CLINICAL GUIDELINES PROGRAM
NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV · HCV · SUBSTANCE USE · LGBT HEALTH

PrEP to Prevent HIV and Promote Sexual Health

Updates, Authorship, and Related Guidelines

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Highlights of changes, additions, and updates in the May 20, 2022 edition	Updates were made to incorporate data that are new since the previous edition was published in Aug. 2021 and to include recommendations for the long-acting injectable formulation of the integrase strand transfer inhibitor cabotegravir as PrEP
Intended users	New York State clinicians who are recommending, initiating, or maintaining PrEP care for individuals at risk of acquiring HIV
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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.

Goals

The New York State Ending the Epidemic (ETE) initiative presents strategies from the ETE Task Force 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 a method to prevent HIV infection. This guideline was developed by the Medical Care Criteria Committee of the NYSDOH AI Clinical Guidelines Program to provide clinicians throughout New York State with the recommendations needed to successfully start and continue patients on PrEP.

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

- Increase awareness and knowledge of PrEP efficacy among clinicians in New York State.
- Assist clinicians in identifying candidates for PrEP and increasing awareness of, access to, and uptake of PrEP among individuals in New York State at risk of acquiring HIV through sexual and drug use exposures.
- Discuss the 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 clinicians with evidence-based recommendations for PrEP initiation, management, monitoring, and discontinuation.

Note on "experienced" and "expert" HIV care providers: Throughout this guideline, when reference is made to "experienced HIV care provider" or "expert HIV care provider," those terms are referring to the following 2017 NYSDOH AI definitions:

- Experienced HIV care provider: Practitioners who have been accorded HIV Experienced Provider status by the American Academy of HIV Medicine or have met the HIV Medicine Association's definition of an experienced provider are eligible for designation as an HIV Experienced Provider in New York State. Nurse practitioners and licensed midwives who provide clinical care to individuals with HIV in collaboration with a physician may be considered HIV Experienced Providers as long as all other practice agreements are met (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 HIV Experienced Providers (10 NYCRR 94.2)
- Expert HIV care provider: A provider with extensive experience in the management of complex patients with HIV.

PrEP Access and Coverage

U.S. Food and Drug Administration (FDA)-approved agents for PrEP: Tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg in a fixed-dose tablet (TDF/FTC; brand name Truvada) is approved by the FDA for use as PrEP as part of a comprehensive HIV prevention strategy for 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 populations.

Tenofovir alafenamide 25 mg/emtricitabine 200 mg in a fixed-dose tablet (TAF/FTC; brand name Descovy) was found to be 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]. TAF/FTC was approved by the FDA in October 2019 for HIV prevention through sexual exposure in those groups; it has not yet been approved for prevention of HIV through receptive vaginal exposure [FDA(a) 2019].

Long-acting injectable cabotegravir (CAB LA; brand name Apretude), an integrase strand transfer inhibitor given as a bimonthly injection after a 5-week oral CAB (brand name Vocabria) lead-in and after 2 initial injections given 4 weeks apart, was statistically superior to oral TDF/FTC as PrEP in MSM and transgender women [Landovitz, et al. 2021] and in cisgender women [Delany-Moretlwe, et al.] CAB LA was approved by the FDA in December 2021 for prevention of HIV via all sexual exposures [FDA(b) 2021].

PrEP uptake: Although new HIV infections and diagnoses have steadily declined in New York State, these decreases have not been uniform across all groups. MSM and people of color, particularly young MSM and women of color, continue to be overrepresented among those newly infected and diagnosed with HIV [NYSDOH 2018]. 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 [NYSDOH 2018]. However, data indicate that people of color, 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 [ETE Dashboard 2020]. For example, in 2020, 19.4% of new HIV diagnoses in New York State were in women, but just 8.1% of all individuals who accessed PrEP in New York State were women. Nationally, although White MSM account for 30% of new HIV infections, nearly 75% of prescriptions for PrEP in the United States have gone to White MSM, illustrating the need to improve outreach to other communities affected by HIV [Townes, et al. 2021; Jenness, et al. 2019; Goedel, et al. 2018; Goldstein, et al. 2018].

Barriers to PrEP access and use: The NYSDOH AI recognizes that a comprehensive approach is necessary to ensure that individuals who will most benefit from the use of PrEP have access to it and that their care is managed effectively while they are taking PrEP. This guideline addresses some structural barriers to PrEP care by advocating for individualization and flexibility in care-delivery models, including monitoring schedules and dosing options.

Barriers to PrEP access include:

- Suboptimal awareness or acceptance of PrEP among some individuals at risk for acquiring HIV and their care providers [Townes, et al. 2021; Bazzi, et al. 2018; Mayer, et al. 2018; Rael, et al. 2018; Bien, et al. 2017; Blackstock, et al. 2017; King, et al. 2014]
- Lack of retention in PrEP care due to individual and structural barriers [D'Angelo, et al. 2021; Serota, et al. 2020; Chan, et al. 2016]
- Stigma, which may keep people who would benefit from PrEP from using it
- Disparities in access to PrEP among populations at high risk of HIV acquisition, including MSM of color, transgender women, Black women, and people who inject drugs [Biello, et al. 2018; CDC(a) 2018; Garnett, et al. 2018; Lancki, et al. 2018; Morgan, et al. 2018; Sullivan, et al. 2018; Page, et al. 2017; Philbin, et al. 2016; Sevelius, et al. 2016; King, et al. 2014]. Emerging evidence suggests that transgender MSM are also at high risk for HIV acquisition [Pitasi, et al. 2019; Scheim, et al. 2017] and are a population for whom PrEP outreach and access are needed.

The availability of injectable PrEP creates unique opportunities and potential challenges for systems to incorporate this option. Populations at the highest risk of acquiring HIV should be prioritized for PrEP outreach and access to ensure they are aware of PrEP and its benefits. PrEP programs will have to develop systems and protocols to make injectable PrEP available.

It is also crucial to address barriers and expand access to PrEP by increasing the number of medical care providers who are aware of and willing to prescribe PrEP. Care providers need to examine any unconscious biases that may influence their willingness to offer PrEP to patients [Calabrese, et al. 2018; Edelman, et al. 2017; Calabrese, et al. 2014], avoid making assumptions about sexual practices, and develop comfort and facility in obtaining routine sexual histories and asking about injection drug use practices to identify potential PrEP candidates. Regardless of disclosed risk, if a patient asks for PrEP and it is not medically contraindicated, they should be offered a prescription and appropriate follow-up.

Coverage under the Affordable Care Act (ACA): In August 2023, the U.S. Preventive Services Task Force (USPSTF) published an updated grade A recommendation stating 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]. The updated USPSTF recommendation statement also includes a review of the evidence on newer HIV PrEP medications, including oral TAF/FTC and long-acting CAB, in addition to oral TDF/FTC. 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 that clinicians can and should provide to their patients.

Coverage in New York State: In July 2019, the New York State Department of Financial Services issued a Circular Letter instructing New York State insurers to cover PrEP without cost-sharing, including copays and deductibles, which have been a major financial barrier for many consumers.

◊ NYSDOH RESOURCES

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

PrEP for Individuals at Risk of Acquiring HIV

☑ RECOMMENDATIONS

Indications

- 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 patients who are completing a course of nPEP and remain at risk for HIV, clinicians should recommend initiation of PrEP immediately after 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 ART regimens for HIV treatment. (A1)
- Clinicians should recommend or refer individuals with confirmed HIV for immediate initiation of 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)

Abbreviations: ART, antiretroviral therapy; CrCl, creatinine clearance; nPEP, non-occupational post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; TAF/FTC, tenofovir alafenamide/emtricitabine (brand name Descovy); TDF/FTC; tenofovir disoproxil fumarate/emtricitabine (brand name 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, who are assessed or who self-identify as being at increased risk of acquiring HIV through sexual or injection drug exposure.

Box 1, below, shows candidates who should be offered PrEP (e.g., those at risk of acquiring HIV through rectal, genital, or blood exposures, and those who request PrEP) and factors that do not disqualify candidates from PrEP.

Box 1: Candidates for PrEP

Offer PrEP to individuals who are candidates for PrEP, including those who:

- 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 [Grov, et al. 2013; Smith, et al. 2012]
- Are attempting to conceive with a partner with HIV who is not consistently virally suppressed or whose status of suppression is unknown, or wants 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 or have 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 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]

Box 1: Candidates for PrEP

- Report injecting substances or having sex partners who inject substances, including illicit drugs, hormones, or silicone
- Are receiving nPEP and anticipate ongoing risk or have used multiple courses of nPEP [Heuker, et al. 2012]
- Request the protection of PrEP even if their sex partners have an undetectable HIV viral load (see discussion of HIV-serodifferent couples, below)
- Self-identify as being at risk without disclosing specific risk behaviors
- Acknowledge the possibility of or anticipate engaging in risk behaviors in the near future

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

Abbreviations: nPEP, non-occupational post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; U=U, undetectable=untransmittable.

Men who have sex with men (MSM): Studies have demonstrated that TDF/FTC as 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 trial demonstrated only a 44% reduction in the rate of HIV acquisition, there was a 92% reduction in sexual transmission when tenofovir was detectable in the blood. No seroconversions occurred in individuals with therapeutic plasma concentrations of TDF/FTC [Grant, et al. 2010]. 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]. Based on intracellular concentrations of tenofovir diphosphate, HIV risk-reduction efficacy in the iPrEX study was estimated to be 99% with 7 doses per week, 96% with 4 doses per week, and 76% with 2 doses per week [Anderson, et al. 2012].

The DISCOVER study showed both TDF/FTC and TAF/FTC to be highly effective in reducing the risk of HIV infection 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; brand name Apretude) prevented HIV in MSM and transgender women. However, CAB LA was statistically superior, with 14 incident infections among participants receiving the regimen, compared with 41 incident infections among participants taking TDF/FTC during the blinded phase of the study, mostly driven by adherence and low tenofovir levels in individuals seroconverting on TDF/FTC [Landovitz, et al. 2022; Landovitz, et al. 2021].

Transgender women: In the iPrEx study, TDF/FTC as PrEP was effective in transgender women who adhered to the regimen. In a subanalysis of transgender women in the iPrEx study, there was no difference in rates of HIV infection between the PrEP and placebo groups; however, none of the transgender women who seroconverted had detectable tenofovir levels, and there were no HIV infections in those who had adequate tenofovir levels [Deutsch, et al. 2015]. Subsequent analysis has shown significant differences in the baseline characteristics between MSM and transgender women in the iPrEX study [Mehrotra, et al. 2019].

Multiple studies have shown that TDF/FTC does not alter estrogen levels [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], although the significance of this difference is unclear. In the larger iBrEATHe study, which used directly observed daily oral TDF/FTC as PrEP for 4 weeks in transgender women on consistent hormone therapy, differences in tenofovir levels measured by dried blood spots did not meet statistical significance [Grant, et al. 2021]. In the ImPrEPT study among transgender individuals taking TDF/FTC as PrEP, no interactions between hormone therapy and PrEP were reported [Blumenthal, et al. 2022]. It is possible that higher levels of adherence are needed among transgender women using

estrogens and taking TDF/FTC for PrEP than among cisgender men, but levels achieved with daily dosing will confer protection from TDF/FTC as PrEP.

TAF/FTC was effective in transgender women in the DISCOVER study, but transgender women made up only 1% of the study population [Mayer, et al. 2020]. There are no formal pharmacokinetic studies of the effects of estrogen at doses used for gender-affirming care on TAF levels, but intracellular PBMC concentrations of tenofovir diphosphate were similar between transgender women taking gender-affirming hormone therapy and MSM in the DISCOVER study [Cespedes, et al. 2020]. There are also no pharmacokinetic studies of the effects of estrogen at doses used for gender-affirming therapy on CAB LA levels, but in the HPTN 083 study, transgender women made up 12.5% of the study population, and CAB LA was effective across all subpopulations. Additionally, oral CAB pharmacokinetics were not significantly altered by low-dose hormones used for oral contraceptives in the HPTN 077 study [Blair, et al. 2020].

Transgender men: 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]. 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]. Tenofovir levels were lower in transgender men than in cisgender women; however, levels were still in a range consistent with effective PrEP with TDF/FTC in clinical trials. There are no data yet on whether testosterone therapy affects CAB levels. However, there is no specific reason to believe that CAB LA will be less effective for vaginal or anal exposures in preventing HIV infection in this population.

Cisgender men and women: Studies have demonstrated that TDF/FTC as PrEP is effective for cisgender men and women. In the Partners PrEP study, there was a 67% overall reduction in HIV acquisition in cisgender men and women and a 90% reduction in those with detectable drug in their blood [Baeten, et al. 2012]. In the TDF2 study, there was a 62% overall reduction in HIV acquisition, and there were only 2 seroconversions in participants who had detectable drug [Thigpen, et al. 2012]. However, the FEM-PrEP and VOICE trials did not demonstrate a benefit of TDF/FTC as PrEP for cisgender women, although subsequent analyses found that the lack of effect was associated with poor adherence to the prescribed daily PrEP regimen [Van Damme, et al. 2012]. TAF/FTC has not been studied in cisgender women. CAB LA was found to be statistically superior to TDF/FTC in the HPTN 084 study of 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 adherence to oral medication [Delany-Moretlwe, et al. 2022].

HIV-serodifferent couples: PrEP may be useful for individuals in a serodifferent partnership, even if the partner with HIV is taking suppressive ART. Data from the Partners in Prevention HSV/HIV Transmission Study and the HPTN 052 study demonstrated reductions up to 92% and 96%, respectively, in HIV transmission risk in serodifferent heterosexual couples when the partner with HIV was on suppressive ART [Cohen, et al. 2011]. HIV is transmissible if an individual's viral load is not fully suppressed, which may take up to 6 months or longer after ART initiation. Once an undetectable viral load is achieved and maintained, HIV is not sexually transmissible [Mujugira, et al. 2016]. For more information, see the NYSDOH AI U=U Guidance for Implementation in Clinical Settings.

In the Partners Demonstration Project, use of TDF/FTC as PrEP as a "bridge" was highly effective in protecting the individual without HIV during the first 6 months of a partner's ART. Subsequently, in the Partner, Partner 2, and Opposites Attract studies, there were no sexual transmissions between serodifferent partners when the partner with HIV had an undetectable viral load [Baeten, et al. 2016]. In September 2017, the NYSDOH endorsed the undetectable = untransmittable (U=U) consensus statement from the Prevention Access Campaign [Prevention Access Campaign 2019; NYSDOH 2017].

In a 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 not necessary in light of U=U data supporting treatment-as-prevention, PrEP should be discussed as an option for prevention and offered when appropriate. It is important to note that 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 protection of PrEP.

Although the efficacy of TDF/FTC as PrEP during attempts to conceive has not been formally studied, it is an option for individuals who do not have HIV, and evidence suggests that it does not affect male fertility [Were, et al. 2014] and is safe during the periconception period [Mugo, et al. 2014]. TAF/FTC has not been studied in the context of attempts to conceive.

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 those with detectable drug in their blood increased efficacy to 74%.

PrEP for Adolescents

☆ 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.

Modeling 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].

TDF/FTC: In May 2018, the U.S. Food and Drug Administration (FDA) approved the use of TDF/FTC as PrEP in adolescents weighing ≥35 kg [FDA 2018]. The Centers for Disease Control and Prevention and the International Antiviral Society–USA previously extended the indication for TDF/FTC to include PrEP for adolescents at increased risk of acquiring HIV [CDC(b) 2018; Marrazzo, et al. 2014].

To date, there is no evidence of increased TDF/FTC toxicity in adolescents taking this combination as part of an ART regimen. TDF/FTC as PrEP was safe and effective in adolescents, with no renal events or bone fractures noted [Hosek, et al. 2017]. Concerns regarding bone loss in younger age groups have been raised, with 2 studies reporting a decline in bone mineral density [Havens, et al. 2017]. Bone density changes associated with TDF use are reversible on discontinuation in adults and MSM 18 to 22 years old [Hosek, et al. 2017]. Data on bone density recovery after discontinuation of TDF/FTC as PrEP are not available for adolescents <18 years old. Studies are in progress to determine the safety of TDF/FTC for adolescents over long periods of time.

TAF/FTC: In October 2019, the FDA approved use of this regimen as PrEP in adults and adolescents weighing ≥35 kg [FDA(a) 2019]. There are no specific data on bone safety in adolescents taking TAF/FTC as PrEP; however, given the more favorable bone biomarkers of TAF compared with TDF, TAF may have an advantage in MSM and transgender female adolescents who have not achieved bone maturation, but this advantage is theoretical. Without clinical data, a clear recommendation cannot be made at this time.

CAB LA: In December 2021, CAB LA was approved by the FDA for use in adolescents ≥12 years old weighing ≥35 kg [FDA(b) 2021].

Assessment and Counseling Before PrEP Initiation

→ SELECTED GOOD PRACTICE REMINDERS

Assessment and Counseling Before PrEP Initiation

- Assess the patient's health literacy [a] and ensure that the purpose, benefits, and risks of PrEP are understood.
- Individualize the decision to initiate PrEP by weighing the benefit of reducing the patient's risk of acquiring HIV against the potential adverse effects of the medication.
- 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 eligibility for injectable PrEP, including the ability to adhere to visits every 2 months for intramuscular injections.
- 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 [b].
- 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.

→ SELECTED GOOD PRACTICE REMINDERS

- 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.

Note:

a. The National Network of Libraries of Medicine defines health literacy as the ability to understand instructions on prescription drug bottles, appointment slips, medical education brochures, and care provider's directions and consent forms; the ability to negotiate complex healthcare systems; reading, listening, analytical, and decision-making skills; and the ability to apply these skills to health situations. See the following resources:
   - Health Literacy Tool Shed (funded by the U.S. National Libraries 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

b. For more information, see the following resources:
   - NYSDOH AI GOALS Framework for Sexual History Taking in Primary Care
   - NYSDOH AI guideline Substance Use Harm Reduction in Medical Care
   - New York City Department of Health and Mental Hygiene Making the Sexual History a Routine Part of Primary Care

Engagement in primary care: PrEP is an integral part of sexual health and well-being. Developing an HIV prevention plan that includes PrEP offers care providers the opportunity to engage individuals in primary care. Clinicians may use this opportunity to encourage age-appropriate health screenings, substance use screening and interventions, linkage to specialty services, and other health maintenance activities, such as immunizations (e.g., hepatitis A and B vaccines, human papillomavirus vaccine for patients ≤45 years old, and meningococcal vaccine when appropriate).

Patient education: Patient education is vital to shared decision-making and the success of PrEP as part of a comprehensive HIV prevention plan. Educate candidates about risks, benefits, and the choice of oral versus injectable PrEP. Discuss individual preferences, needs, and circumstances. Adherence may improve when patients participate in medication-related decisions [Johnson, et al. 2012] and are informed about the strong efficacy of PrEP when taken as directed (see guideline sections Choosing and Prescribing a PrEP Regimen > Engagement in Care and Adherence). Education provided in the individual's native or preferred language and tailored to the individual's level of comprehension will help ensure understanding of:

- How PrEP works
- The benefits and risks of PrEP
- The need for adherence to the dosing schedule for PrEP to be protective
- The importance of regular monitoring and adherence to the visit schedule
- How safer sex or safer drug injection practices decrease the risk of pregnancy and the risk of acquiring drug-resistant HIV, other sexually transmitted infections (STIs), and hepatitis C virus (see Be in the KNOW > Sex and HIV and NYSDOH Syringe Access and Disposal).

Health literacy assessment: Use a health literacy assessment to evaluate the individual's knowledge of the:

- Purpose of PrEP
- Importance of adherence to PrEP
- Importance of scheduled HIV testing and routine monitoring
- Potential adverse effects of PrEP
- Process for obtaining regular pharmacy refills for PrEP
- Methods of paying for PrEP or access to payment assistance for PrEP medications and related care services

See An Introduction to Health Literacy from the National Library of Medicine for more details on the various aspects of health literacy, including tools for assessing health literacy.

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 the offer of further counseling and referrals, such as for substance use treatment (see NYSDOH Office of Addiction Services and Supports: Treatment).

Status of sex partner(s) with HIV: The 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 [Prevention Access Campaign 2019; NYSDOH 2017; Rodger, et al. 2016]. If the patient's partner has detectable virus and genotypic information is unavailable, knowledge of the partner's ART regimen may be helpful. The risk of acquisition is increased when an individual is exposed to HIV that is resistant to the components of their PrEP regimen [Knox, et al. 2017; NYC Health 2016]. The potential for drug resistance is an important consideration when choosing a PrEP regimen. If there is a risk of drug resistance in a sex partner with HIV, it is essential to advise the individual without HIV to use additional prevention measures, including condoms.

Reproductive counseling: Inquire about the patient's reproductive plans and provide preconception counseling when indicated. Determine whether the patient or the patient's partner is pregnant or breastfeeding, 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 PAYMENT ASSISTANCE

- For PrEP payment assistance, see NYSDOH Payment Options for Adults and Adolescents for PrEP and PrEP Patient Assistance Program (PrEP-AP).
- In October 2020, based on the U.S. Preventive Services Task Force grade A recommendation for PrEP, the New York State Department of Financial Services issued a Circular Letter instructing health insurers to provide coverage for PrEP medications without cost-sharing, including copays, deductibles, and tests related to PrEP.

PrEP in Comprehensive HIV Prevention Planning

A comprehensive HIV prevention plan includes counseling and education about PrEP options, adherence to PrEP, ongoing monitoring with laboratory tests, education about risk reduction, and discussion of additional HIV prevention options, including the use of condoms and safe drug injection practices [Blashill, et al. 2015; Daughtridge, et al. 2015; Liu, et al. 2014; Marcus, et al. 2014].

Risk reduction: At every visit, clinicians should encourage risk reduction through condom use, safer sex practices, and if applicable, safer injection techniques [Bramson, et al. 2015; Abdul-Quader, et al. 2013; Jarlais 2013]. Discussions about risk reduction should be tailored to patients' specific needs. However, condom use is not a prerequisite for PrEP use.

Decreased condom use has been observed in some individuals taking PrEP and has been associated with a concomitant rise in other viral and bacterial STIs for which PrEP offers no protection; however, this is not a valid reason to withhold PrEP (see guideline section Ongoing Laboratory Testing > Routine Laboratory Testing > STI screening) [Traeger, et al. 2018; Werner, et al. 2018; Hojilla, et al. 2016; Kuhns, et al. 2016; Golub 2014; Liu, et al. 2013].

Risk compensation: Increased engagement in high-risk sexual behaviors, such as condomless sex or multiple sex partners, can lead to an increase in STI incidence and is sometimes cited by care providers as a reason not to offer PrEP. A meta-analysis of 20 studies found that rates of sexual risk behaviors and STIs in MSM taking PrEP remained stable or decreased in the majority of the studies [Werner, et al. 2018]. In a separate meta-analysis limited to open-label studies in which participants knew they were receiving active drug, a majority of the studies reported an increase in condomless sex but no significant increase in the proportion of MSM participating in condomless sex, indicating that participants were not using condoms consistently before they started PrEP [Traeger, et al. 2018].

High baseline STI rates in PrEP clinical trial participants demonstrate that risk behavior often precedes engagement in PrEP care. Initiating PrEP care for individuals at risk for HIV provides an opportunity for routine STI screening and treatment. One modeling study demonstrated that increased PrEP engagement along with routine STI screening and treatment would lower STI rates through detection and treatment of asymptomatic STIs that might otherwise remain undiagnosed. Modeling

indicated that STI rates decline more rapidly as higher numbers of at-risk individuals initiate PrEP and related STI screening services, with an even greater reduction in STIs the more frequently STI testing occurs, even in the event of a 40% to 80% decrease in condom use [Jenness, et al. 2017].

PrEP after PEP: Patients who remain at increased risk of HIV exposure after completing a course of nPEP and who are negative for HIV at the 4-week test should be offered PrEP to begin immediately after the last dose of nPEP.

→ KEY POINTS

- PrEP effectively enhances protection during periods when individuals, including adolescents, are at greatest risk of acquiring HIV.
- PrEP is highly effective but is not 100% protective against HIV acquisition and does not protect against other STIs.
- Duration of PrEP use will depend on the length of time an individual remains at increased risk for HIV (see guideline section Discontinuing PrEP).

Contraindications to PrEP Use

HIV infection: The 2-drug PrEP regimens of TDF/FTC and TAF/FTC and the single-drug regimen of CAB LA are not adequate for treating established HIV infection; therefore, PrEP should not be initiated unless an individual is tested for HIV within 1 week before the proposed initiation. If HIV infection is confirmed, PrEP should immediately be converted to a fully suppressive HIV treatment regimen. For more information, see the NYSDOH AI guidelines Rapid ART Initiation and Selecting an Initial ART Regimen.

Renal dysfunction: TDF can cause renal toxicity and is contraindicated for patients with a CrCl <60 mL/min at the time of PrEP initiation [FDA 2016]. There are no data for adjusting TDF dosing in those with an estimated CrCl <50 mL/min.

TAF/FTC can be initiated in individuals with a creatinine clearance ≥30 mL/min and can be used in cisgender MSM and transgender women who have a CrCl <60 mL/min on initiation or a CrCl that drops to <50 mL/min while taking TDF/FTC.

Increased monitoring for adverse effects is appropriate for individuals with a CrCl <30 mL/min receiving CAB LA. Serum creatinine levels can vary and be affected by factors other than renal disease; therefore, before a decision is made to forgo 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) should be ruled out. Potentially reversible causes, such as the use of nonsteroidal anti-inflammatory medications, may also be addressed.

CAB LA is an appropriate PrEP option for individuals who cannot take a tenofovir-containing regimen because of renal dysfunction. To decrease drug exposure, on-demand dosing of TDF/FTC may also be considered when appropriate for cisgender MSM with borderline renal function or other kidney disease with a preserved calculated CrCl (see guideline section Choosing and Prescribing a PrEP Regimen > Preferred Oral Regimen for Daily or On-Demand Dosing: TDF/FTC).

When medication cannot be used for PrEP, education regarding other prevention options, such as condom use and safer sex practices, is essential.

PrEP Failure

HIV acquisition despite adherence to PrEP is rare. PrEP failure is directly related to suboptimal adherence in all but a small number of cases. In most cases of HIV acquisition despite adherence to PrEP, there was unrecognized HIV infection at the time of PrEP initiation.

There are case reports of individuals who acquired HIV despite adherence to TDF/FTC as PrEP, measured by tenofovir concentration in hair or dried blood spot samples. These case reports have noted that some individuals were exposed to HIV that was resistant to tenofovir and emtricitabine [Knox, et al. 2017; NYC Health 2016]. One individual acquired HIV with mutations that should still have conferred sensitivity to TDF/FTC [Cohen, et al. 2019]. Another acquired wild-type virus while using PrEP [Hoornenborg(a), et al. 2017]. It is theorized that in the case of wild-type virus acquisition despite good adherence, exposure to HIV was potentially very high given the number of condomless exposures over the 6-month period and the presence of rectal STIs.

PrEP failures with CAB LA were rare and mainly occurred before the initiation of study drug, during oral lead-in, in individuals who missed a scheduled injection, or during the tail phase after treatment was discontinued. In the HPTN 083 study, 6 individuals acquired HIV despite on-time CAB LA injections [Landovitz, et al. 2022; Landovitz, et al. 2021]. Analysis is under

way to better understand these failures. In the HPTN 084 study, there were no incident HIV infections with on-time CAB LA injections in cisgender women [Marzinke(b), et al. 2021].

Although PrEP failure with CAB LA is rare, 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 one infection occurring in an individual who received on-time injections. There was no finding of integrase resistance among these participants [Marzinke(b), et al. 2021]. There is concern with long-acting injectable medications 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 will 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.

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)
- If daily dosing is a barrier to adherence or if episodic dosing is preferred, clinicians should inform candidates about dosing and adherence requirements for available PrEP regimens and engage them in informed, shared decision-making regarding the choice of regimen. (A3)

TDF/FTC

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

TAF/FTC

- Clinicians should recommend TAF/FTC as the preferred oral PrEP regimen for cisgender MSM and transgender women with preexisting renal disease or osteoporosis. (A1)
- Clinicians should not recommend TAF/FTC for protection against HIV exposure through receptive vaginal sex. (A1)

Patients With HBV Infection

- Clinicians should discuss daily TDF/FTC or TAF/FTC as the preferred regimens for patients with HBV infection who require treatment. (A2†)
- Clinicians should closely monitor patients with chronic HBV infection for a 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 to 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 CAB LA as PrEP. (A1)
- If a patient at ongoing risk of HIV acquisition discontinues CAB LA injections, the clinician should recommend an oral PrEP regimen to be started 2 months after the last injection and continued for at least 1 year to prevent potential acquisition of INSTI-resistant HIV. (A3)
- Given the current lack of safety data on CAB LA during pregnancy, clinicians should engage pregnant patients and those planning to conceive in shared decision-making regarding the options of continuing CAB LA or switching to daily oral TDF/FTC. (A3)

Resource: Appendix: Care Provider Checklists for PrEP Initiation, Regimen Choice, and Follow-Up

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

Comparison of Available Regimens

All current 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 Tables 1 and 2, below).

Table 1: Comparison of Key Clinical and Logistical Factors in Choosing a PrEP Regimen (details provided in discussion that follows; also see Appendix: Care Provider Checklists for PrEP Initiation, Regimen Choice, and Follow-Up)

TDF/FTC (tenofovir disoproxil fumarate/emtricitabine; Truvada)	**TAF/FTC** (tenofovir alafenamide/ emtricitabine; Descovy)	**CAB LA** (long-acting injectable cabotegravir; Apretude)	**Comments**
Efficacy			
All exposures, including sexual and injection drug use	• Sexual exposures in cisgender MSM, transgender women, and adolescents weighing ≥35 kg [a] • Not approved for receptive vaginal sexual exposure • Not approved for injection drug exposure	• Sexual exposures in all adults and adolescents weighing ≥35 kg • Not approved for injection drug exposure	A 2017 amendment to the NYCRR grants minors capacity to consent to PrEP and PEP without parental/guardian involvement
Time to Protection [b]			
• Rectal exposure: 7 days of daily dosing • Genital and blood exposure: 7 days of daily dosing, with maximal protection after 20 days • Cisgender MSM: After 2 doses taken 2 to 24 hours before risk exposure	No data	No data	—
Renal Safety			
• Do not initiate if CrCl <60 mL/min • Discontinue if confirmed CrCl <50 mL/min • Potential effect on renal tubular function; meta-analysis shows good safety [c]	• Improved renal biomarkers compared with TDF • Can be used if CrCl ≥30 mL/min in MSM and transgender women • Do not initiate if CrCl <30 mL/min	Increased monitoring for adverse effects is recommended with CrCl <30 mL/min	• Inform patients with risk factors of the increased possibility of kidney disease with TDF/FTC or TAF/FTC as PrEP; weigh risks and benefits • More frequent monitoring may be required for patients at increased risk of renal disease (i.e., hypertension, diabetes, >40 years old)
Bone Safety			
Potential decrease in bone mineral density; meta-analysis shows good safety [c]	• Favorable bone biomarkers compared with TDF • Preferred regimen for cisgender men and transgender women with osteoporosis	Preferred option for prevention of sexual exposures in all individuals with osteopenia or osteoporosis	Inform patients with preexisting risk factors or documented osteopenia, osteomalacia, or osteoporosis of the risk of bone loss with TDF/FTC; weigh the risks and benefits

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TDF/FTC (tenofovir disoproxil fumarate/emtricitabine; Truvada)	**TAF/FTC** (tenofovir alafenamide/ emtricitabine; Descovy)	**CAB LA** (long-acting injectable cabotegravir; Apretude)	**Comments**
Weight and LDL Cholesterol			
• Weight neutral • Small decreases in LDL	• Mild weight gain was observed in studies • Small increases in LDL	• Mild weight gain was observed in MSM and transgender women • No significant effect on lipids	—
Dosing			
• Daily dosing is preferred • On-demand dosing is an option in cisgender MSM	Daily dosing only	• Optional 30-day oral lead-in • First 2 IM injections are administered 4 weeks apart; thereafter, injections are given every 2 months	—
Same-Day Initiation			
Generic TDF/FTC is a preferred insurance option and is usually available for same-day initiation	May require prior authorization	• May require prior insurance authorization for oral or injectable CAB • Implementation challenges may interfere	—
Common Adverse Effects			
Diarrhea (6%), nausea (5%) [d]	Diarrhea (5%), nausea (4%) [e]	Injection site reactions (32% to 81%) [f], which are mostly mild and greatest initially	—
Use During or When Planning Pregnancy			
• Can be used. Weigh risks and benefits in shared decision-making • May be continued through pregnancy and breastfeeding • Prospectively report information regarding the use of TDF/FTC as PrEP during pregnancy to the Antiretroviral Pregnancy Registry	Do not use for vaginal exposure; no data in pregnancy	• If attempting to conceive or if pregnancy occurs, continue only if the expected benefit justifies the potential risk to the fetus • Recommend TDF/FTC if it is an appropriate option for patients who wish to continue PrEP	• HIV acquisition risk is increased during pregnancy and is highest late in pregnancy and early postpartum • Suppressive ART (TasP) for a partner with HIV is important for risk reduction • Acute seroconversion significantly increases the risk of perinatal transmission during pregnancy and while breastfeeding
Use With Oral Contraceptives			
No interaction expected based on PK data	Not for use as PrEP for vaginal sexual exposure	No interaction expected based on PK data	—

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TDF/FTC (tenofovir disoproxil fumarate/emtricitabine; Truvada)	**TAF/FTC** (tenofovir alafenamide/ emtricitabine; Descovy)	**CAB LA** (long-acting injectable cabotegravir; Apretude)	**Comments**
Use With Gender-Affirming Hormones			
• Does not alter estrogen levels • Does not alter testosterone levels in transgender men • Estrogen may lower tenofovir levels, but levels achieved with daily dosing are protective	No data; no interaction expected based on PK profiles and lack of significant interactions with oral contraceptives	No data; no interaction expected based on PK profiles and lack of significant interactions with oral contraceptives	—
Patients With Active Chronic HBV [g,h]			
• Active against and FDA-approved for treatment of HBV infection • Daily dosing required when used for PrEP and HBV treatment	• Active against and FDA-approved for treatment of HBV infection • Daily dosing required when used for PrEP and HBV treatment	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 infection
Drug-Drug Interactions			
See NYSDOH AI Resource: ART Drug-Drug Interactions > TDF and TAF Interactions	See NYSDOH AI Resource: ART Drug-Drug Interactions > TDF and TAF Interactions	See NYSDOH AI Resource: ART Drug-Drug Interactions > CAB Interactions	—
Generic Formulation Availability			
Generic TDF/FTC is available	Brand only	Brand only	TAF/FTC and CAB may require prior insurance authorization

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; CAB, cabotegravir; CrCl, creatinine clearance; FDA, U.S. Food and Drug Administration; FTC, emtricitabine; 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; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; TAF, tenofovir alafenamide; TasP, treatment-as-prevention; TDF, tenofovir disoproxil fumarate.

Notes:

a. Transgender women made up only 1% of the DISCOVER study population [Mayer, et al. 2020].
b. Time to protection has not been definitively established for any available PrEP regimen (see guideline section Choosing and Prescribing a PrEP Regimen > Time to Protection, below).
c. [Pilkington, et al. 2018]
d. [Glidden, et al. 2016]
e. [Mayer, et al. 2020]
f. [Delany-Moretlwe, et al. 2022; Landovitz, et al. 2021]
g. TDF and TAF are approved by the FDA as treatment for HBV. 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.
h. Evaluate individuals with chronic HBV who are not PrEP candidates for recommended treatment (see NYSDOH AI guideline Prevention and Management of Hepatitis B Virus Infection in Adults With HIV).

Table 2: Comparison of Benefits, Limitations, and Risks of Available PrEP Regimens		
All PrEP Regimens	**Oral PrEP With TDF/FTC or TAF/FTC**	**Injectable PrEP With CAB LA**
Benefits		
• Highly effective when taken as directed • May decrease anxiety regarding HIV acquisition • 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 • Single tablet taken daily • Good safety profiles in people who do not have HIV • Minimal adverse effects, most of which resolve in a brief period of time or can be managed • TDF/FTC appears to be safe for use during attempts to conceive and during pregnancy • Treats HBV infection	• Statistical superiority to TDF/FTC has been attributed to a lack of adherence to the oral regimen • Indicated for all sexual exposures • Administered once every 2 months • Directly observed therapy • Potential 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 challenges
Limitations		
• Protection correlates with adherence to the dosing schedule • No significant protection against STIs other than HIV [a]	• Requires close adherence to the daily administration schedule • Requires planning and adherence when TDF/FTC is dosed on demand • Requires additional monitoring in patients with chronic HBV infection • Cost of TAF/FTC (no generic available) • No data on TAF/FTC for individuals who inject drugs	• Requires deep IM injection • Lack of data on use during pregnancy or breastfeeding • No data for individuals who inject drugs • Requires oral medications as bridging therapy when injections are missed • Requires ≥6 in-person healthcare visits per year • Does not treat HBV coinfection • Not appropriate for individuals with injectable silicone or other fillers in the gluteal area • Implementation logistics • Cost (no generic available)
Risks		
• Potential for delayed detection of HIV infection using standard HIV testing algorithms • Continued use after undiagnosed HIV infection may result in development of drug-resistant virus	• Safety concerns for individuals with impaired kidney function • Compared with TAF, TDF may be associated with reversible decreases in bone density	• Potential injection site reactions and other adverse events, including pyrexia • Long tail phase once treatment is discontinued • Potential for breakthrough infections despite on-time injections

Abbreviations: CAB LA, long-acting injectable cabotegravir (brand name Apretude); HBV, hepatitis B virus; HSV, herpes simplex virus; IM, intramuscular; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide/emtricitabine (brand name Descovy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (brand name Truvada).

Note:

a. Some protection against HSV has been reported in heterosexual populations without HIV [Celum, et al. 2014].

Time to Protection

The time to protection against HIV infection after PrEP initiation is not definitively established. No studies have directly assessed time to protection, and the site of PrEP action in blood, rectal, and genital tissues has not been settled. 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 has been effective if initiated 36 to 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]. No data are available on protective concentrations of TDF/FTC in penile tissue. Based on these data, the 2017 Centers for Disease Control and Prevention and NYSDOH AI PrEP guidelines recommended 7 days of TDF/FTC as PrEP for rectal exposure and 20 days of PrEP for vaginal, penile, and injection exposures to achieve protection.

Other pharmacokinetic modeling data suggest that TDF/FTC is likely protective within 1 week of dosing in rectal and genital compartments and peripheral blood mononuclear cells (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].

Some guidelines have suggested shorter intervals to PrEP protection with TDF/FTC. Both the 2017 World Health Organization (WHO) and the 2018 British HIV Association (BHIVA) guidelines recommend a 7-day PrEP lead-in for protection against HIV via vaginal and injection exposures [BHIVA 2019; WHO 2017]. The WHO guidelines recommend a time to protection of 7 days for all sites of exposure, but the BHIVA guidelines advise that protection against rectal exposure is achieved 24 hours after an initial double (loading) dose, based on the efficacy shown in the IPERGAY study of on-demand TDF/FTC and pharmacokinetics indicating achievement of protective concentrations of TDF/FTC sooner with a loading dose. Although concrete guidance on efficacy would be best, and accumulating evidence points to an earlier time to protection for vaginal exposure, a definitive answer to this question is not yet available, and experts disagree in their interpretation of the evidence [AVAC 2017].

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.

CAB LA: At this time, there are no data available on time to protection for CAB LA, and specific guidance cannot be provided.

→ KEY POINTS

- Time to protection after initiation of TDF/FTC as PrEP is based on pharmacokinetic modeling studies and has not been clinically determined.
- For rectal exposures, TDF/FTC as PrEP achieves protective levels after 7 days of daily dosing and possibly earlier, or 2 hours to 24 hours after a loading dose of 2 tablets taken simultaneously on the day of initiation.
- For genital and blood exposures, protection against HIV acquisition is likely achieved after 7 days of daily TDF/FTC as PrEP, but optimal drug concentrations are achieved after 20 days.
- Taking 2 tablets of TDF/FTC as PrEP on the day of initiation is protective for rectal exposures and will decrease the time needed to achieve protective drug concentrations for all sites of exposure.
- Time to protection for TAF/FTC or CAB LA as PrEP is unknown.

Preferred Oral Regimen for Daily or On-Demand Dosing: TDF/FTC

When TDF/FTC is preferred: TDF/FTC is the preferred oral regimen for PrEP because of its proven efficacy and safety in clinical trials, its suitability for use as PrEP in most populations (including individuals who inject drugs), and its cost, which is lower than that of TAF/FTC. However, for cisgender MSM and transgender women with preexisting renal disease or osteoporosis, TAF/FTC is the preferred oral regimen; see 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 2016].

For cisgender MSM, the data on daily dosing of TDF/FTC are more robust than for on-demand dosing, with longer follow-up. Daily dosing remains the preferred dosing strategy.

On-demand dosing: For TDF/FTC as PrEP, an on-demand dosing strategy (also called intermittent, event-driven, or coitally timed PrEP) is an option for MSM when lifestyle, sexual practices, or stated preferences make it a more acceptable choice.

On-demand dosing of TDF/FTC is not recommended for protection against vaginal sexual exposure, blood exposure through injection drug use, or in individuals with HBV infection. It should be used with caution in transgender women taking gender-affirming hormones.

When used on-demand, 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.

Considerations for on-demand PrEP: Successful on-demand PrEP requires planning ahead for sex by at least 2 hours. Patients have to review their usual practices in planning for sex to assess the feasibility of this approach, and clinicians have to ensure that patients understand the complex dosing schedule.

The logistical challenge of determining the amount of medication to prescribe for patients taking PrEP on demand should not preclude using this strategy when it is appropriate. Switching back and forth between daily and on-demand PrEP may be an appealing, evidence-based option for some individuals [Molina, et al. 2022; Hoornenborg(b), et al. 2017].

Evidence for the efficacy of on-demand dosing includes the results of the IPERGAY and Prevenir studies, which found that "2-1-1" dosing effectively prevented HIV acquisition in MSM [Molina, et al. 2015]. Concerns have been raised as to whether the efficacy observed in the IPERGAY study resulted from the frequency of dosing when PrEP was used on-demand in this study. The average number of PrEP doses taken per month by participants in the IPERGAY study was 15 (approximately 4 doses per week) [Molina, et al. 2015], which was the minimum level of adherence necessary for protection in the iPrEx study [Anderson, et al. 2012]. The iPrEx-OLE study, an open-label extension of the iPrEx study, confirmed that 4 or more doses of TDF/FTC as PrEP per week were protective [Grant, et al. 2014]. However, in a substudy of IPERGAY, PrEP dosed on demand remained effective even in participants with less frequent sexual activity [Antoni, et al. 2020]. The HPTN 067 ADAPT study investigated daily versus time-driven (twice per week with an additional dose after sex) versus event-driven dosing and found that adherence with event-driven dosing was lower than daily dosing [Velloza, et al. 2019].

TDF/FTC as PrEP for transgender women: 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. Levels of adherence needed for transgender women using estrogen and taking TDF/FTC for PrEP may be higher than for cisgender men, but the drug concentrations achieved with daily dosing of TDF/FTC as PrEP will confer protection (see guideline section PrEP for Individual at Risk of Acquiring HIV > PrEP Candidates > Transgender women).

The significance of this potential difference in tenofovir concentrations with regard to on-demand dosing for transgender women is less clear; therefore, on-demand dosing cannot be uniformly recommended for this population. However, if neither daily oral dosing nor injections are viable options for a transgender woman at high risk of acquiring HIV, it is reasonable to discuss the risks and benefits of on-demand dosing, including the lack of data, and engage the patient in informed, shared decision-making regarding this dosing strategy.

Not recommended: The effectiveness of on-demand TDF/FTC as PrEP for vaginal exposure has not been established. In the HPTN 067 ADAPT study, levels of orally administered tenofovir were much lower in the vagina than in the anal compartment [Anderson, et al. 2016]. Other data suggest that vaginal sex requires nearly 100% adherence to PrEP to achieve protective levels [Cottrell, et al. 2016]. Without more data, the differential pharmacokinetics for vaginal exposure with TDF/FTC as PrEP precludes a recommendation for on-demand dosing for cisgender women or transgender men engaging in receptive vaginal sex. Data are also lacking for men who have sex with women.

On-demand dosing cannot be recommended for protection against blood exposure. Based on data from the Bangkok Tenofovir Study, which studied TDF alone in people who inject drugs, it appears that the rate of PrEP adherence required for protection must be higher for people who inject drugs than for other populations [Choopanya, et al. 2013].

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 adverse effect in >10% of individuals in either arm [Mayer, et al. 2020].

Renal impairment and loss of bone density: Both have been observed in individuals taking TDF/FTC as treatment for HIV, 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 arms [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 [Pilkington, et al. 2018]. The meta-analysis did find a borderline statistically significant difference in creatinine elevation of all grades when comparing TDF/FTC with placebo and adding in grade 1 and 2 elevations.

The DISCOVER study, which compared TDF/FTC with TAF/FTC for PrEP, did find 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 [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 Patients Taking PrEP). If an increase in serum creatinine or a decrease in calculated CrCl is observed, evaluate potential causes other than TDF or TAF 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 cisgender MSM and transgender women with CrCl ≥30 mL/min. When appropriate, on-demand dosing of TDF/FTC can also be considered to decrease drug exposure for MSM with borderline renal function.

Bone density losses with TDF/FTC as PrEP are minimal and have not been associated with bone fractures [Havens, et al. 2020; Spinelli, et al. 2019]. No additional monitoring of bone mineral density is recommended.

For cisgender MSM and transgender women at high risk of fracture due to osteoporosis or at increased risk of developing osteoporosis, TAF/FTC is the preferred oral regimen and should be considered.

→ KEY POINT

- TAF/FTC is not recommended for on-demand dosing because there are no data currently available on intermittent dosing of this oral PrEP regimen.

Alternative Oral Regimen for Daily Dosing: TAF/FTC

TAF/FTC is an alternative PrEP regimen for cisgender MSM and transgender women.

When TAF/FTC is preferred: It is the preferred oral regimen for cisgender MSM and transgender women with preexisting renal disease or osteoporosis, and it may be preferable in MSM and transgender women with 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(a) 2019].

On-demand dosing: On-demand dosing has not been studied for TAF/FTC; this regimen should not be dosed on-demand in any population.

TAF/FTC was noninferior to TDF/FTC in cisgender MSM and in the small group of transgender women who participated in the DISCOVER trial, a large, double-blinded, active-control study [Mayer, et al. 2020]. In that trial, the TAF component was associated with improved biomarkers for renal and bone safety; however, the clinical significance of these changes is unclear, and there was no difference in clinical outcomes regarding adverse events. TAF use was associated with small increases in weight gain and low-density lipoprotein (LDL) cholesterol levels compared with TDF, but the clinical significance of these differences is unclear [Mayer, et al. 2020; Orkin, et al. 2018].

TAF may have an advantage in MSM and transgender female adolescents who have not achieved bone maturation, given favorable bone biomarkers compared with TDF, but this advantage is theoretical, and without clinical data, a clear recommendation cannot be made at this time [Havens, et al. 2020; Mayer, et al. 2020; Spinelli, et al. 2019; Hosek, et al. 2017].

TAF/FTC has not yet been studied for vaginal exposures in human trials. Study results to date suggest that tenofovir concentrations in vaginal tissue after administration of TAF are lower than for TDF [Cottrell, et al. 2017], although TAF does reach high intracellular concentrations in PBMCs, and oral TAF/FTC was effective in preventing vaginal simian HIV infections in macaques [Massud, et al. 2019]. Further study of TAF/FTC for protection in vaginal and injection HIV exposures is needed. TAF/FTC has also not been studied in insertive partners in the context of vaginal sex.

Common adverse effects: 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].

→ KEY POINTS

- Daily dosing is preferred for oral PrEP regimens based on robust existing data.
- On-demand PrEP with TDF/FTC is an alternative option for cisgender MSM.
- On-demand dosing with TDF/FTC may be appropriate for transgender women taking gender-affirming hormone therapy who are at high risk of HIV acquisition and cannot or will not take daily pills or injectable PrEP, after discussing the risks and limited data.
- There are no contraindications to on-demand dosing for transgender women who are not taking hormone therapy.
- On-demand dosing of TAF/FTC for PrEP has not been studied; TAF/FTC should not be dosed in this way.
- On-demand PrEP is not recommended for individuals who engage in vaginal sex, 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.

Manage adverse effects: Two weeks after oral PrEP initiation, a care team member should follow up 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 [Grant, et al. 2014; Grant, et al. 2010] and Partners [Mujugira, et al. 2016] trials of TDF/FTC as PrEP, rash was not reported as a common adverse effect. Patients who develop a rash while taking TDF/FTC or TAF/FTC as PrEP should be assessed for syphilis and acute HIV [Apoola, et al. 2002].

Preferred Injectable Regimen: CAB LA Every 2 Months

In December 2021, the FDA approved CAB LA for use as PrEP for sexual exposures in adults and adolescents weighing ≥35 kg [FDA(b) 2021].

HPTN 083, a study of a diverse multinational population of 4,566 MSM and transgender women, found CAB LA to be statistically superior to TDF/FTC in MSM and transgender women [Landovitz, et al. 2021]. HPTN 084, a study of 3,224 cisgender women in 7 sub-Saharan African countries, also found CAB LA to be statistically superior to TDF/FTC [Delany-Moretlwe, et al. 2022]. Both studies found CAB LA to be safe and well tolerated, with the main adverse effects being injection site reactions, which were generally mild and decreased in incidence over time.

When CAB LA is preferred: CAB LA is a preferred agent for protection against sexual exposure to HIV in adults and adolescents weighing ≥35 kg.

CAB LA is a preferred agent for individuals who are open to injectable PrEP, because of its statistically superior efficacy in preventing HIV compared with TDF/FTC and its protection against HIV through all types of sexual exposure [Delany-Moretlwe, et al. 2022; Landovitz, et al. 2021]. CAB LA is a good option when oral medication poses a challenge to PrEP use.

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 patients received a long-acting injection [Delany-Moretlwe, et al. 2022; Landovitz, et al. 2021]. There are no data on the safety or efficacy of CAB LA when used for PrEP without an oral lead-in.

However, in clinical trials of injectable long-acting CAB plus rilpivirine (CAB/RPV LA) for HIV-1 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 as PrEP. As a result, the oral lead-in phase for CAB LA as PrEP is now optional.

Some care providers or patients concerned about ensuring tolerability before initiating a long-acting treatment 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.

TDF/FTC (or TAF/FTC if appropriate) can be used as an alternative oral lead-in therapy for same-day initiation when oral CAB or CAB LA is not immediately available because of insurance or logistics issues. Some care providers may choose to briefly overlap oral TDF/FTC or TAF/FTC with CAB to maintain protection against HIV while CAB levels are attaining steady-state.

Oral CAB as bridge therapy: Oral CAB can also be used as bridge therapy when it is anticipated that an 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.

CAB LA injections: CAB LA as PrEP is administered as a 600 mg IM injection every 2 months after the first 2 injections are given 4 weeks apart. See Box 2, below, for details on the preparation and administration of CAB LA as PrEP.

The median time from the last injection to when CAB LA concentrations decreased below the lower limit of quantification was 43.7 weeks for male participants and 67.3 weeks for female participants in the HPTN 077 trial [Landovitz, et al. 2020]. Because of the long decay time for CAB LA to be eliminated, if a patient chooses to discontinue CAB LA and there is an ongoing risk for HIV exposure, they should be transitioned to an oral PrEP regimen 2 months after the last injection. 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 patients in the HPTN 083 study who acquired HIV during the tail phase had INSTI resistance mutations [Landovitz, et al. 2021].

Box 2: Preparation and Administration of CAB LA as PrEP (see package insert)

CAB LA as PrEP is given as a 3 mL (600 mg) deep IM gluteal injection. After the first injection, a second injection is administered 4 weeks later, after which injections are administered bimonthly (within 1 week before or after the next planned dose).

- 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.
- If a planned injection visit is missed by 8 weeks or more (i.e., 16 weeks after the previous dose), then the next 2 injections should be administered 4 weeks apart before returning to a bimonthly injection schedule.

Abbreviations: CAB LA, long-acting injectable cabotegravir; IM, intramuscular; PrEP, pre-exposure prophylaxis.

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. 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].

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].

CAB LA implementation: The logistics of implementing an injectable option in PrEP programs may be challenging and requires institutional, clinician, and patient preparation. Medication storage, scheduling and reminders, tracking systems, and staffing levels must be addressed with implementation plans appropriate to each setting (see Box 3, below).

Box 3: Implementation Strategies for Long-Acting Injectable Cabotegravir as PrEP

Institutional and clinician preparations:

- Assess pharmacy resources and on-site procedures for storage of oral and injectable medications.
- 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 a system to remind patients of appointments and make call-backs after missed doses.
- Plan for treatment continuation during pandemic-related shutdowns or other catastrophic events.
- Educate patients about the use of oral bridging therapy when appropriate.
- Educate patients about possible adverse effects of long-acting injectable cabotegravir and how to manage them.
- Ensure that patients know how to reach a medical care provider if needed.
- Schedule appointments for administration in advance.

Patient preparations:

- Obtain prior authorizations for insurance or third-party coverage.
- Confirm ability to maintain required clinic visit schedule for injections, including transportation availability.
- Confirm ability to adhere to the injection regimen.
- Confirm ability to tolerate a large-volume intramuscular injection regularly.

Abbreviation: PrEP, pre-exposure prophylaxis.

Engagement in Care

Engagement in care is a challenge for PrEP programs. Flexibility in visit frequency and provision of alternative modalities, such as telehealth, can enhance care access and engagement. The availability of both oral and injectable PrEP options increases choices for individuals and may also enhance persistence in care.

Challenges: Multiple studies have shown that persistence on PrEP remains a challenge [Wagner, et al. 2023; Blumenthal, et al. 2021; Chan, et al. 2016]. One study that examined PrEP programs in 3 midsized cities found the rate of persistence in PrEP care at 6 months to be 60%, owing to individual and structural barriers [Chan, et al. 2016]. “Overmedicalization” of PrEP care may pose a barrier to persistence by requiring healthy individuals to engage frequently with health care through at least quarterly clinic visits and laboratory tests. Although quarterly assessments remain the standard for oral PrEP monitoring, flexibility regarding in-person visits is encouraged when needed or appropriate. Quarterly laboratory testing is recommended even with a decision to adjust visit frequency, but flexibility for individual patients regarding this time frame is appropriate because quarterly screening is a best practice rather than an evidence-based recommendation. Barriers to engagement in care should be explored with all patients, and individualized solutions should be explored with those struggling to remain in care who wish to continue PrEP use. Novel models, such as annual visits with quarterly at-home HIV testing [Siegler, et al. 2019], are promising, and telemedicine visits should be encouraged when appropriate to remove structural barriers for patients having difficulty with PrEP persistence.

Injectable PrEP may increase PrEP uptake and persistence among individuals for whom regular oral medication is a barrier to care, those with preexisting renal disease, or those who prefer the convenience of an injection once every 2 months to daily oral PrEP. However, CAB LA as PrEP requires visits every 2 months for both monitoring and injections. This could be a barrier for patients who prefer visits only every 6 to 12 months (with quarterly laboratory tests in the interim), as indicated for current oral PrEP options, or who have life or work challenges that make visits every 2 months logistically challenging. Institutions will need sufficient appointment availability and flexibility in days and hours of care to increase access to care and persistence with CAB LA. Tracking systems and reminder calls can help increase adherence to injection visits. Alternative care models, including home visits for injections, will help increase access to this treatment.

Episodic PrEP: PrEP use may be noncontinuous, as individuals may cycle off and on PrEP based on fluctuations in their risk of acquiring HIV [Reed, et al. 2021]. Therefore, discontinuation of PrEP may not indicate program failure. However, for individuals who want to remain on PrEP, it is essential to remove barriers and individualize care.

Gender-affirming care: Transgender women have high rates of PrEP discontinuation [Scott, et al. 2019]. Providing gender-affirming and transition-related care to transgender individuals may increase PrEP uptake and persistence [Sevelius, et al. 2016]. Transgender women may avoid PrEP or miss doses because they are concerned that drugs active against HIV lower estrogen levels. Multiple studies have shown that TDF/FTC does not lower estrogen plasma concentrations [Blumenthal, et al. 2022; Grant, et al. 2021; Hiransuthikul, et al. 2019]. Addressing this directly with transgender women and providing reassurance regarding estrogen levels may improve their willingness to take and adhere to PrEP. Currently, there are no data directly evaluating the effect of TAF/FTC or CAB LA on estrogen plasma concentration; however, no interaction is expected based on the pharmacokinetic profiles of TAF/FTC and CAB LA and their lack of significant interactions with oral contraceptives.

Other services: Clinicians should partner with care providers within or outside of their organization to provide other services, including mental health and substance use treatment, case management, navigation and linkage services, housing assistance, and income/benefits assessments. Refer patients to support groups if indicated. However, PrEP should not be withheld from individuals who are not interested in primary care or who may choose to obtain PrEP from a location other than where they receive primary care.

→ KEY POINTS

- Individualized strategies to support PrEP adherence may improve PrEP persistence and PrEP adherence to recommended monitoring when an ongoing risk of HIV infection exists.
- 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 does not lower estrogen levels, and addressing this directly with transgender women may improve willingness to take and adhere to PrEP.
- Based on available data, TAF/FTC and CAB are also not expected to lower estrogen levels.

Adherence

Challenges: Daily adherence to oral PrEP is challenging for some patients for a wide variety of complex and intersecting reasons, including pill counts and sizes, adverse effects related to PrEP medications, privacy concerns, PrEP-related stigma, neurocognitive disorders, mental health conditions, active substance use, psychological trauma, personal belief systems, travel requirements, occupation, and health literacy. Although the availability of a once-daily single-tablet oral option for PrEP is helpful to adherence, studies and real-world experience demonstrate ongoing challenges with adherence to daily oral PrEP for some individuals. The use of long-acting agents for PrEP can potentially address the adherence challenges that some individuals face, and studies have shown a high interest in long-acting agents for PrEP in the general population and in specific subpopulations [Philbin, et al. 2021; Koren, et al. 2020; Rael, et al. 2020; Meyers, et al. 2014]. CAB LA is the only long-acting injectable PrEP option currently approved by the FDA; however, other injectable and long-acting agents are under study.

The degree of adherence to TDF/FTC as PrEP required to prevent HIV varies by exposure site. Based on modeling studies of rectal exposure, 4 doses per week of TDF/FTC appears sufficient to protect against HIV [Grant, et al. 2014]; however, modeling studies also suggest that vaginal and injection HIV exposures require closer to 7 doses of TDF/FTC per week for efficacy [Cottrell, et al. 2016; Choopanya, et al. 2013; Patterson, et al. 2011]. There are no data on adherence needed for penile insertive exposure. Currently, no data are available regarding adherence levels required for TAF/FTC or CAB LA effectiveness.

Strategies for adherence support: In studies of TDF/FTC as PrEP, efficacy was highly dependent on adherence [Sidebottom, et al. 2018], and on-time injections of CAB LA are essential to avoiding viral breakthrough [Landovitz, et al. 2021]. Some reasons for decreased adherence are adverse effects, fear of long-term toxicity, perceived low risk of infection, insurance issues, depression, substance use, and difficulty with daily dosing. For patients who struggle with adherence to PrEP, strategies such as more frequent visits or contact with medical and nonmedical care providers may be helpful. Adherence decreased when visits went from monthly to quarterly in adolescent patients [Hosek, et al. 2017]. Assessing and addressing individual reasons for suboptimal adherence to PrEP is important [Goodreau, et al. 2018; Jenness, et al. 2016].

Some care providers use peer supporters to reinforce adherence to medication and appointments. If patients are consistently unable to adhere to an oral PrEP regimen despite interventions to improve adherence or if they decline to take oral PrEP daily, it may be appropriate to explore alternative dosing schedules, such as on-demand PrEP (for cisgender MSM only, with TDF/FTC), injectable PrEP, or seasonal or vacation use of PrEP. It may also be appropriate to discuss discontinuing PrEP and using other risk-reduction strategies that better meet the needs of the individual.

→ KEY POINTS

- The minimum degree of adherence to TDF/FTC as PrEP required for protection against HIV varies by site of exposure. Nevertheless, a high degree of adherence is essential.
- Data regarding the degree of adherence needed for TAF/FTC or CAB LA as PrEP are not currently available.

PrEP During Pregnancy

HIV acquisition risk is higher in pregnancy and is highest in the late pregnancy and early postpartum periods [Thomson, et al. 2018], and PrEP should be recommended if the risk of HIV exposure continues. Risk of perinatal transmission is also significantly higher during pregnancy and breastfeeding in cases of acute seroconversion [Drake, et al. 2014; Singh, et al. 2012]. Encourage pregnant individuals to inform their obstetric and pediatric care providers when using PrEP medications or any other prescription or over-the-counter medications.

TDF/FTC: Pregnancy is not a contraindication to the use of TDF/FTC as PrEP. Clinicians should counsel pregnant patients about the risks and benefits of continuing TDF/FTC for HIV prevention during pregnancy. Available data suggest that TDF/FTC as PrEP does not increase the risk of congenital anomalies (the use of ART medications during pregnancy is monitored through the Antiretroviral Pregnancy Registry). 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]. One study suggested up to a 15% decrease in bone mineral density in infants exposed to TDF in utero compared with infants who were not exposed to TDF [Siberry, et al. 2015], whereas another study found no association between in utero TDF exposure and infant bone mineral density [Vigano, et al. 2011]. In a study of pregnant women who did not have HIV in whom TDF was used as prophylaxis to prevent transmission of HBV, there was no difference in bone mineral density at 1 year in TDF-exposed infants compared with infants not exposed to TDF in utero [Salvadori, et al. 2019].

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]. Longer-term follow-up studies of TDF-exposed infants are ongoing and will provide further information and guidance on the use of PrEP in this population [Mugwanya, et al. 2016]. 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.

CAB LA: There are insufficient data on the safety of CAB LA as PrEP in pregnancy, and CAB LA should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus. In animal reproduction studies, parturition was delayed, and stillbirths and neonatal deaths increased when oral CAB was given at >28 times the recommended human dose [FDA(a) 2021]. More data should become available over time. In the interim, care providers should recommend that individuals planning to conceive or become pregnant while receiving CAB LA as PrEP switch to TDF/FTC if it is an appropriate option and they wish to continue PrEP.

Laboratory Testing Before PrEP Initiation

☑ RECOMMENDATIONS

Laboratory Testing Before PrEP Initiation

- 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).

☑ RECOMMENDATIONS

- Clinicians should perform baseline laboratory testing as recommended in Table 3: Recommended Laboratory Tests for All Patients Within 1 Week Before Initiating PrEP.
- Clinicians should recommend same-day PrEP initiation pending laboratory test results 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 (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 same-day initiation is not an option, clinicians should repeat lab-based HIV-1/2 Ag/Ab and HIV RNA testing if more than 1 week has lapsed since HIV testing was performed (A3) and should ensure that the HIV test results are available and acted upon within 7 days of initiation. (A3)
- If a patient has been exposed to HIV within the previous 72 hours, the clinician should recommend PEP before PrEP (A1).
- Clinicians should not wait to initiate PrEP in individuals who may be in the window period for seroconversion when an HIV test cannot detect infection; doing so risks additional exposures and significant delays in PrEP (A*).
- If a patient has a positive HIV test result within 1 week 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 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. (A1) To consult an expert, call the NYSDOH AI CEI Line at 1-866-637-2342.
- Clinicians should repeat HIV testing 1 month after PrEP initiation in patients who report a risk exposure in the 30 days before initiation of PrEP. (A2†)

Resource: Appendix: Care Provider Checklists for PrEP Initiation, Regimen Choice, and Follow-Up

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

HIV Testing

Risk assessment: Before starting PrEP, all patients should be evaluated for possible HIV infection and assessed for acute HIV. The goal of risk assessment is to identify potential HIV exposures in the prior 4 weeks and flu- or mono-like symptoms in the previous 6 weeks.

Both an HIV-1/2 Ag/Ab combination immunoassay and an HIV RNA test should be performed within 1 week before PrEP is started. HIV RNA (viral load) testing is performed 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 patients with undiagnosed HIV who initiated PrEP with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC; brand name Truvada), tenofovir alafenamide/emtricitabine (TAF/FTC; brand name Descovy), or CAB LA [Molina, et al. 2022; Landovitz, et al. 2021; Cox, et al. 2020; Lehman, et al. 2015].

Same-day initiation of oral PrEP: Once laboratory specimens are obtained (see Table 3, below), PrEP may be initiated while test results are pending if the patient 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, as long as laboratory results will be available and addressed within 7 days and a rapid HIV test result is negative. In HIV care, the rapid start of treatment has been shown to better engage patients in care [Ford, et al. 2018]. Same-day initiation of PrEP has been shown to be safe, and delayed initiation of PrEP 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 patients more fully in care and reduce exposures to HIV 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 risks starting a nonsuppressive ART regimen in someone with HIV. However, if laboratory results are available promptly, then 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 CAB is initiated, the care provider 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). TAF/FTC may require a prior authorization, which makes same-day initiation a challenge, but generic TDF/FTC is usually available for same-day initiation.

Same-day initiation of an oral CAB lead-in or CAB LA: If prior insurance authorization is required, same-day CAB initiation (oral or injection) may not be an option. Implementation challenges such as stocking and storing medications in advance may also be prohibitive. If same-day CAB initiation is not an option, prescription of an oral regimen should be discussed as an interim option while barriers to accessing CAB LA injections are addressed.

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

→ KEY POINT

- Same-day initiation of PrEP is the goal whenever possible.

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 initiation to help identify potentially positive individuals in a timely manner (see guideline section Ongoing Laboratory Testing).

Recommended Laboratory Testing

Table 3, below, lists the baseline laboratory tests that should be performed at the pre-prescription visit for individuals who will initiate PrEP. When an individual is engaged in care to receive PrEP, primary healthcare may be offered as indicated, including vaccinations against hepatitis A and B viruses, human papillomavirus, meningococcus, influenza, and COVID-19.

For more information, see Centers for Disease Control and Prevention Recommended Adult Immunization Schedule for Ages 19 Years or Older, United States, 2022 and COVID-19 ACIP Vaccine Recommendations and NYSDOH Health Advisory: NYSDOH Meningococcal Vaccine Recommendations for HIV-Infected Individuals and Those at High Risk of HIV Infection.

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

Purpose (rating)	Test	Comments
HIV status (A*)	• Baseline HIV-1/2 Ag/Ab combination immunoassay [b] • HIV RNA assay	• For same-day initiation, a rapid HIV test plus a laboratory-based test is required • A negative HIV test result more confidently rules out acute HIV infection, as patients may be reluctant to disclose risk behavior
Renal function (A*)	Serum creatinine and calculated CrCl	• **TDF/FTC:** Do not initiate or continue in patients with confirmed CrCl <60 mL/min • **TAF/FTC:** Do not initiate or continue in patients with confirmed CrCl <30 mL/min • **CAB LA:** Increase monitoring for adverse effects in patients with CrCl <30 mL/min
Pregnancy status (A3)	Pregnancy test for all individuals of childbearing potential	• Discuss the importance of preventing HIV during pregnancy with anyone contemplating pregnancy or who becomes pregnant while taking PrEP • **TDF/FTC:** Discuss risks, benefits, and available data suggesting no increased risk of congenital anomalies • **TAF/FTC and CAB LA:** Discuss the lack of data regarding safety during pregnancy

Table 3: Recommended Laboratory Tests for All Patients Within 1 Week Before Initiating PrEP [a]		
Purpose (rating)	**Test**	**Comments**
HBV infection status (A2†)	HBV serologies: HBsAg, anti-HBs, and anti-HBc (IgG or total)	• Vaccinate nonimmune patients (A2) • **Chronic HBV:** Treat and monitor HBV [c] or refer to an HBV specialist
Syphilis screening (A2†)	All patients: Syphilis testing [d]	Screen for syphilis according to the laboratory's testing algorithm [d]
Gonorrhea and chlamydia screening (A2†)	• All patients, all potential exposure sites: NAAT [d] • MSM and transgender women: Routine 3-site testing (genital, rectal, and pharyngeal) regardless of reported exposure sites	• Detecting urethral infection: Urine specimens are preferred over urethral specimens • Vaginal and cervical testing: Vaginal swabs are preferred over urine-based testing • Transgender women with a neovagina: Data are insufficient to support a recommendation regarding urine-based testing vs. vaginal swab [e] • Self-collected swabs from the pharynx, vagina, and rectum are reasonable and noninferior options for patients who may prefer them over clinician-obtained swabs
HCV infection status (A3)	HCV serology with reflex to RNA	Inform patients 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 for HAV infection; see footnote [g]	Vaccinate nonimmune patients
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

Abbreviations: Ab, antibody; Ag, antigen; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; CAB LA, long-acting injectable cabotegravir (brand name 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; MSM, men who have sex with men; NAAT, nucleic acid amplification test; TAF/FTC, tenofovir alafenamide/emtricitabine (brand name Descovy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (brand name 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 Hepatitis B Virus 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 in the absence of HAV vaccination.

→ SELECTED GOOD PRACTICE REMINDERS [a]

Follow-up after PrEP initiation:

- Instruct patients to notify their care provider immediately if they experience adverse effects.
- Oral PrEP: Within 2 weeks, ensure that the patient has filled the PrEP prescription, understands how to take the medication, knows how to manage any adverse effects, and has identified and solved any problems with payment for PrEP.
- Injectable PrEP: Within 1 week of the first injection, assess for tolerability and injection site reactions.

At each visit [b]:

- Make every effort to avoid discontinuing PrEP or withholding it from a patient at risk of acquiring HIV.
- Inquire about adverse effects and offer advice for management if needed.
- Assess adherence, identify challenges, and discuss strategies for maintaining adherence.
- Schedule the next visit, arrange for confirmation and reminders, and individualize ongoing care and monitoring to meet the patient's needs; explore alternative modalities such as telehealth visits and in-home testing.
- Offer contraception to individuals of childbearing potential who wish to avoid pregnancy while using PrEP.

Risk reduction:

- At each visit, discuss risk reduction as essential to sexual health; offer female/receptive or male/insertive condoms.
- For patients who inject drugs or misuse mood-altering drugs, refer for substance use treatment and mental health support as appropriate.
- Prescribe clean syringes and needles or refer to needle-exchange programs as indicated (see NYSDOH Expanded Syringe Access Program (ESAP): Overview of the Law and Regulations and Directory of New York State Syringe Exchange Programs).

Notes:

a. See Appendix: Care Provider Checklists for PrEP Initiation, Regimen Choice, and Follow-Up.
b. 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.

Ongoing Laboratory Testing

☑ RECOMMENDATIONS

HIV Testing

- For any patient who reports an exposure to HIV that occurred in the 30 days before PrEP initiation, clinicians should repeat HIV testing 30 days after the patient starts PrEP. (A2†)
- Clinicians should perform an FDA-approved plasma or serum HIV-1/2 Ag/Ab combination immunoassay every 3 months in patients taking oral PrEP. (A3)
- Clinicians should perform an HIV-1/2 Ag/Ab combination immunoassay and HIV RNA test in patients 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 patients who report missing PrEP doses during times of sexual activity and possible HIV exposure. (A3)
- For patients receiving CAB LA, clinicians should perform an HIV-1/2 Ag/Ab combination immunoassay and HIV RNA test at every injection visit; if the patient completed an oral CAB lead-in, the clinician should perform an HIV-1/2 Ag/Ab combination immunoassay and HIV RNA test upon completion. (A2)
- Regardless of the PrEP regimen used, clinicians should perform an HIV-1/2 Ag/Ab combination immunoassay and HIV RNA test whenever there has been an interruption in PrEP of >1 week with a risk of exposure during that time off PrEP. (A3)

Renal Function Testing

- Clinicians should perform renal function testing (serum creatinine level and calculated CrCl) as recommended in Table 4: Recommended Routine Laboratory Testing for Patients Taking PrEP.

☑ RECOMMENDATIONS

- Clinicians should discontinue daily TDF/FTC as PrEP if a patient develops a confirmed CrCl <50 mL/min and consider alternative options; see discussion in text for options for patients with reduced renal function. (A3)
- Clinicians should discontinue TAF/FTC as PrEP if a patient develops a confirmed calculated CrCl <30 mL/min. (A3)
- Clinicians should perform urinalysis at baseline and annually to assess urine glucose and protein in patients taking tenofovir-based oral PrEP. (B3)

STI Screening

- At every visit, a care team member should assess patients 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 Patients Taking PrEP.

HCV Screening

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

Pregnancy Screening

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

Resource: Appendix: Care Provider Checklists for PrEP Initiation, Regimen Choice, and Follow-Up

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

Services for follow-up and monitoring of patients 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 Patients Taking PrEP

	Laboratory Testing Indications		
Test	**All PrEP Regimens**	**Oral PrEP With TDF/FTC or TAF/FTC**	**Injectable PrEP With CAB LA**
HIV-1/2 Ag/Ab combination immunoassay [a]	• When a patient has symptoms of acute HIV infection [b] (A2) • 1 month after PrEP initiation if an HIV exposure occurred ≤1 month before the start of PrEP (A2†)	• Every 3 months (A3) • When PrEP has been interrupted for >1 week in the past month and a potential exposure occurred (A3) • When a patient reports missing PrEP doses during times of sexual activity and possible HIV exposure (A3)	• At the end of the oral CAB lead-in (if used) (A2) • Every injection visit (A2)
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) • When a patient reports missing PrEP doses during times of sexual activity and possible HIV exposure (A2)	• At the end of the oral CAB lead-in, if implemented (A2) • At every injection visit (A2)

Table 4: Recommended Routine Laboratory Testing for Patients Taking PrEP			
	Laboratory Testing Indications		
Test	**All PrEP Regimens**	**Oral PrEP With TDF/FTC or TAF/FTC**	**Injectable PrEP With CAB LA**
Serum creatinine and calculated CrCl	—	• 3 months after oral PrEP initiation (B3) • Every 6 months thereafter (A3) • Consider more frequent screening in those at high risk, e.g., >40 years old, other comorbidities (A3)	At least annually (A3)
Syphilis screening (A2†) Note: Screening can be less frequent in those at lower risk	• At baseline • Ask about symptoms at every visit; if present, perform diagnostic testing and treat as indicated	Every 3 months	Every 2 to 4 months based on reported risk
HCV serology [d]	At least annually if at risk (A3)	—	—
Pregnancy test in patients of childbearing potential	• At every visit, assess for the possibility of pregnancy (A3) • Test for pregnancy when appropriate and on patient request (A3) • Offer contraception when requested or indicated (A3)	—	—
Urinalysis	N/A	Annually (B3)	N/A

Abbreviations: Ab, antibody; Ag, antigen; CAB, cabotegravir (brand name Vocabria); CAB LA, long-acting cabotegravir (brand name Apretude); CrCl, creatinine clearance; HCV, hepatitis C virus; MSM, men who have sex with men; NAAT, nucleic acid amplification test; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide/emtricitabine (brand name Descovy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (brand name 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 patients who prefer them over clinician-obtained swabs. See STI self-collection outside of a clinic setting in New York State Question & Answer.
d. See NYSDOH AI guideline Hepatitis C Virus Screening, Testing, and Diagnosis in Adults.

HIV Testing

For individuals taking 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, or CAB LA in the presence of HIV 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 patients who are stable on oral PrEP.

Breakthrough HIV infections among individuals adherent to oral PrEP are rare. When failure of an oral PrEP regimen (TDF/FTC or TAF/FTC) occurs, it is usually associated with poor adherence and is infrequently associated with the development of resistance. When drug resistance does develop, 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 patients 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 POINTS

Routine HIV RNA testing is not recommended for individuals stable on 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 the detection of new infections.
- Failure of these regimens infrequently leads to resistance.
- The M184V/I mutation has little impact on response to HIV treatment, including initial therapies.

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 patient. 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. It is reasonable for patients established on oral PrEP to be tested for HIV every 3 months, either on-site or at an outside laboratory, and to 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 PrEP access and monitoring barriers.

Routine HIV testing with CAB LA: CAB LA injections are administered at in-office visits every 2 months; there are currently no alternative administration models. HIV 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 testing should include an HIV-1/2 Ag/Ab combination immunoassay *and* HIV RNA test using FDA-approved tests and sample types (plasma or serum). Studies have reported atypical test results with missed diagnoses when the Centers for Disease Control and Prevention/American Public Health Laboratories Laboratory Testing Algorithm in Serum/Plasma was used with individuals on antiretroviral therapy (ART) at the time of HIV seroconversion. In the HPTN 083 study, there was a median delay of 62 days from the time of infection to HIV diagnosis for unrecognized baseline infections in individuals on CAB LA, and of 98 days for incident infections, with the subsequent development of integrase resistance mutations in 5 individuals [Eshleman, et al. 2022; Marzinke(a), et al. 2021].

Because there may be delays in HIV-1/2 Ag/Ab combination immunoassay positivity and indeterminate or negative results for supplemental HIV-1/HIV-2 Ab differentiation tests, concomitant routine HIV RNA testing can improve timely detection of breakthrough HIV infection.

ART can blunt viral load response. In one study, qualitative RNA testing was the most reliable detection method in cases with retrospective testing; however, the sensitivity of newer quantitative viral load tests is equal to available qualitative RNA tests. [Marzinke(a), et al. 2021].

HIV testing if exposure is suspected: For patients 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 patients 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 taking 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 the safe use of PrEP.
- If an individual taking 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 transmission of HIV if HIV seroconversion has occurred.

Routine Laboratory Testing

Renal function testing: One sign of tenofovir toxicity is the development of proteinuria. A baseline urinalysis helps to identify preexisting proteinuria before initiating PrEP. 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 the use of creatine supplements.

More frequent creatinine screening may be appropriate in individuals >40 years old because renal toxicity is more likely to occur in this population [Gandhi, et al. 2016]. More frequent screening may also be appropriate for patients with comorbidities, such as diabetes or hypertension, and patients taking concomitant nephrotoxic drugs that might increase the risk of renal dysfunction.

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

STI screening: Many patients who elect to initiate PrEP are at high risk of acquiring STIs, including syphilis and gonorrheal and chlamydial infections. Initiating PrEP care for individuals at risk for HIV provides an opportunity for routine STI monitoring and treatment. One modeling study demonstrated that increased PrEP engagement along with routine STI screening and treatment would lower STI rates through detection and treatment of asymptomatic STIs that might otherwise remain undiagnosed [Jenness, et al. 2017].

Data from New York State and other jurisdictions show high rates of STIs, a majority of which are asymptomatic, making an inquiry about symptoms insufficient, and supporting testing for syphilis and gonococcal and chlamydial infections at frequent intervals [Tang, et al. 2020; Golub, et al. 2016; Liu, et al. 2016]. Less frequent testing can be considered for individuals at lower risk of acquiring STIs. However, frequent testing leads to early diagnosis and treatment of asymptomatic STIs and can decrease the development of complicated infections, such as neurosyphilis or pelvic inflammatory disease, and decrease transmission to sex partners.

STI testing is recommended every 3 months for individuals taking oral PrEP. Individuals receiving CAB LA as PrEP require visits every 2 months; STI screening can be performed at each injection visit for those at highest risk or every 4 months for those with average risk. The frequency of STI screening in all patients on PrEP can be adjusted based on risk assessment and occur less often in those at low risk for STI acquisition.

Routine syphilis serologic testing should be performed for all patients taking PrEP, and all patients should be asked about anatomic sites of potential exposure and screened for gonococcal and chlamydial infections accordingly. Men who have sex with men (MSM) and transgender women have particularly high rates of extragenital STIs, and performing only urine-based

screening misses a majority of infections [Pitasi, et al. 2019; Patton, et al. 2014]. Three-site testing (genital, pharyngeal, and rectal) for gonococcal and chlamydial infections should be the default testing plan for MSM and transgender women unless such testing is declined because of lack of exposure at a site. A recent study 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 as well.

Because nucleic acid amplification testing has much higher sensitivity than culture, it is preferred for the diagnosis of gonococcal or chlamydial infection. The U.S. Food and Drug Administration has approved diagnostic extragenital gonorrhea and chlamydia tests [FDA(b) 2019], making access to testing more readily available.

Vaginal swabs are preferred over urine-based testing for cervical infections because of their sensitivity. For urethral infections, urine testing is preferred 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-obtained swabs for vaginal, rectal, and pharyngeal specimen types have performed well in many studies and are preferred by many patients (see STI self-collection outside of a clinic setting in New York State Question & Answer) [Dize, et al. 2016; Lunny, et al. 2015; Workowski and Bolan 2015; Taylor, et al. 2013].

→ 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.
- STI rates decline as the number of at-risk individuals who initiate PrEP increases and continue to decline as the frequency of STI testing increases, even with a 40% to 80% decrease in condom use [Jenness, et al. 2017].

Annual HCV screening: An increased risk for HCV acquisition has been noted in MSM using PrEP [Price, et al. 2019; Hoornenborg(b), et al. 2017]. MSM with HIV [Fierer and Factor 2015; Bradshaw, et al. 2013; Fierer 2010] and to a lesser degree MSM without HIV [McFaul, et al. 2015] are at increased risk for acute HCV. A case-control study of MSM with HIV found that the presence of recent ulcerative STIs or risk behaviors, such as unprotected receptive anal intercourse, sharing of sex toys, unprotected fisting, injecting drugs, and sharing straws when snorting drugs, contributed to an increased risk of HCV acquisition [Vanhommerig, et al. 2015]. These may also be important risk factors in the general population. New elevations in liver enzymes can be a sign of acute HCV. Annual screening for HCV in MSM, transgender women, and individuals using injection drugs who are using PrEP is recommended, with more frequent screening considered for those at highest risk or with any elevations of liver function tests.

Pregnancy screening: In individuals of childbearing potential taking PrEP, routine assessment for the possibility of pregnancy and testing as appropriate decrease potential concerns associated with unplanned pregnancies. Individuals of childbearing potential who are using PrEP and wish to avoid pregnancy should be offered contraception. TDF/FTC as PrEP does not affect levels of hormonal contraceptives, and CAB LA does not affect levels of oral contraceptives and is not expected to affect levels of long-acting contraception.

Managing a Positive HIV Test Result

☑ RECOMMENDATIONS

Suspected Acute HIV

- For patients 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)

☑ RECOMMENDATIONS

- Clinicians should inform patients 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 the risk of transmitting HIV to a partner without HIV until acute infection is ruled out. (A2)

Asymptomatic Patients With a 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

TDF/FTC, TAF/FTC, or CAB LA used as PrEP may alter viral load and immune response and cause ambiguous HIV test results when following the current CDC/APHL HIV testing algorithm.

- Clinicians should consider a reactive HIV-1/2 Ag/Ab combination immunoassay result with a positive qualitative HIV RNA or a quantitative HIV RNA of any level a positive HIV test result. (A2)
- In the case of an ambiguous HIV test results (a reactive HIV-1/2 Ag/Ab combination immunoassay result 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 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 or Ambiguous HIV Test Result

- For patients taking TDF/FTC or TAF/FTC as PrEP, clinicians should add a third antiretroviral agent with a high resistance barrier, such as DRV/COBI, DTG, or BIC (available as TAF/FTC/BIC) while awaiting resistance test results. (A2)
- For patients receiving CAB LA, clinicians should initiate ART with a non-INSTI-based regimen while awaiting resistance test results. (A2)

Abbreviations: Ag/Ab, antigen/antibody; APHL, Association of Public Health Laboratories; ART, antiretroviral therapy; BIC, bictegravir; CAB LA, long-acting injectable cabotegravir (brand name Apretude); CDC, Centers for Disease Control and Prevention; CEI, Clinical Education Initiative; DRV/COBI, cobicistat-boosted darunavir (brand name Prezcobix); DTG, dolutegravir (brand name Tivicay); INSTI, integrase strand transfer inhibitor; PrEP, pre-exposure prophylaxis; TAF/FTC, tenofovir alafenamide/emtricitabine (brand name Descovy); TAF/FTC/BIC, tenofovir alafenamide/emtricitabine/bictegravir (brand name Biktarvy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (brand name Truvada).

Suspected Acute HIV

Vigilance for signs and symptoms of potential HIV seroconversion in patients receiving PrEP is crucial. TDF/FTC, TAF/FTC, or CAB LA as PrEP are not adequate treatments for acute or chronic HIV infection, and continued use in the presence of HIV may lead to the emergence of viral resistance to these drugs.

The mean time from HIV exposure to onset of symptoms is generally 2 to 4 weeks, with a range of 5 to 29 days; however, some patients 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 patients who acquire HIV while on PrEP, and symptoms of acute HIV infection may be blunted by TDF/FTC, TAF/FTC, or CAB use. While evaluating patients for acute HIV, advise them to refrain from sexual activity or use condoms to minimize the risk of transmitting HIV to a partner without HIV.

For patients 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 initiation of ART.

For patients who have a nonreactive HIV test result but have an HIV RNA level <200 copies/mL, clinicians should repeat HIV RNA testing and repeat 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 presence of TDF/FTC, TAF/FTC, or CAB. Unless suspicion for acute HIV is low, initiate ART while a definitive diagnosis is sought.

Asymptomatic Patients With a Reactive HIV Screening Test Result

HIV acquisition in patients who are fully adherent to oral PrEP is rare. If a patient taking oral PrEP tests positive for HIV on a routine HIV-1/2 Ag/Ab combination immunoassay, determine if there has been any medication interruption or decreased adherence. A false-positive test result is more likely to occur when patients are not fully adherent to PrEP. There is an increased possibility of a true-positive test result if an individual reports gaps in adherence, medication access, or symptoms consistent with acute HIV in the period since their last HIV test. There are no commercially available tests of TDF concentrations to confirm longer-term adherence in someone with possible seroconversion on PrEP. Hair samples and dried blood spots are utilized as tests in research only. Because false-positive HIV-1/2 Ag/Ab combination immunoassay results do occur and there is a risk of HIV exposure if PrEP is discontinued, it is recommended that PrEP be continued. Clinicians should decide whether to continue PrEP or intensify to a fully suppressive ART regimen (see above) while awaiting confirmatory test results based on the degree of suspicion for a false-positive versus a true-positive HIV test result. Clinicians should perform supplemental diagnostic testing as soon as possible according to the standard HIV laboratory testing algorithm.

For asymptomatic patients with a positive HIV test result who are receiving CAB LA, assess for missed injections or adherence to the oral CAB during lead-in (if implemented). If PrEP has been interrupted, there is a much higher likelihood of a true-positive HIV test result. There were 4 breakthrough HIV infections with CAB LA despite on-time injections in the HPTN 083 study [Landovitz, et al. 2021], although there were no breakthrough infections with on-time injections in the HPTN 084 study [Delany-Moretlwe, et al. 2022]. Therefore, adherence to the CAB LA injection schedule does not guarantee protection, although breakthrough infections are uncommon. If a patient is nonadherent to either oral or injectable CAB, the clinician should prescribe a non-INSTI-based ART regimen, as discussed above, while awaiting confirmation of HIV and resistance test results. If a patient has been receiving injections on time, the possibility of a false-positive HIV test is higher, and the clinician can choose whether to await confirmation or prescribe a non-INSTI-based ART regimen pending test results.

If supplemental laboratory testing confirms HIV infection, 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 in ART Selection For Patients Who Acquire HIV While on PrEP, below.

→ KEY POINTS

- Clinicians must report confirmed cases of HIV according to New York State Law (see NYSDOH Provider Reporting & Partner Services).
- Offer assistance notifying partners or refer patients to other sources for partner notification assistance (see New York City Health Contact Notification Assistance Program).
- **Reporting of suspected seroconversion on PrEP:** Clinicians who manage the care of patients on PrEP are strongly encouraged to immediately report any cases of suspected PrEP/PEP breakthrough HIV infection.
  - **In New York City:** Report cases to the New York City Department of Health and Mental Hygiene immediately by calling 212-442-3388 and following the directions detailed in the attached Health Alert.
  - **Rest of state:** Report cases to the NYSDOH by calling 518-474-4284 or using the Medical Provider Report Form (DOH-4189) and contacting the local Partner Services Program to discuss the case (see November 2016 NYSDOH/NYC Health Dear Colleague Letter).

Ambiguous HIV Test Results

The use of TDF/FTC, TAF/FTC, or CAB LA as PrEP may alter viral load and immune response and cause ambiguous HIV test results when the current CDC/APHL HIV testing algorithm is followed [Zucker, et al. 2018; Hoornenborg(a), et al. 2017; Knox, et al. 2017; Markowitz, et al. 2017]. Viral load may be suppressed. An HIV-1/2 Ag/Ab combination immunoassay may be reactive, but supplemental testing (HIV-1/HIV-2 Ab differentiation, HIV RNA, or Western blot) may not consistently be reactive, or the time to reactivity may be delayed. In the HPTN 083 study of CAB LA as PrEP, in which there were 12 incident HIV infections, the use of HIV Ag/Ab testing alone led to a significant delay in detection of HIV infection, and retrospective analysis found ambiguous test results [Marzinke(a), et al. 2021].

In cases of ambiguous HIV test results in individuals taking PrEP, repeat HIV testing in a few days may resolve ambiguity if the initial results were due to early infection or technical issues.

If ambiguity persists, the options are to 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 patient does have HIV. However, discontinuing PrEP leaves an uninfected individual at risk. 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 (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]).

ART Selection For Patients Who Acquire HIV While on PrEP

Because HIV acquisition in individuals taking oral PrEP is most often due to nonadherence, the majority of infections are found to be wild-type virus. When resistance does occur, FTC-associated resistance due to the emergence of the M184V/I mutation is commonly found; tenofovir-associated resistance with the K65R mutation is rare [Girometti, et al. 2022; Mayer, et al. 2020; Lehman, et al. 2015]. Among individuals receiving CAB LA in the HPTN 083 study, INSTI-associated mutations were observed in 1 individual with baseline HIV infection and 4 individuals with incident HIV infection [Landovitz, et al. 2021]. No participants in the HPTN 084 study developed INSTI resistance [Marzinke(b), et al. 2021]. There are no definitive protocols for specific antiretroviral agents to use in the case of suspected seroconversion in individuals taking PrEP. However, for patients taking oral PrEP, given the rarity of tenofovir-associated mutations during PrEP use, a reasonable option would be to continue TDF/FTC or TAF/FTC and add a third agent with a high resistance barrier, such as DRV/COBI, DTG, or BIC (available as TAF/FTC/BIC) while awaiting HIV confirmation and resistance test results. For patients receiving CAB LA, initiation of a non-INSTI-based ART regimen is recommended 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 more information, see the NYSDOH AI guidelines Rapid ART Initiation and Selecting an Initial ART Regimen.

Discontinuing PrEP

☑ RECOMMENDATIONS

Discontinuing PrEP

- Clinicians should discontinue PrEP in any patient with a confirmed positive HIV test result (see recommendations in guideline section Managing a Positive HIV Test Result). (A1)
- Clinicians should discontinue PrEP if a patient does not adhere to HIV testing requirements despite repeated efforts at engagement in care. (A3)
- Clinicians should discontinue TDF/FTC as PrEP in patients who develop a confirmed calculated CrCl <50 mL/min. (A2)
- For patients who develop kidney dysfunction and must discontinue TDF/FTC but wish to continue with PrEP, clinicians should switch their regimen to CAB LA or to TAF/FTC if CrCl is ≥30 mL/min (for MSM and transgender women only). (A3)
- Clinicians should closely monitor patients with chronic HBV infection for a potential viral rebound when PrEP with TDF/FTC or TAF/FTC is discontinued and develop an alternative treatment plan if necessary. (A2)

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

The 2-drug PrEP regimens of TDF/FTC and TAF/FTC and the single-drug regimen of CAB LA are not adequate as HIV antiretroviral therapy (ART). If HIV infection is confirmed, PrEP should be converted immediately to a fully suppressive HIV ART regimen (see guideline section Managing a Positive HIV Test Result).

Renal function should be monitored 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, spurious elevations due to creatine supplementation, or recent heavy exercise leading to muscle breakdown, and repeat testing to confirm the finding before considering discontinuation. To decrease drug exposure, on-demand TDF/FTC dosing can be considered for MSM with borderline renal function.

TDF/FTC as PrEP should be discontinued in patients who develop a confirmed CrCl <50 mL/min to avoid further toxicity. Although TDF/FTC for treatment of HIV can be adjusted to every-other-day dosing in patients 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 MSM and transgender women with CrCl ≥30 mL/min. CAB LA as PrEP is an option for all individuals with renal dysfunction who are at risk for HIV infection via sexual exposure. Increased monitoring for adverse effects is recommended for those with severe or end-stage renal impairment.

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. 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.

Because discontinuation of TDF/FTC or TAF/FTC in patients with chronic, active HBV 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 CDC Recommendations for Routine Testing and Follow-up for Chronic Hepatitis B Virus Infection.

→ KEY POINTS

- PrEP can be discontinued for individuals no longer at risk of HIV acquisition because they have eliminated the sex or drug use behaviors that put them at risk.
- If renal dysfunction develops while an individual is taking TDF/FTC or TAF/FTC for PrEP, address potentially reversible causes before discontinuing oral PrEP.
- CAB LA is an option 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: Care Provider Checklists for PrEP Initiation, Regimen Choice, and Follow-Up

CHECKLIST 1: PrEP INITIATION	
Confirm PrEP eligibility	· Discuss HIV risk, including self-reported risk, history of potential exposure, or signs, and assess for signs and symptoms of acute HIV infection · If exposure within ≤72 hours, recommend and initiate PEP before PrEP
Obtain medical history	· Assess for contraindications or factors that may affect PrEP choice: HIV; HBV; kidney impairment; osteoporosis; potential drug-drug interactions; current or planned pregnancy
Order baseline laboratory testing and arrange for specimen collection	· HIV-1/2 Ag/Ab combination immunoassay* · HIV RNA assay · Serum creatinine and calculated CrCl · Serum liver enzymes · HBV and HCV serologies · HAV serology (MSM and if at risk) · Urinalysis · Syphilis testing · Gonorrhea and chlamydia NAATs (all potential exposure sites) · Pregnancy test (if of childbearing capacity) *Same-day PrEP: Perform rapid and laboratory-based HIV test; ensure laboratory results will be available within 1 week of PrEP start
Review PrEP options and assist patient in making informed choice	· Explain purpose, benefits, potential risks (including possible adverse effects), and time to protection · Discuss available options, including factors and limitations that may influence choice of regimen · If injectable PrEP is chosen, decide whether to use oral medication lead-in · If on-demand oral PrEP is chosen, ensure understanding of 2-1-1 dosing
Provide patient education	· Symptoms of acute HIV infection and recommended response, including who to contact and how · Adherence requirements: Dosing, laboratory testing, visit schedule · Strategies to address modifiable barriers to access and adherence · Possible adverse effects, suggestions for management, and when and how to request assistance
Counsel on harm reduction	· Discuss STI prevention, access to contraceptives, access to needle exchange · Link to support services as needed
Arrange for follow-up	· Obtain and document contact information for remote follow-up (phone, text, email) · Review potential adverse effects and how to manage, including when and how to contact care provider
Abbreviations: Ag/Ab, antigen/antibody; CrCl, creatinine clearance; 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 2: KEY FACTORS IN CHOICE OF PrEP REGIMEN

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

Abbreviations: CAB LA, long-acting injectable cabotegravir (brand name Apretude); HBV, hepatitis B virus; IM, intramuscular; MSM, men who have sex with men; ND, no data; PrEP, pre-exposure prophylaxis; TAF/FTC, tenofovir alafenamide/emtricitabine (brand name Descovy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (brand name Truvada); TGW, transgender women.

CHECKLIST 3: PrEP FOLLOW-UP		
INJECTABLE PrEP: CAB LA	If HIV infection is diagnosed	• Contact patient immediately to recommend HIV treatment • Obtain baseline laboratory testing including genotype testing • Consult with an experienced HIV care provider regarding an appropriate regimen for immediate ART initiation
	2 weeks after oral CAB lead-in start	• *If used*, contact patient to address problems with acquiring or taking medications; assess adherence, tolerance, and adverse effects; confirm first injection date
	Within 1 week of first injection	• Contact patient to assess tolerability and advise on adverse effect management if needed • Confirm next injection date
	Every injection visit	• Repeat HIV testing with HIV-1/2 Ag/Ab combination immunoassay and HIV RNA assay • Ask about STI symptoms
	STI testing every 2 to 4 months regardless of symptoms	• Base testing frequency on reported risk • Syphilis screening and NAATs for gonococcal and chlamydial infections at all exposure sites • All MSM and TGW: Perform 3-site testing routinely, 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 • If indicated, adjust schedule for next injection
	If PrEP is discontinued	• Recommend oral PrEP for ≥1 year to prevent acquisition of HIV with potential INSTI resistance mutations • *If risk is ongoing:* Provide risk-reduction counseling and emergency PEP access information • Discuss option of restarting PrEP later
ORAL PrEP: TDF/FTC or TAF/FTC	If HIV infection is diagnosed	• Order baseline laboratory testing including genotype testing • Intensify patient's PrEP regimen to fully suppressive ART or refer the patient to an experienced HIV care provider for ART
	Within 2 weeks of PrEP start	• Contact patient to address problems with acquiring or taking PrEP medications; assess tolerance and adherence; advise on adverse effect management; confirm next visit
	1 month after PrEP start	• Repeat laboratory HIV testing if exposure occurred ≤1 month before PrEP initiation • Ask about adherence; symptoms of acute HIV (repeat HIV testing if reported); STI symptoms (ask at every visit); harm reduction; pregnancy status (test if indicated or requested) • Arrange for laboratory testing at month 3: HIV-1/2 Ag/Ab combination immunoassay; syphilis screening and NAATs for gonococcal and chlamydial infections at all exposure sites; pregnancy testing if indicated or requested (every visit)
	3 months after PrEP start	• Serum creatinine and calculated CrCl (every 6 months thereafter)
	Every 3 months regardless of symptoms	• Assess adherence • Ask about symptoms and test for STIs regardless of symptoms (can decrease frequency based on risk) • For all MSM and TGW, routine 3-site testing for gonorrhea and chlamydia should be performed, unless declined and regardless of sites of reported exposure • Arrange for next laboratory testing • Pregnancy testing if indicated or requested (every visit)
	Every 6 months	• Obtain serum creatinine and calculated CrCl
	At least annually	• Obtain urinalysis and HCV serology for those at risk
	If PrEP is interrupted	• Order laboratory-based HIV testing (HIV-1/2 Ag/Ab combination immunoassay and HIV RNA assay) whenever patient reports PrEP interruption of >1 week within the past month and exposure and whenever patient 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 emergency PEP access information • Discuss option of restarting PrEP later

Abbreviations: Ag/Ab, antigen/antibody; ART, antiretroviral therapy; CAB, cabotegravir (brand name Vocabria); CAB LA, long-acting injectable cabotegravir (brand name 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; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide/emtricitabine (brand name Descovy); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine (brand name Truvada); TGW, transgender women.

All Recommendations

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

Indications

- 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 patients who are completing a course of nPEP and remain at risk for HIV, clinicians should recommend initiation of PrEP immediately after 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 ART regimens for HIV treatment. (A1)
- Clinicians should recommend or refer individuals with confirmed HIV for immediate initiation of 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)
- If daily dosing is a barrier to adherence or if episodic dosing is preferred, clinicians should inform candidates about dosing and adherence requirements for available PrEP regimens and engage them in informed, shared decision-making regarding the choice of regimen. (A3)

TDF/FTC

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

TAF/FTC

- Clinicians should recommend TAF/FTC as the preferred oral PrEP regimen for cisgender MSM and transgender women with preexisting renal disease or osteoporosis. (A1)
- Clinicians should not recommend TAF/FTC for protection against HIV exposure through receptive vaginal sex. (A1)

Patients With HBV Infection

- Clinicians should discuss daily TDF/FTC or TAF/FTC as the preferred regimens for patients with HBV infection who require treatment. (A2†)
- Clinicians should closely monitor patients with chronic HBV infection for a 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 to 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 CAB LA as PrEP. (A1)

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

- If a patient at ongoing risk of HIV acquisition discontinues CAB LA injections, the clinician should recommend an oral PrEP regimen to be started 2 months after the last injection and continued for at least 1 year to prevent potential acquisition of INSTI-resistant HIV. (A3)
- Given the current lack of safety data on CAB LA during pregnancy, clinicians should engage pregnant patients and those planning to conceive in shared decision-making regarding the options of continuing CAB LA or switching to daily oral TDF/FTC. (A3)

Laboratory Testing Before PrEP Initiation

- 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).
- Clinicians should perform baseline laboratory testing as recommended in Table 3: Recommended Laboratory Tests for All Patients Within 1 Week Before Initiating PrEP.
- Clinicians should recommend same-day PrEP initiation pending laboratory test results 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 (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 same-day initiation is not an option, clinicians should repeat lab-based HIV-1/2 Ag/Ab and HIV RNA testing if more than 1 week has lapsed since HIV testing was performed (A3) and should ensure that the HIV test results are available and acted upon within 7 days of initiation. (A3)
- If a patient has been exposed to HIV within the previous 72 hours, the clinician should recommend PEP before PrEP (A1).
- Clinicians should not wait to initiate PrEP in individuals who may be in the window period for seroconversion when an HIV test cannot detect infection; doing so risks additional exposures and significant delays in PrEP (A*).
- If a patient has a positive HIV test result within 1 week 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 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. (A1) To consult an expert, call the NYSDOH AI CEI Line at 1-866-637-2342.
- Clinicians should repeat HIV testing 1 month after PrEP initiation in patients who report a risk exposure in the 30 days before initiation of PrEP. (A2†)

HIV Testing

- For any patient who reports an exposure to HIV that occurred in the 30 days before PrEP initiation, clinicians should repeat HIV testing 30 days after the patient starts PrEP. (A2†)
- Clinicians should perform an FDA-approved plasma or serum HIV-1/2 Ag/Ab combination immunoassay every 3 months in patients taking oral PrEP. (A3)
- Clinicians should perform an HIV-1/2 Ag/Ab combination immunoassay and HIV RNA test in patients 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 patients who report missing PrEP doses during times of sexual activity and possible HIV exposure. (A3)
- For patients receiving CAB LA, clinicians should perform an HIV-1/2 Ag/Ab combination immunoassay and HIV RNA test at every injection visit; if the patient completed an oral CAB lead-in, the clinician should perform an HIV-1/2 Ag/Ab combination immunoassay and HIV RNA test upon completion. (A2)

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

- Regardless of the PrEP regimen used, clinicians should perform an HIV-1/2 Ag/Ab combination immunoassay and HIV RNA test whenever there has been an interruption in PrEP of >1 week with a risk of exposure during that time off PrEP. (A3)

Renal Function Testing

- Clinicians should perform renal function testing (serum creatinine level and calculated CrCl) as recommended in Table 4: Recommended Routine Laboratory Testing for Patients Taking PrEP.
- Clinicians should discontinue daily TDF/FTC as PrEP if a patient develops a confirmed CrCl <50 mL/min and consider alternative options; see discussion in text for options for patients with reduced renal function. (A3)
- Clinicians should discontinue TAF/FTC as PrEP if a patient develops a confirmed calculated CrCl <30 mL/min. (A3)
- Clinicians should perform urinalysis at baseline and annually to assess urine glucose and protein in patients taking tenofovir-based oral PrEP. (B3)

STI Screening

- At every visit, a care team member should assess patients 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 Patients Taking PrEP.

HCV Screening

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

Pregnancy Screening

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

Suspected Acute HIV

- For patients 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 patients 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 the risk of transmitting HIV to a partner without HIV until acute infection is ruled out. (A2)

Asymptomatic Patients With a 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)

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

Ambiguous HIV Test Results

TDF/FTC, TAF/FTC, or CAB LA used as PrEP may alter viral load and immune response and cause ambiguous HIV test results when following the current CDC/APHL HIV testing algorithm.

- Clinicians should consider a reactive HIV-1/2 Ag/Ab combination immunoassay result with a positive qualitative HIV RNA or a quantitative HIV RNA of any level a positive HIV test result. (A2)
- In the case of an ambiguous HIV test results (a reactive HIV-1/2 Ag/Ab combination immunoassay result 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 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 or Ambiguous HIV Test Result

- For patients taking TDF/FTC or TAF/FTC as PrEP, clinicians should add a third antiretroviral agent with a high resistance barrier, such as DRV/COBI, DTG, or BIC (available as TAF/FTC/BIC) while awaiting resistance test results. (A2)
- For patients receiving CAB LA, clinicians should initiate ART with a non-INSTI-based regimen while awaiting resistance test results. (A2)

Discontinuing PrEP

- Clinicians should discontinue PrEP in any patient with a confirmed positive HIV test result (see recommendations in guideline section Managing a Positive HIV Test Result). (A1)
- Clinicians should discontinue PrEP if a patient does not adhere to HIV testing requirements despite repeated efforts at engagement in care. (A3)
- Clinicians should discontinue TDF/FTC as PrEP in patients who develop a confirmed calculated CrCl <50 mL/min. (A2)
- For patients who develop kidney dysfunction and must discontinue TDF/FTC but wish to continue with PrEP, clinicians should switch their regimen to CAB LA or to TAF/FTC if CrCl is ≥30 mL/min (for MSM and transgender women only). (A3)
- Clinicians should closely monitor patients with chronic HBV infection for a potential viral rebound when PrEP with TDF/FTC or TAF/FTC is discontinued and develop an alternative treatment plan if necessary. (A2)

Resource: Appendix: Care Provider Checklists for PrEP Initiation, Regimen Choice, and Follow-Up

Abbreviations: Ag/Ab, antigen/antibody; APHL, Association of Public Health Laboratories; ART, antiretroviral therapy; BIC, bictegravir; CAB LA, long-acting injectable cabotegravir (brand name Apretude); CDC, Centers for Disease Control and Prevention; CEI, Clinical Education Initiative; CrCl, creatinine clearance; DRV/COBI, cobicistat-boosted darunavir (brand name Prezcobix); DTG, dolutegravir (brand name Tivicay); 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; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide/emtricitabine (brand name Descovy); TAF/FTC/BIC, tenofovir alafenamide/emtricitabine/bictegravir (brand name Biktarvy); TDF/FTC; tenofovir disoproxil fumarate/emtricitabine (brand name 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 • Contributing members • 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. • 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. • 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. • A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years. • 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.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Recommendation development	• The lead author drafts recommendations to address the defined scope of the guideline based on available published data. • Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations. • When published data are not available, support for a recommendation may be based on the committee's expert opinion. • 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.
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. • 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. • 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. • 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. • 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 B. Moderate 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.