assess all individuals for HIV risk as a routine part of primary care. (A3)
- Clinicians should recommend PrEP for individuals, including adolescents, who do not have but are at risk of acquiring HIV. (A1)
- Clinicians should prescribe PrEP for any individual who self-identifies as being at risk of acquiring HIV. (A*)
- For individuals who are completing a course of nPEP and remain at risk of acquiring HIV, clinicians should recommend PrEP be initiated immediately upon completion of nPEP. (A3)

**Contraindications to PrEP**

- Clinicians should not prescribe oral or injectable PrEP for any patient with a documented HIV diagnosis; none of the available PrEP regimens are adequate for HIV treatment. (A1)
- Clinicians should recommend individuals with confirmed HIV immediately initiate a fully suppressive ART regimen. (A1)
- Clinicians should not initiate TDF/FTC as PrEP for any individual with a confirmed CrCl <60 mL/min and should discontinue it in patients with a confirmed CrCl <50 mL/min; in such cases, TDF/FTC as PrEP is contraindicated. (A1)
- Clinicians should not prescribe TAF/FTC as PrEP for any individual with a confirmed CrCl <30 mL/min; in such cases, TAF/FTC as PrEP is contraindicated. (A1)

**Choice of Regimen**

- Clinicians should engage in shared decision-making with PrEP candidates to identify an optimal and safe regimen and dosing strategy based on patient preference, clinical considerations, and individual patient factors. (A3)

**TDF/FTC**

- In the absence of contraindications, clinicians should recommend TDF/FTC as the preferred oral PrEP regimen for adults and adolescents aged 19 years or older who are at risk of acquiring HIV through rectal and genital sexual or injection drug use exposures. (A1)

**TAF/FTC**

- Clinicians should recommend TAF/FTC as the preferred oral PrEP regimen for sexual exposures in adults who have preexisting renal disease or osteoporosis. (A1)
  - TAF/FTC is an alternative oral PrEP regimen if TDF/FTC is not tolerated or desired. (A3)
- Clinicians should recommend TAF/FTC as a preferred PrEP regimen for individuals aged 19 years or younger, given the potential for irreversible bone loss in this age group. (A2)

**Patients With HBV**

- Clinicians should recommend daily TDF/FTC or TAF/FTC as the preferred PrEP regimen for patients who require HBV treatment. (A2†)
- Clinicians should closely monitor patients with chronic HBV for potential viral rebound when PrEP with TDF/FTC or TAF/FTC is discontinued and develop an alternative treatment plan if necessary. (A2)

**CAB LA**

- Clinicians should recommend CAB LA as a preferred PrEP regimen for protection against HIV through sexual exposure for individuals who are willing to receive regular IM injections and have no contraindications or barriers to its use. (A1)
- An oral CAB lead-in is optional before initiation of CAB LA injections; if challenges adhering to daily oral medication have been identified, clinicians should engage patients in shared decision-making to weigh the risk of HIV acquisition against the benefit of an oral CAB lead-in. (A3)
- Clinicians should administer CAB LA as indicated in Box 2: Preparation and Administration of Long-Acting Injectable Cabotegravir as Pre-Exposure Prophylaxis. (A1)
- If a patient at ongoing risk of HIV acquisition discontinues CAB LA, the clinician should recommend an alternative PrEP regimen be started 2 months after the last injection and continued for at least 1 year to prevent potential acquisition of INSTI-resistant HIV. (A3)
- Clinicians should discuss potential risks and benefits and engage individuals who are or may become pregnant in shared decision-making when considering CAB LA as PrEP. (A3)

## ☑ ALL RECOMMENDATIONS: PrEP TO PREVENT HIV AND PROMOTE SEXUAL HEALTH

**SC LEN**

- Clinicians should recommend SC LEN as a preferred PrEP regimen for protection against HIV through sexual exposure for individuals who are willing to receive subcutaneous injections every 6 months and have no contraindications or barriers to its use. (A1)
- Clinicians should administer SC LEN as indicated in Box 3: Dosing, Preparation, and Administration of Subcutaneous Lenacapavir as Pre-Exposure Prophylaxis. (A1)
- If a patient at ongoing risk of HIV acquisition discontinues SC LEN, the clinician should recommend an alternative PrEP regimen be started 6 months after the last injection and continued for 6 months to prevent potential acquisition of capsid inhibitor–resistant HIV.
- Clinicians should discuss potential risks and benefits and engage individuals who are or may become pregnant in shared decision-making when considering SC LEN as PrEP. (A3)

**Preinitiation Assessment**

- Before prescribing PrEP, clinicians should assess all candidates for:
  - Symptoms or signs of acute HIV, including febrile, flu-like, or mono-like illness in the previous 6 weeks (A3)
  - Risk encounters within the previous 72 hours that require PEP before PrEP (A3)
  - Reproductive plans (A3)
  - Potential drug-drug interactions or increased risk of nephrotoxicity with concomitant medications (A3)

**Baseline Laboratory Testing**

- Clinicians should perform baseline laboratory testing as recommended in Table 3: Recommended Laboratory Tests for All Individuals Within 1 Week Before Initiating PrEP.

**Same-Day Initiation**

- Clinicians should recommend same-day PrEP initiation while laboratory results are pending in candidates for whom there are no signs or symptoms of acute HIV infection, no history of renal disease, and no concern for HIV exposure in the previous 72 hours requiring PEP. (A2)
- For same-day initiation of PrEP, clinicians should obtain a rapid HIV test and order a laboratory-based HIV-1/2 Ag/Ab combination immunoassay and an HIV RNA test for all candidates unless there are laboratory-based HIV test results in the past 7 days (A3) and ensure that HIV test results are available and acted upon within 7 days of initiation. (A3)
  - See the NYSDOH AI guideline HIV Testing.
- If a patient has a positive baseline HIV test result after oral PrEP initiation, the clinician should intensify the PrEP regimen to fully suppressive ART and refer the patient to an experienced HIV care provider for ongoing care. (A3)
- If a long-acting injectable PrEP regimen is chosen but same-day initiation is not possible, the clinician should initiate oral PrEP until injectable PrEP is available unless the individual declines. (A3)
- If same-day initiation is not possible, clinicians should repeat laboratory-based HIV-1/2 Ag/Ab and HIV RNA testing if more than 1 week has lapsed since HIV testing was performed (A3) and ensure that HIV test results are available and acted upon within 7 days of initiation. (A3)
- If an individual has been exposed to HIV within the previous 72 hours, the clinician should recommend PEP before PrEP. (A1)

**Initiating PrEP During the HIV Testing Window Following Exposure**

- Clinicians should not wait to initiate PrEP in individuals who have had a potential exposure to HIV and are no longer eligible for PEP (>72 hours) but are still in the window period for seroconversion when an HIV test cannot detect infection; doing so risks additional exposures and significant delays in PrEP. (A*)
- Clinicians should repeat HIV testing 1 month after PrEP initiation in individuals who report a risk exposure in the 30 days before PrEP initiation. (A2†)
- If a patient has a positive HIV test result after receiving the first CAB LA injection, the clinician should consult with an experienced HIV care provider to identify the best strategy for ART intensification. (A3) To consult an expert, call the NYSDOH AI CEI Line at 1-866-637-2342.
- If a patient has a positive HIV test result after receiving the first dose of SC LEN, clinicians should initiate any preferred ART regimen, or alternative ART regimen based on individual patient need, and refer the patient to an experienced HIV care provider for ongoing care. (A3)

**Ongoing Laboratory Testing**

- Clinicians should perform ongoing laboratory testing as recommended in Table 4: Recommended Routine Laboratory Testing for Individuals Using PrEP.

## ☑ ALL RECOMMENDATIONS: PrEP TO PREVENT HIV AND PROMOTE SEXUAL HEALTH

**HIV Testing**

- For any individual who reports an HIV exposure that occurred in the 30 days before PrEP initiation, clinicians should repeat HIV testing 30 days after initiation. (A2†)
- Clinicians should perform an FDA-approved plasma or serum HIV-1/2 Ag/Ab combination immunoassay every 3 months in individuals taking oral PrEP. (A3)
- Clinicians should perform an FDA-approved plasma or serum HIV-1/2 Ag/Ab combination immunoassay at each injection visit for patients receiving SC LEN or CAB LA as PrEP. (A3)
- Clinicians should perform an HIV-1/2 Ag/Ab combination immunoassay and HIV RNA test in individuals who present with or report symptoms or signs of acute HIV infection. (A2)
- Clinicians should perform an HIV-1/2 Ag/Ab combination immunoassay and HIV RNA test in individuals who report inconsistent adherence to or an interruption of oral PrEP of more than 1 week or delays in injectable PrEP administration (without oral bridging) during times of sexual activity and possible HIV exposure. (A3)

**Renal Function Testing**

- Clinicians should discontinue daily TDF/FTC as PrEP if an individual develops a confirmed CrCl <50 mL/min and consider alternative options. (A3)
- Clinicians should discontinue TAF/FTC as PrEP if an individual develops a confirmed calculated CrCl <30 mL/min. (A3)
- Clinicians should perform urinalysis at baseline and annually to assess urine glucose and protein in individuals taking TDF/FTC or TAF/FTC as PrEP. (B3)

**STI Screening**

- At every visit, a care team member should assess individuals for signs and symptoms of STIs, including syphilis and gonococcal and chlamydial infections, as part of a sexual history, perform testing as indicated, and treat STIs empirically based on symptoms while test results are pending. (A2†)
- Clinicians should perform routine STI screening as recommended in Table 4: Recommended Routine Laboratory Testing for Individuals Using PrEP.

**HCV Screening**

- Clinicians should perform HCV testing at least annually for at-risk individuals. (A3)

**Pregnancy Screening**

- At every visit, clinicians should assess the possibility of pregnancy in individuals of childbearing potential. (A3)

**Suspected Acute HIV**

- For individuals with any symptoms of acute retroviral illness and for whom acute HIV is suspected, clinicians should perform a plasma HIV RNA test in conjunction with a laboratory-based HIV-1/2 Ag/Ab combination immunoassay. (A2)
  - See the NYSDOH AI guidelines HIV Testing and Diagnosis and Management of Acute HIV Infection.
- In the case of a reactive HIV-1/2 Ag/Ab combination immunoassay result and an HIV RNA test result that indicates the virus at any level, a diagnosis of HIV can be made and the clinician should initiate treatment. (A1)
- In the case of a nonreactive HIV-1/2 Ag/Ab combination immunoassay result and an HIV RNA level ≥200 copies/mL, the clinician can make a presumptive diagnosis of acute HIV infection and should proceed with treatment as outlined below. (A3)
- Clinicians should inform individuals with suspected acute HIV about the increased risk of transmitting HIV during acute HIV infection and advise them to refrain from sexual activity or use condoms to minimize transmission risk until acute infection is ruled out. (A2)

**Reactive HIV Screening Test Result While Using PrEP**

- Clinicians should assess for dosing interruption of any duration and identify any access or adherence barriers (A3); potential risk exposures since the previous HIV test (A*); and signs and symptoms of acute HIV since the last visit (A2).
- Clinicians should perform supplemental diagnostic testing as soon as possible according to the standard HIV laboratory testing algorithm. (A1)
- If supplemental laboratory testing confirms HIV, the clinician should perform quantitative HIV RNA testing (if not already obtained) to measure viral load, order ART initiation laboratory testing, perform genotypic resistance testing, and initiate ART as outlined below. (A2)

**Ambiguous HIV Test Results**

- Clinicians should consider a reactive HIV-1/2 Ag/Ab combination immunoassay result with a positive HIV-1/2 differentiation and/or a qualitative HIV RNA or a quantitative HIV RNA of any level as a positive HIV test result. (A2)

**☑ ALL RECOMMENDATIONS: PrEP TO PREVENT HIV AND PROMOTE SEXUAL HEALTH**

- In the case of an ambiguous HIV test result (a reactive HIV-1/2 Ag/Ab combination immunoassay result with negative HIV-1/2 differentiation test and a negative HIV RNA test result, or a nonreactive HIV-1/2 Ag/Ab combination immunoassay result and an HIV RNA level <200 copies/mL), the clinician should repeat HIV diagnostic testing to either exclude a false-positive result or identify a true-positive result with a blunted viral response due to the presence of antiretroviral agents used as PrEP. (A3)
- In the case of continued ambiguous HIV test results, the clinician should continue PrEP or intensify to a fully suppressive ART regimen and consult with an experienced HIV and PrEP care provider for guidance on appropriate next steps. (A3) To consult an expert, call the NYSDOH AI CEI Line at 1-866-637-2342.

**ART Selection for a Positive HIV Test Result or When Choosing to Intensify ART for an Ambiguous HIV Test Result**

- For individuals taking TDF/FTC or TAF/FTC as PrEP, clinicians should intensify with DTG or BIC. (A3)
- For individuals receiving SC LEN as PrEP, clinicians should initiate any preferred ART regimen. (A3)
- For individuals receiving CAB LA as PrEP, clinicians should initiate a PI-based ART regimen while awaiting resistance test results. (A2)

**Discontinuing PrEP**

- Clinicians should discontinue PrEP in any individual with a confirmed positive HIV test result and initiate a fully active HIV regimen (see recommendations in the guideline section Managing a Positive HIV Test Result). (A1)
- Clinicians should discontinue oral PrEP if an individual does not adhere to HIV testing requirements despite repeated efforts at engagement in care. (A3)
- Clinicians should discontinue injectable PrEP if there are repeated episodes of late or missed injections without oral bridging medication despite repeated efforts to engage the individual in care. (A3)
- Clinicians should discontinue TDF/FTC as PrEP in individuals who develop a confirmed calculated CrCl <50 mL/min and discontinue TAF/FTC as PrEP in individuals who develop a confirmed CrCl <30 mL/min (A2); switch to an alternate PrEP regimen in those who wish to continue PrEP. (A3)
- Clinicians should closely monitor individuals with chronic HBV for potential viral rebound when PrEP with TDF/FTC or TAF/FTC is discontinued and develop an alternative treatment plan if necessary. (A2)
- For individuals who decide to discontinue PrEP but have a recent HIV exposure, clinicians should advise them to continue PrEP until 48 hours after last rectal exposure (A2†) and 72 hours after last vaginal receptive exposure (A3).
- Clinicians should educate individuals about the "tail" phase of long-acting injectable PrEP medications and the risk of developing drug resistance after HIV acquisition with use of subtherapeutic levels of antiretroviral medications during this period and should provide individualized guidance on alternative PrEP options and prevention planning if HIV risk continues. (A1)
- Clinicians should advise individuals on how to access PrEP in the future should they want to restart it. (A3)

**Resources:** Checklist 1: Key Factors in Choice of PrEP Regimen; Checklist 2: Assessment and Counseling Before PrEP Initiation; Checklist 3: Implementation Strategies for Long-Acting Injectable PrEP Regimens; Checklist 4: PrEP Initiation; Checklist 5: PrEP Follow-Up

**Abbreviations:** Ag/Ab, antigen/antibody; APHL, Association of Public Health Laboratories; ART, antiretroviral therapy; CAB LA, long-acting injectable cabotegravir (Apretude); CDC, Centers for Disease Control and Prevention; CEI, Clinical Education Initiative; CrCl, creatinine clearance; FDA, U.S. Food and Drug Administration; HBV, hepatitis B virus; HCV, hepatitis C virus; IM, intramuscular; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; nPEP, non-occupational post-exposure prophylaxis; oral CAB, oral cabotegravir (Vocabria); PEP, post-exposure prophylaxis; PI, protease inhibitor; PrEP, pre-exposure prophylaxis; SC LEN, subcutaneous lenacapavir (Yeztugo); STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide/emtricitabine (Descovy); TDF/FTC; tenofovir disoproxil fumarate/emtricitabine (Truvada).

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# Supplement: Guideline Development and Recommendation Ratings

| Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program | |
|---|---|
| **Developer** | New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program |
| **Funding source** | NYSDOH AI |
| **Program manager** | Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases. See Program Leadership and Staff. |
| **Mission** | To produce and disseminate evidence-based, state-of-the-art clinical practice guidelines that establish uniform standards of care for practitioners who provide prevention or treatment of HIV, viral hepatitis, other sexually transmitted infections, and substance use disorders for adults throughout New York State in the wide array of settings in which those services are delivered. |
| **Expert committees** | The NYSDOH AI Medical Director invites and appoints committees of clinical and public health experts from throughout New York State to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of New York State, all relevant clinical practice settings, key New York State agencies, and community service organizations. |
| **Committee structure** | • Leadership: AI-appointed chair, vice chair(s), chair emeritus, clinical specialist(s), JHU Guidelines Program Director, AI Medical Director, AI Clinical Consultant, AVAC community advisor<br>• Contributing members<br>• Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders |
| **Disclosure and management of conflicts of interest** | • Annual disclosure of financial relationships with commercial entities for the 12 months prior and upcoming is required of all individuals who work with the guidelines program, and includes disclosure for partners or spouses and primary professional affiliation.<br>• The NYSDOH AI assesses all reported financial relationships to determine the potential for undue influence on guideline recommendations and, when indicated, denies participation in the program or formulates a plan to manage potential conflicts. Disclosures are listed for each committee member. |
| **Evidence collection and review** | • Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update.<br>• A comprehensive literature search and review is conducted for a new guideline or an extensive update using PubMed, other pertinent databases of peer-reviewed literature, and relevant conference abstracts to establish the evidence base for guideline recommendations.<br>• A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years.<br>• Title, abstract, and article reviews are performed by the lead author. The JHU editorial team collates evidence and creates and maintains an evidence table for each guideline. |
| **Recommendation development** | • The lead author drafts recommendations to address the defined scope of the guideline based on available published data.<br>• Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations.<br>• When published data are not available, support for a recommendation may be based on the committee's expert opinion.<br>• The writing group assigns a 2-part rating to each recommendation to indicate the strength of the recommendation and quality of the supporting evidence. The group reviews the evidence, deliberates, and may revise recommendations when required to reach consensus. |

| Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program | |
|---|---|
| **Review and approval process** | • Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee.<br>• Recommendations must be approved by two-thirds of the full committee. If necessary to achieve consensus, the full committee is invited to deliberate, review the evidence, and revise recommendations.<br>• Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication. |
| **External reviews** | • External review of each guideline is invited at the developer's discretion.<br>• External reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback. |
| **Update process** | • JHU editorial staff ensure that each guideline is reviewed and determined to be current upon the 3-year anniversary of publication; guidelines that provide clinical recommendations in rapidly changing areas of practice may be reviewed annually. Published literature is surveilled to identify new evidence that may prompt changes to existing recommendations or development of new recommendations.<br>• If changes in the standard of care, newly published studies, new drug approval, new drug-related warning, or a public health emergency indicate the need for immediate change to published guidelines, committee leadership will make recommendations and immediate updates and will invite full committee review as indicated. |

| Table S2: Recommendation Ratings and Definitions | | |
|---|---|---|
| **Strength** | **Quality of Evidence** | |
| A: Strong<br>B: Moderate<br>C: Optional | 1 | Based on published results of at least 1 randomized clinical trial with clinical outcomes or validated laboratory endpoints. |
| | * | Based on either a self-evident conclusion; conclusive, published, in vitro data; or well-established practice that cannot be tested because ethics would preclude a clinical trial. |
| | 2 | Based on published results of at least 1 well-designed, nonrandomized clinical trial or observational cohort study with long-term clinical outcomes. |
| | 2† | Extrapolated from published results of well-designed studies (including nonrandomized clinical trials) conducted in populations other than those specifically addressed by a recommendation. The source(s) of the extrapolated evidence and the rationale for the extrapolation are provided in the guideline text. One example would be results of studies conducted predominantly in a subpopulation (e.g., one gender) that the committee determines to be generalizable to the population under consideration in the guideline. |
| | 3 | Based on committee expert opinion, with rationale provided in the guideline text. |