Follow-Up Care and Monitoring on HIV PrEP

This is a PDF version of the following document:
Module 1: HIV PrEP Fundamentals
Lesson 5: Follow-Up Care and Monitoring on HIV PrEP

You can always find the most up-to-date version of this document at https://www.hivprep.uw.edu/go/hiv-prep-fundamentals/follow-up-monitoring-on-prep/core-concept/all.

Models for Follow-Up Care in Persons Receiving HIV PrEP

Different models exist for the type of follow-up visits. For the models used below, some clinics use a hybrid model, such as clinic visits alternating with virtual visits, with an option to allow the person receiving HIV PrEP to drop in for laboratory and self-testing at their convenience. For persons receiving oral HIV PrEP with tenofovir DF-emtricitabine (TDF-FTC) or tenofovir alafenamide-emtricitabine (TAF-FTC), there may be options for virtual visits and off-site (or home) laboratory testing. Since persons receiving long-acting injectable cabotegravir (CAB-LA) are seen in the clinic every 2 months for cabotegravir injections, there is no real need or benefit for routine virtual visits or non-clinic-based laboratory testing.

- **In-Clinic Visit / In-Clinic Laboratory Testing**: With this model, the blood draw and sexually transmitted infection (STI) testing are ideally done on the same day as the clinic visit. The STI testing samples for chlamydia and gonorrhea can be obtained through either self-collected swabs or clinician-collected swabs.
- **Virtual Visit (Telemedicine) / In-Clinic Laboratory Testing**: With this model, the blood draw and STI testing are ideally done in the clinic several days prior to (or after) the 3-month follow-up virtual visit, or alternately, are ordered at the time of the virtual visit, with the goal for completion as soon as possible after the visit. The STI testing samples for chlamydia and gonorrhea can be obtained through either self-collected swabs or clinician-collected swabs.
- **Virtual Visit (Telemedicine) / Off-Site or Mail-In Laboratory Testing**: With this model, the individual has a virtual visit, and shortly before or after the virtual visit, the individual visits an off-site laboratory testing facility (that may be at a more convenient location than the clinic) or they obtain self-collected blood samples and STI samples at home. Samples collected at home are then mailed to an appropriate laboratory. The model that utilizes home testing is the least common of the three models, since mail-in, home self-testing has not become widely available, especially with testing that requires obtaining blood samples.

Telehealth Resources

Prime Health, in partnership with Washington University in St. Louis, has developed an outstanding, comprehensive suite of resources for health care providers who are interested in integrating telehealth services into HIV PrEP programs. These TelePrEP Hub resources include

- Practical information on designing a TelePrEP program,
- TelePrEP Readiness Assessment (a guide for program managers to assist in implementing TelePrEP),
- TelePrEP Billing and Compliance,
- TelePrEP Regulations and Policies, TelePrEP Client Navigation and Education, Electronic Device and

Technology Assistance for TelePrEP Clients,
- TelePrEP Mental Health and Support Services,
- TelePrEP Counseling,
- HIV Prevention Support Tools and PrEP Messaging, *and*
- TelePrEP and Lab Testing, and TelePrEP and Pharmacies.

Follow-Up and Monitoring of Persons Receiving HIV PrEP

Follow-Up and Monitoring for Persons Receiving Oral HIV PrEP

Frequency of Visits in Persons Taking Oral HIV PrEP

For persons taking oral HIV PrEP (with either TDF-FTC or TAF-FTC), longitudinal and consistent follow-up is important in order to (1) screen for HIV and STIs, (2) discuss adherence, (3) assess for medication-related adverse effects, (4) refill the medication prescription, and (5) review HIV risk and ensure that ongoing HIV PrEP prescriptions are indicated. For persons taking daily oral HIV PrEP, the typical follow-up monitoring is every 3 months, with each refill consisting of a 90-day supply of medications.[1] When starting oral HIV PrEP, some experts recommend an initial follow-up visit after 1 month to address any medication-related side effects and to discuss adherence.[1] Persons receiving on-demand (2-1-1) oral HIV PrEP with TDF-FTC should also have regularly scheduled visits and monitoring, but refills for persons receiving on-demand HIV PrEP are typically for a 30-day supply, since a 30-day supply should last at least 90 days for most people taking on-demand HIV PrEP.[1]

Laboratory Monitoring in Person Taking TDF-FTC

The following summarizes recommendations in the 2021 CDC HIV PrEP Guidelines for laboratory monitoring in persons receiving oral TDF-FTC for HIV PrEP (Figure 1).[1] Note that the CDC laboratory monitoring recommendation for HIV testing in persons receiving TDF-FTC includes both HIV-1 RNA and HIV-1/2 antigen-antibody testing every 3 months.[1] Due to the high cost of the HIV-1 RNA test, some clinics, especially public health clinics, have not been able to include HIV-1 RNA testing in routine monitoring. Although HIV-1 RNA testing is recommended as part of monitoring, the inability to include this test in monitoring should not prohibit the use of oral HIV PrEP for individuals who have an indication for HIV PrEP.[Q] Monitoring eCrCl on Tenofovir DF-Emtricitabine

Laboratory Monitoring in Persons Taking TAF-FTC

The following summarizes recommendations in the 2021 CDC HIV PrEP Guidelines for laboratory monitoring in persons receiving oral TAF-FTC for HIV PrEP (Figure 2).[1] Note that the CDC laboratory monitoring recommendation for HIV testing in persons receiving TAF-FTC includes both HIV-1 RNA and HIV-1/2 antigen-antibody testing every 3 months.[1] Due to the high cost of the HIV-1 RNA test, some clinics, especially public health clinics, have not been able to include HIV-1 RNA testing in routine monitoring. Although HIV-1 RNA testing is recommended as part of monitoring, the inability to include this test in monitoring should not prohibit the use of oral HIV PrEP for individuals who have an indication for HIV PrEP.[Q] Monitoring for HCV While on TAF-FTC

Follow-Up and Monitoring for Persons Receiving CAB-LA

Frequency of Visits in Persons Receiving CAB-LA

After the first injection, a second initiation injection is given 1 month later. Subsequent injections are given every 2 months and are referred to as continuation injections. For persons receiving CAB-LA for HIV PrEP, the timing of longitudinal follow-up is linked to the timing of the in-clinic injections. Regular monitoring of persons who are receiving CAB-LA is important to (1) assess for symptoms, such as injection site reactions, (2) regularly test for HIV infection, (3) screen for STIs, (4) review any changes in risk for HIV acquisition to reevaluate that ongoing HIV PrEP is appropriate, and (5) schedule and/or confirm dates for future cabotegravir injections.

Laboratory Monitoring in Persons Receiving CAB-LA

Since persons receiving CAB-LA require in-clinic injections every 2 months, the typical laboratory monitoring

in persons receiving CAB-LA continuation injection is every 2 or 4 months. Note that routine renal monitoring is not indicated for persons receiving CAB-LA since this medication does not cause nephrotoxicity, and it can safely be administered to persons without renal insufficiency without a need for dose adjustment.[1] The following summarizes recommendations in the 2021 CDC HIV PrEP Guidelines for laboratory monitoring of persons receiving CAB-LA for HIV PrEP (Figure 3).[1][Q] HIV Testing When Receiving injectable Cabotegravir

Scheduling and Tracking CAB-LA Dosing

Clinics providing CAB-LA should ideally have a mechanism and designated clinic personnel for scheduling and tracking all persons receiving CAB-LA. When administering every 2-month CAB-LA, the acceptable dosing window is 7 days before or 7 days after the 2-month period from the prior injection. Likewise, the same 7-day before and after window exists when administering the 1-month second initiation dose. When patients are scheduled for injection, it is optimal to schedule the next injection as close as possible to the exact 2-month interval (or up to 7 days prior to this exact 2-month date). From a practical standpoint, this timing of scheduling at or slightly early is particularly important since it will allow for several days to contact and reschedule if an individual misses a planned injection. For example, if a missed injection was scheduled exactly 2 months apart from the prior injection, and they miss the clinic visit for the injection, this will allow the clinic staff 7 days to contact, reschedule, and administer CAB-LA and still have the injection given within the acceptable 7-day late window.

Oral Bridge Dosing

For individuals who plan to miss a scheduled 2-month injection (perhaps due to travel or other conflicts) by more than 7 days, oral HIV PrEP bridging medication should be used. The cabotegravir prescribing information recommends using oral cabotegravir bridging for up to 2 months, which serves to cover 1 missed injection. In clinical practice, it has been very difficult to obtain oral cabotegravir for bridging and most clinics have used TDF-FTC or TAF-FTC for oral bridging, with the caveat that TAF-FTC should not be used as an oral bridge for prevention of vaginal acquisition of HIV. Further, some clinics take a proactive approach and address the possibility for missed doses (planned and/or unplanned) and provide individuals with an oral HIV PrEP prescription to have as a back-up for use as an oral bridge. If this strategy of proactively prescribing oral HIV PrEP for potential missed doses is used, it is important to have a recent estimated creatinine clearance, evaluate hepatitis B virus status, and make sure that TDF-FTC or TAF-FTC is appropriate. As outlined below, the CAB-LA dosing after an oral bridge depends on the time from the last CAB-LA dose.

Restarting CAB-LA After Missed Second Initiation Injection

When starting CAB-LA after a missed second initiation injection, the recommendation for restarting CAB-LA depends on the time that has elapsed since the first initiation injection was given (Figure 4). If the gap is 2 months or less, then a dose of CAB-LA should be given as soon as possible, then every 2-month continuation doses of CAB-LA can be administered beginning 2 months after this late second initiation dose was administered. If more than 2 months have elapsed, then CAB-LA should be restarted with 2 initiation injections given 1 month apart, followed by the continuation injections every 2 months.

Restarting CAB-LA After Missed Continuation Injection

When starting CAB-LA after a missed continuation injection dose, the recommendation for restarting CAB-LA depends on the time that has elapsed since the last injection was given (Figure 5). If 3 months or less have elapsed since the last CAB-LA dose was given, then CAB-LA should be administered as soon as possible and the continuation doses continued on an every 2-month schedule thereafter, with the next dose administered 2 months from the time the late injection was given (and not based on the time of the original scheduled dose). If the time from the last injection was longer than 3 months, the recommendation is to restart, with 2 initiation injections given 1 month apart, followed by continuation injections every 2 months. When missed doses have occurred, it is important to retest for HIV prior to (or at the time the late doses are given), especially if the gap from the prior injection was longer than 3 months.

Discontinuing HIV PrEP

At each HIV PrEP follow-up visit, HIV risk and the appropriateness of continuing HIV PrEP should be reassessed.[1] Discontinuing HIV PrEP may be appropriate if the need for HIV PrEP no longer exists. Sometimes, despite an ongoing risk for HIV acquisition, an individual may decide to stop HIV PrEP due to personal preference, a decrease in HIV risk perception, insurance barriers, medication tolerability, problems with medication adherence, difficulty making medical appointments, or other barriers.[2] In some instances, interventions may help address barriers, including changing the HIV PrEP medication if it will help to address the main reason for stopping HIV PrEP. If discontinuation of HIV PrEP is planned due to the person no longer needing HIV PrEP, it is important to provide counseling for the individual regarding how long they should continue HIV PrEP after the last possible exposure to HIV. In addition, it is important to counsel that HIV PrEP can be restarted in the future if risk for HIV acquisition changes, and that repeat baseline laboratory testing will be needed before restarting HIV PrEP.

Discontinuing Oral HIV PrEP

Overall Risk of Acquiring HIV After Stopping Oral PrEP

In a retrospective cohort study that used electronic health record data from the Kaiser network in California, investigators tracked linkage, initiation, discontinuation, and reinitiation of HIV PrEP and found the risk of acquiring HIV was significant for many persons who stop HIV PrEP (Figure 6).[3] In this study, the HIV incidence was highest for individuals who stopped oral HIV PrEP and never restarted, lower for those who stopped and later resumed, and zero (over 9,139 person-years of follow-up) for those who never stopped.[3]

How Long Does Oral HIV PrEP Medications Provide Protection After Discontinuation?

The 2021 CDC HIV PrEP Guidelines cite that after stopping daily oral HIV PrEP, protection against HIV acquisition wanes over 7 to 10 days.[1] This estimate is based on data from an intensive TDF-FTC pharmacokinetic study that analyzed peripheral blood mononuclear cell concentrations of tenofovir-diphosphate after stopping TDF-FTC; this study found that after stopping TDF-FTC, 80% of the concentrations remained above the EC_{90} after 2 days and 48% after 7 days.[4] The investigators concluded that a high level of protection against HIV acquisition may persist for several days after stopping oral TDF-FTC.[4] Separate pharmacologic studies comparing tenofovir alafenamide (TAF) and tenofovir DF (TDF) have shown the intracellular half-life of the active metabolite drug (tenofovir diphosphate) in peripheral blood mononuclear cells persists at least as long with TAF as with TDF.[5,6] There are no clinical data that firmly establish how many days a person is protected from HIV acquisition after stopping oral HIV PrEP.

Duration of Oral HIV PrEP After Last Exposure

There are currently no official recommendations on how long to continue oral HIV PrEP after the last sexual exposure.[1] Expert opinion recommendations range from continuing HIV PrEP for 2 days after the last sexual exposure (similar to recommendations with on-demand [2-1-1] dosing) to continuing for 28 days after the last sexual exposure (similar to recommendations for duration with nonoccupational PEP).[7,8,9]

Potential HBV Flare After Stopping Oral HIV PrEP in People with Chronic HBV

Because TDF-FTC and TAF-FTC have antiviral activity against hepatitis B virus (HBV), persons with chronic HBV infection who take either one of these medications for HIV PrEP will be treated for HBV.[10] In this situation, if the person with chronic HBV discontinues the oral HIV PrEP medication, the HBV DNA levels will rise, potentially abruptly, which may result in elevations in hepatic aminotransferase levels and acute hepatic inflammation—a situation referred to as a hepatic flare (Figure 7).[11] In the iPrEx trial, among the six individuals with chronic HBV who received TDF-FTC for HIV PrEP, five had hepatic transaminases levels monitored after discontinuation, and the only abnormality detected was a grade 1 elevation in one

participant.[12] Although reports of HBV-related hepatic flares following discontinuation of oral HIV PrEP have been rare, the risk impact of such a flare may be greater in persons with cirrhosis or during pregnancy.[13]

Recommendations for Persons Discontinuing Oral HIV PrEP

- Individuals who are planning to stop oral HIV PrEP should receive counseling regarding the time to continue HIV PrEP following the last possible HIV exposure. Expert opinion ranges from 2 days after the last sexual exposure (similar to recommendations with on-demand [2-1-1] dosing) to 28 days after the last sexual exposure (similar to recommendations for duration with nonoccupational PEP).
- Protection against HIV acquisition probably occurs for at least several days after stopping daily oral HIV PrEP. Since there are no clinical data that firmly establish how many days a person is protected after stopping oral HIV PrEP, we recommend counseling a person who is stopping HIV PrEP to utilize other protective measures to prevent HIV acquisition as soon as they discontinue oral HIV PrEP.
- At the time of HIV PrEP discontinuation, it is important to document the patient's HIV status, reason for stopping, recent medication adherence, as well as current and future risk for HIV acquisition.
- Persons who have stopped HIV PrEP should receive counseling about the potential to immediately resume HIV PrEP or restart HIV PrEP at a later time.
- Persons stopping oral HIV PrEP should have counseling regarding the use of other HIV prevention measures after stopping HIV PrEP, including reducing the number of sex partners, consistent use of condoms, and, if applicable, utilizing a needle exchange program.
- If a person has an ongoing risk of acquiring HIV and bacterial STIs after stopping HIV PrEP, testing for HIV (HIV-1/2 antigen-antibody test) and screening for STIs should occur at appropriate intervals (e.g., every 3 to 6 months).
- If a person has chronic HBV and stops taking oral HIV PrEP, it is important to monitor for an HBV flare, ideally with a monthly check of hepatic aminotransferase levels for 3 months. If there is an indication for ongoing HBV treatment, consider continuing the oral PrEP medication for HBV treatment, switching to a different HBV therapy, or referring to a viral hepatitis specialist for help making this decision.

Discontinuing CAB-LA HIV PrEP

Risk of Acquiring HIV After Stopping CAB-LA

Similar to HIV acquisition that can occur after stopping oral HIV PrEP, individuals can acquire HIV after stopping CAB-LA for HIV PrEP. In the HPTN 083 trial, which evaluated the use of CAB-LA in men who have sex with men (MSM) and transgender women who have sex with men, three HIV infections occurred in individuals who had started CAB-LA but had no recent injections; in two of the three cases, the person had stopped CAB-LA and been prescribed oral HIV PrEP.[14] If a person misses or stops receiving CAB-LA, the risk of HIV acquisition should be assessed and resumption of HIV PrEP should be discussed.

How Long Does Cabotegravir Remain in the Body After Discontinuation?

Intramuscular cabotegravir has an extremely long half-life of approximately 40 days.[15] In the HPTN 077 study, which compared injectable cabotegravir to placebo, the median time from the last CAB-LA injection to detection of a concentration below the lower limit of quantification was 44 weeks for male participants and 67 weeks for female participants (male or female was based on sex assigned at birth).[16] In addition, at 76 weeks after the last injection, detectable plasma cabotegravir was present in 13% of the males and in 42% of the females (Figure 8).[16] Further analysis revealed the terminal phase half-life was longer for participants with a higher body mass index (BMI).[16] In the HPTN 083 and HPTN 084 trials, which compared injectable cabotegravir to daily, oral tenofovir DF-emtricitabine as HIV PrEP, HIV infections did not occur during the tail phase in persons receiving cabotegravir.[14,17] Nevertheless, experience with cabotegravir use for HIV PrEP in clinical practice remains relatively limited, and there is a potential risk of acquiring infection and developing integrase resistance after cabotegravir is discontinued (during the tail phase).

Recommendations for Persons Discontinuing Injectable Cabotegravir

- If an individual decides to stop CAB-LA, the clinician should counsel the individual about the very long cabotegravir tail phase and the risk of developing HIV drug resistance if HIV is acquired after stopping CAB-LA.
- At the time of CAB-LA discontinuation, it is important to document the individual's HIV status, reason for stopping, as well as current and future risk for HIV acquisition.
- Individuals with an ongoing risk of HIV acquisition who decide to stop CAB-LA should transition to an appropriate oral HIV PrEP regimen that begins within 8 weeks after the last CAB-LA injection.[1,18] They should remain on oral HIV PrEP until the risk of HIV acquisition is no longer present.
- Individuals without an ongoing risk of HIV acquisition who decide to stop CAB-LA do not require continuation of HIV PrEP. In this situation, the individual should receive counseling about restarting HIV PrEP (either CAB-LA or oral HIV PrEP) if they anticipate future activities that might carry a risk of HIV acquisition. This counseling message is especially important because of the long tail phase of cabotegravir and persistent low levels of cabotegravir that are detectable in plasma.
- Persons who discontinue CAB-LA should have follow-up visits quarterly visits for 12 months after discontinuation of CAB-LA to reassess HIV risk, potential indications to restart HIV PrEP, and to perform HIV testing (HIV-1 RNA assay and HIV-1/2 antigen-antibody test).[1] Individuals who elect to discontinue HIV PrEP, despite an ongoing risk of acquiring HIV and bacterial STIs, should have screening for these infections at appropriate intervals (e.g., every 3 to 6 months).[Q] Transition to Oral PrEP when Discontinuing Cabotegravir

Acquisition of HIV in Persons Prescribed HIV PrEP

It is important to gain a conceptual understanding of the three main time periods when HIV acquisition can occur among persons who are prescribed HIV PrEP: prior to HIV PrEP initiation, while taking HIV PrEP, and after discontinuing HIV PrEP. Regardless of when the HIV infection is acquired, a timely diagnosis of HIV is important for two main reasons: (1) minimize the chance and extent of HIV drug resistance to the HIV PrEP medications and (2) to provide fully suppressive antiretroviral therapy to reduce the risk of transmission of HIV to others.

- **Prior to Initiating HIV PrEP**: A person who is starting HIV PrEP could have preexisting HIV infection that is not diagnosed at the time of the initial HIV PrEP evaluation. This most likely would occur in a person who had a very recent acquisition of HIV, since acute HIV infection could be missed on the initial HIV screening. This scenario underscores the importance of screening for symptoms of acute (primary) HIV and documenting the absence of HIV infection before starting either oral or injectable HIV PrEP.
- **During HIV PrEP**: Individuals actively taking HIV PrEP can acquire HIV, and this most often occurs when there is low adherence with oral medications or missed CAB-LA injections without oral bridge dosing. It is also possible to acquire drug-resistant HIV despite having 100% medication adherence; this situation typically involves the acquisition of an HIV strain that is resistant to the HIV PrEP medication(s); this is not common, but rare cases have been reported.
- **After Discontinuing HIV PrEP**: After stopping HIV PrEP, persons may continue to have a significant risk for HIV and can acquire HIV during this time. Since this risk is substantial, there should be ongoing monitoring, screening for HIV, and discussions about restarting HIV PrEP, if indicated.

Watch the brief video below titled **Timing of Potential HIV Acquisition in People Prescribed HIV PrEP** (*8 minutes*) to explore this topic in more detail.

This video is part of our Min-Lectures section.

Cases of HIV Acquisition in Persons Taking Oral HIV PrEP

If a person acquires HIV after starting oral HIV PrEP, it typically results from low adherence, with adequate adherence generally considered as taking at least 4 doses per week.[1,19,20,21] A retrospective review in England evaluated persons diagnosed with HIV who were taking or recently had taken oral HIV PrEP and found that 87% (45 of 52) of these individuals reported a significant problem with medication adherence.[22] In several large HIV PrEP trials, HIV infection in persons taking oral HIV PrEP was usually associated with low adherence (typically less than two doses per week).[23,24,25,26,27] There are rare, but clearly documented, cases of HIV acquisition in persons with good oral medication adherence.[22] In addition, in one clinical trial with oral HIV PrEP, there were several suspected cases of baseline HIV infection that was not originally detected.[25]

Case of HIV Acquisition in Persons Taking CAB-LA

In an evaluation of 51 incident infections during the blinded phase of HPTN 083 (12 in the CAB-LA arm and 39 in the oral TDF-FTC arm), low or unquantifiable drug levels at the time of HIV acquisition were identified in 5 persons taking CAB-LA and 37 taking TDF-FTC.[27] In the HPTN 083 study, investigators reported 4 HIV

infections despite on-time CAB-LA injections and adequate plasma cabotegravir levels (out of 2,282 participants who were assigned to receive CAB-LA).[14,27] The reason for cabotegravir failure in the HPTN 083 trial has not been confirmed; such failures did not occur in HPTN 084.[17] It has been postulated that certain individuals may have increased absorption of cabotegravir following injection, with steeper declines in peak and trough plasma cabotegravir concentrations, which could potentially leave persons vulnerable to infection in the period just before the next injection.[28]

Diagnosing HIV in Persons Prescribed HIV PrEP

Establishing a diagnosis of HIV in a person taking HIV PrEP can be more difficult and complicated than in a person who is not receiving HIV PrEP. For most people who acquire HIV and are not taking HIV PrEP, there is a typical and predicable pattern observed with laboratory markers in the very early (acute) phase of infection (Figure 9).[29,30,31] In contrast, among some individuals who acquire HIV while taking HIV PrEP, especially when intermittently taking HIV PrEP, the HIV PrEP medications may be providing partial HIV treatment, potentially blunting the very high initial plasma HIV RNA levels that typically occur with acute HIV and blocking the host antibody responses to HIV. Further, in this situation, HIV p24 antigen levels may remain below a detectable level.[14,20,32] To this end, among people taking HIV PrEP who acquire HIV, the diagnosis of HIV may be significantly delayed, and ambiguous HIV testing results may develop.

Delays In HIV Diagnosis

In the HPTN 083 study that compared oral TDF-FTC with CAB-LA, the diagnosis of HIV was frequently delayed—when using standard HIV-1/2 antigen-antibody testing—for a substantial number of participants who had incident HIV infection (e.g., infections that occurred after they started receiving HIV PrEP); the delay in HIV diagnosis was proven by retrospective testing of these blood samples using a highly sensitive HIV-1 RNA assay.[14,27] For example, in the TDF-FTC arm, 18% (7 of 39) had a delayed HIV diagnosis, with a median delay for the incident infection of 31 days for these 7 individuals.[14,27] For persons in the CAB-LA arm, the diagnosis of HIV was delayed in 58% (7 of 12) of the incident infections, and the median delay for these 7 incident infections was 98 days.[14,27] The investigators noted that using a common quantitative HIV RNA test (viral load) would also have detected most of the cases that qualitative HIV RNA detected. Because of the potential significant diagnostic delays when only using HIV-1/2 antigen-antibody immunoassay for HIV screening in persons receiving HIV PrEP, the 2021 CDC HIV PrEP Guidelines recommend including HIV-1 RNA testing in conjunction with an HIV-1/2 antigen-antibody immunoassay as the HIV screening method for persons taking HIV PrEP.[1]

Ambiguous HIV Test Results

Interpreting ambiguous HIV screening results in persons taking HIV PrEP can be complicated. For assistance with HIV diagnostic considerations in persons receiving HIV PrEP, expert consultation is available through the National Clinical Consultation Center (NCCC); see the NCCC Resource Page on this website for contact information. It is important to consider the possible causes for false-negative and false-positive HIV testing results in persons taking HIV PrEP.[33,34] In general, repeated false-positive HIV antibody (or HIV-1/2 antigen-antibody immunoassay) tests are rare, but they can occur in persons who have received recent immunizations or have certain medical conditions, such as COVID-19 or with pregnancy.[35,36,37,38,39] False-negative antibody tests can occur very early in HIV infection and are more likely to occur in persons taking HIV PrEP (or if antiretroviral therapy is initiated) due to blunting of the HIV RNA levels, p24 antigen levels, and host immune responses.[40,41,42] Although rarely occurring in the United States, HIV-2 infection can be a cause of false-negative HIV RNA testing, since the main commercial assays used detect only HIV-1 RNA.

Management of person with Ambiguous HIV Test Results

The management of persons who are receiving or recently have received HIV PrEP and have ambiguous test results can be extremely complicated. Based on the interpretation of the ambiguous HIV test results, there are three main options as outlined below. For all three of these situations, we strongly recommend obtaining expert consultation.[43]

- Option 1 / Continue HIV PrEP and perform additional HIV testing
- Option 2 / Start full antiretroviral therapy and perform additional HIV testing
- Option 3 / Discontinue HIV PrEP and perform additional HIV testing

HIV Drug Resistance in Persons Prescribed HIV PrEP

Mechanism and Timing for Acquisition of HIV Drug Resistance

Most individuals who are diagnosed with HIV after receiving HIV PrEP will have wild-type HIV documented with baseline drug-resistance testing—in this context, wild-type HIV refers to HIV that does not have drug resistance.[14,17,44,45,46] Nevertheless, drug resistance can occur with oral HIV PrEP and with injectable cabotegravir, especially when HIV diagnosis is not recognized at the time HIV PrEP is started or the diagnosis is delayed if HIV is acquired while a person is taking HIV PrEP.[27,47,48,49] For persons newly diagnosed with HIV who are receiving HIV PrEP (or recently received HIV PrEP), it is important to conceptually understand how HIV drug resistance may have potentially developed. The following description and video below summarizes possible scenarios for how HIV drug resistance can occur in persons prescribed HIV PrEP medications.

Scenario 1 / Acquires HIV Prior to Initiating HIV PrEP

In this situation, there is failure to detect existing HIV infection prior to starting HIV PrEP medications—most often this would occur in a person who had a very recent acquisition of HIV that was not detected on an HIV-1/2 antigen-antibody immunoassay.

- When HIV is acquired before starting HIV PrEP, it is usually wild-type HIV. After the person with undiagnosed HIV begins taking HIV PrEP medications, resistance can develop, since they are not taking a complete HIV treatment regimen that will fully suppress HIV RNA levels.
- Less often in this situation, a person acquires drug-resistant HIV before starting HIV PrEP. After they start HIV PrEP medications, further HIV drug resistance is likely to develop, with the potential for extensive drug resistance to develop.

Scenario 2 / Acquires HIV while Receiving HIV PrEP

In this situation, the individual starts taking HIV PrEP, and they acquire HIV at some point after starting HIV PrEP.

- Individuals who acquire HIV while receiving HIV PrEP most often have wild-type HIV, especially if the new HIV infection occurs in the setting of problems with adherence.[50] If the person unknowingly acquires HIV and continues to take HIV PrEP, drug resistance can develop, since they are not taking a complete HIV treatment regimen that will fully suppress HIV RNA levels.[50]
- Although infrequent, it is possible the person taking HIV PrEP can acquire drug-resistant HIV while taking HIV PrEP, even with excellent medication adherence.[32,51,52,53] If the person acquires HIV (and the diagnosis is not promptly made), continuing to take HIV PrEP would likely result in more extensive drug resistance.

Scenario 3 / Acquires HIV after HIV PrEP is Discontinued

This situation can involve HIV acquisition at any time after stopping HIV PrEP. Resistance is most likely to occur if HIV acquisition occurs in the setting of low residual levels of drugs, particularly if the drug level is not adequate for HIV prevention but is high enough to potentially trigger drug resistance. Residual levels of oral HIV PrEP medications are unlikely after 1 month, but low levels of cabotegravir can persist for longer than 1 year.

- Acquisition of HIV after HIV PrEP has been stopped usually involves wild-type HIV. In this situation, drug resistance can develop if the individual has residual low levels of medication.
- Acquisition of HIV after HIV PrEP has been stopped infrequently involves the acquisition of drug-resistant HIV. In this situation, development of more extensive drug resistance could develop if the individual had residual levels of HIV PrEP medications.

HIV Drug Resistance with Oral HIV PrEP

When HIV drug resistance occurs among individuals prescribed oral nucleoside reverse transcriptase inhibitors (NRTIs) for HIV PrEP (TDF-FTC or TAF-FTC), the resistance related to these medications involves mutations in the reverse transcriptase gene. Since TDF and TAF are prodrugs converted to tenofovir (TFV) after oral ingestion, the following discussion related to TDF and TAF will describe resistance to these medications as resistance to TFV.

- In a meta-analysis of oral HIV PrEP studies conducted through April 2015, investigators identified resistance to TFV and and/or FTC in 4.4% (12 of 273) persons who had HIV diagnosed after being randomized to receive TDF-FTC or TDF alone.[49] Drug resistance was identified in 27% (7 of 26) of persons who had unrecognized acute HIV at enrollment, which was much higher than the 2% (5 of 247) in persons who acquired HIV after receiving the HIV PrEP medications during the trial.[49] Resistance to FTC was more common than resistance to TFV.[49] The M184V/I was the most frequently identified mutation associated with FTC resistance, and K65R and/or K70E were the mutations most often identified with TFV resistance.[49]
- A literature review of oral HIV PrEP randomized controlled trials published through 2018 identified 3% (19 of 622) persons with HIV seroconversions that occurred after study entry or randomization who had mutations that conferred resistance to FTC and/or tenofovir.[45] Among the 19 cases with drug resistance, 13 were in a treatment arm and 6 in a placebo arm; 15 participants had resistance to FTC, 2 had resistance to TFV, and 2 had resistance to both FTC and TFV.[45] Overall, the M184V/I mutation (FTC resistance) was the most commonly detected mutation.[45] Resistance to TFV involved K65R and K70E mutations.[45]
- In a retrospective review from the 56 Dean Street Clinic in London, England, investigators reported on 52 persons diagnosed with HIV at the clinic during 2016-2020 who had recent or current HIV PrEP use.[20] After the HIV diagnosis, HIV drug resistance testing was successfully performed in 43 of these individuals. Resistance mutations were identified in 30% (13 of 52) of the cases, and all 13 had the M184V mutation (FTC resistance).[20]
- A retrospective review from New York City analyzed resistance data from 4,246 people with newly diagnosed HIV during 2015-2022 and a drug resistance genotype obtained within 30 days of the HIV diagnosis.[54] Among these cases of newly diagnosed HIV, there were 260 (6%) who had received recent or past oral HIV PrEP (TDF-FTC or TAF-FTC) and 3,986 (5%) with no known HIV PrEP use.[54] Rates of detection of the M184V/I mutation (FTC resistance) on the baseline drug resistance genotype was significantly higher in persons with recent HIV PrEP use (14%) or past HIV PrEP use (8%) than in persons without known HIV PrEP use (2%).[54] Five persons had a K65R mutation (TFV resistance) detected on the baseline genotype and these all occurred in persons with no known HIV PrEP use.[54]

HIV Drug Resistance with Injectable Cabotegravir

When an individual acquires HIV just before starting injectable cabotegravir, while receiving injectable cabotegravir, or after discontinuing injectable cabotegravir, antiretroviral drug resistance may occur.[55] The resistance occurs as a result of mutations in the HIV integrase gene, which may impact future antiretroviral regimen choices, since these integrase mutations may significantly reduce the effectiveness of other INSTIs, including the most commonly used INSTIs for HIV treatment (dolutegravir and bictegravir). Use of HIV-1 RNA screening at baseline reduces rates on INSTI resistance in persons receiving CAB-LA.[56]

- In the HPTN 083 randomized controlled trial, which compared CAB-LA every 2 months to daily, oral TDF-FTC for cisgender men who have sex with men and transgender women who have sex with men, INSTI drug resistance was detected in 1 of 4 participants randomized to the long-acting cabotegravir arm who were later confirmed to have baseline infection (initially undetected at study entry).[14] In addition, 4 of 9 participants who were confirmed to have incident HIV infection (acquired while receiving CAB-LA) had evidence of INSTI resistance.[14] In this trial, no cases of HIV drug resistance were detected among individuals who acquired HIV during the tail phase of CAB-LA. The INSTI

resistance mutations identified included major mutations (E138E/K, G140A/S,Q148K/R, R263K) and several minor INSTI mutations.[14]

- A more in-depth analysis of the cases of HIV acquisition in the HPTN 083 trial adds more detailed results.[27] Among participants in the CAB-LA arm who acquired HIV and had genotype data, INSTI resistance mutations were confirmed in 36% (5 of 14) cases.[27] The INSTI mutations detected included the major mutations E138A/K, G140A/S, Q148K/R, and R263K.[27] Among those with INSTI resistance, there was a high degree of cross-resistance between cabotegravir, raltegravir, elvitegravir, and dolutegravir.[27]
- Another analysis examined HIV acquisitions in 18 HPTN 083 participants that occurred after the study was unblinded.[28] For 3 of these 18 participants, INSTI mutations were detected.[28] This study also summarized the frequency of INSTI resistance detected for all 32 HIV acquisition cases in the CAB-LA arm, combining data for those that occurred before and after unblinding.[28] Overall, major INSTI resistance mutations were detected in 31% (10 of 32) cases, all of whom received CAB-LA within 6 months of their first HIV-positive visit (due to delays in detection of HIV infection).[28] A total of 14 of the HIV acquisition cases in the CAB-LA arm occurred more than 6 months after the last CAB-LA administration and zero instances of INSTI resistance were detected in this group.[28]

Management of Persons on HIV PrEP Newly Diagnosed with HIV

Initial Laboratory Testing and Evaluation for Drug Resistance

For persons taking HIV PrEP who newly test positive for HIV, the following laboratory studies should promptly be performed.

- **Confirmatory HIV Testing (if not already done)**: In some instances, the initial positive HIV test may be a preliminary positive result (e.g., point-of-care HIV test), or the individual may be newly positive but with ambiguous results. Thus, it is extremely important to perform the necessary confirmatory testing to document and clarify whether true HIV infection is present.
- **Quantitative HIV RNA**: If a quantitative HIV RNA test has not been done, this should be performed. Note that persons taking HIV PrEP who newly test positive often have relatively low HIV RNA levels secondary to HIV PrEP medications in the system. In some cases, the HIV RNA levels may be very low or even undetectable. In addition, with early infection in persons who are taking HIV PrEP, these levels may fluctuate between low-level detectable and undetectable.
- **CD4 Cell Count**: With any person newly diagnosed with HIV, it is important to obtain a baseline CD4 count. In most persons who acquire HIV while taking (or recently taking) HIV PrEP, one would not expect to see a major decline in the CD4 count.
- **HIV Genotypic Drug Resistance Testing**: If a person acquires HIV, and they have current or past exposure only to oral HIV PrEP medications, a standard HIV drug-resistance assay is recommended; the standard genotypic drug-resistance test includes resistance testing for mutations in the reverse transcriptase and protease genes. If, however, a person newly diagnosed with HIV has a history of exposure to cabotegravir (regardless of time since the last injection), the baseline drug-resistance testing should also include a genotypic drug-resistance test for mutations in the integrase gene. Since many commercially available standard genotypic drug-resistance tests do not include integrase resistance testing, this test may need to be ordered separately. In general, genotypic drug-resistance tests cannot be reliably performed in persons with an HIV RNA level less than 200 copies/mL. Since persons who newly acquire HIV while being prescribed HIV PrEP may have low or very low HIV RNA levels, the performance of standard HIV drug-resistance assays can be problematic in some cases in this setting.
- **HIV Proviral DNA Drug Resistance Testing**: In persons newly diagnosed with HIV who have an HIV RNA level less than 200 copies/mL, some experts would consider performing HIV proviral DNA drug-resistance testing. Proviral DNA drug-resistance testing can be performed in persons who have very low or undetectable HIV RNA levels. At this time, however, HIV proviral DNA drug-resistance testing is not considered a routinely recommended test, even in persons with low-level or undetectable HIV RNA. Most commercially available proviral DNA resistance tests include testing for mutations in the reverse transcriptase, protease, and integrase genes, but the sensitivity of the DNA genotype for detecting mutations in any class is imperfect.

[Q] Drug-Resistance Testing on Cabotegravir

Timing of Initiating Antiretroviral Therapy

For persons taking HIV PrEP who have confirmed HIV infection, immediate conversion of the HIV PrEP regimen to a fully suppressive antiretroviral treatment regimen is indicated.[1,57] In this situation, an empiric antiretroviral treatment regimen should be initiated without delay while resistance testing is pending and then modified as needed based on the HIV drug resistance test results. Note the initial empiric choice of antiretroviral regimen depends on whether the person was taking oral HIV PrEP or CAB-LA HIV PrEP (Figure 11).[57]

Choosing an Antiretroviral Therapy Regimen in Persons Taking Oral HIV PrEP

If the patient is taking oral HIV PrEP with either TDF-FTC or TAF-FTC, and they acquire HIV, the Adult and Adolescent ARV Guidelines recommend continuing the dual nucleoside reverse transcriptase inhibitors (NRTIs) and immediately adding a third medication—an integrase strand transfer inhibitor (INSTI), either dolutegravir or bictegravir.[57] The addition of the third medication should not be delayed while the HIV drug resistance testing is pending.[1,57] If bictegravir is used, it can only be given as the fixed-dose, single-tablet regimen bictegravir-TAF-FTC. Dolutegravir can be added to either TDF-FTC or TAF-FTC. Thus, the full initial antiretroviral regimen should consist of 2 NRTIs plus an INSTI. When the HIV drug resistance testing results become available, they should be carefully reviewed to determine if the antiretroviral regimen needs adjusting. The following situations address the most common resistance scenarios (M184I/V with or without a K65R mutation) that may be observed among persons who acquire HIV while receiving oral HIV PrEP.[18]

- **No NRTI Resistance**: In this situation, the antiretroviral regimen does not need adjusting from regimens that are recommended as initial therapy for most people with HIV.[57]
- **M184I or M184V Alone**: In this situation, the regimen does not need adjusting. Available data suggest that with the M184I or M184V mutation alone, excellent virologic responses are seen in persons receiving (1) bictegravir-TAF-FTC or (2) dolutegravir plus either TDF-FTC or TAF-FTC.[58,59,60]
- **M184I/V plus K65R**: If the HIV drug resistance genotype shows both the M184V and K65R mutations, the regimen may need adjusting. One study (the NADIA Trial) has shown that most individuals with a K65R mutation have a very good virologic response to dolutegravir plus TDF-FTC, but the risk of developing dolutegravir resistance is higher in the presence of a K65R mutation than when no K65R mutation is detected.[61,62] For this reason, in this situation, some clinicians would adjust the antiretroviral regimen and add another antiretroviral agent, such as doravirine or boosted darunavir, especially if the initial HIV RNA level is high (e.g., greater than 100,000 copies/mL) or the patient is experiencing symptoms of acute HIV.

Choosing an Antiretroviral Therapy Regimen in Persons Who Received CAB-LA

If a person acquires HIV and has a history of receiving CAB-LA for HIV PrEP, the initial choice of antiretroviral therapy is more complicated, due to the possible risk of INSTI resistance. Thus, while awaiting the drug resistance genotype report, the Adult and Adolescent ARV Guidelines recommend using an initial antiretroviral regimen that consists of 2 NRTIs (typically TAF-FTC or TDF-FTC) plus boosted darunavir (a protease inhibitor boosted with either cobicistat or ritonavir); this option includes a fixed-dose, single-tablet regimen of darunavir-cobicistat-TAF-FTC.[18,57] When drug resistance testing results are available, they should be carefully reviewed, with the potential to change to a standard recommended first-line regimen consisting of 2 NRTIs plus 1 INSTI—ether (1) bictegravir-TAF-FTC or (2) dolutegravir plus either TDF-FTC or TAF-FTC.[57] For questions about ART choice with HIV seroconversion during or after HIV PrEP, expert consultation is available through the National Clinical Consultation Center (NCCC); see the NCCC resource page on this website.
[Q] Initial ART in Person with Recent Cabotegravir

HIV PrEP Tools for Clinicians: Laboratory Monitoring

The *National HIV PrEP Curriculum* has created **HIV PrEP Tools for Clinicians** based on the 2021 CDC HIV PrEP Guidelines.[1] These tools include a component on monitoring of **Laboratory Tests** that provides specific recommendations for Baseline Labs (when starting HIV PrEP) and Monitoring Labs (while taking HIV PrEP). In addition, these recommendations are specific for each of the three medications used for HIV PrEP: TDF-FTC, TAF-FTC, and CAB-LA. It is important to note these tools are intended to help guide and educate clinicians, but all final decisions regarding indications for HIV PrEP, medication choices, and monitoring of laboratory tests should be based on the clinician's judgment. See the online version of these tools below and practice using these tools to determine recommended monitoring of Laboratory Tests for persons taking HIV PrEP medications (Figure 12). Access these tools by clicking TOOLS on the top navigation bar; once on the Tools page you can use any of the tools directly on the website and by installing it on your mobile device.

Summary Points

- For people receiving follow-up care for HIV PrEP, different models can be utilized to provide HIV PrEP services. The use of virtual visits (TelePrEP) can provide increased flexibility for patient follow-up options.
- Regular HIV testing should be performed every 3 months in persons receiving oral HIV PrEP and every 2 months in persons receiving CAB-LA.
- For persons receiving HIV PrEP, regular STI testing is indicated, with more frequent testing recommended for MSM and transgender women. Baseline HCV and HBV testing is recommended for all persons starting HIV PrEP and repeat yearly HCV testing is recommended for people who inject drugs, MSM, and transgender women.
- Careful counseling and follow-up are needed when HIV PrEP is stopped, as this is a time when significant risk for acquisition of HIV may occur.
- For persons planning to stop oral HIV PrEP, the exact time needed to continue the oral HIV PrEP after the last sexual exposure is unknown. Recommendations range from 2 days (similar to on-demand/2-1-1 dosing) to 28 days (similar to nonoccupational PEP dosing).
- Cabotegravir has a very long half-life when administered as CAB-LA, and special counseling should be given regarding the risk of HIV acquisition after stopping CAB-LA. For individuals who stop CAB-LA and have a continued need for HIV PrEP, oral HIV PrEP should be initiated within 8 weeks of the last CAB-LA injection.
- For persons prescribed HIV PrEP, HIV infection can occur just prior to starting HIV PrEP, while taking HIV PrEP, or after stopping HIV PrEP. Drug resistance infrequently occurs among persons who acquire HIV while taking HIV PrEP.
- Diagnosing HIV infection while a person is receiving HIV PrEP can be complicated by a negative initial HIV-1/2 antigen-antibody test and ambiguous test results.
- If HIV is acquired in a person who is taking (or recently took) oral HIV PrEP, baseline testing should include a standard HIV drug resistance genotype test; recommended initial antiretroviral therapy should consist of an integrase strand transfer inhibitor plus two nucleoside reverse transcriptase inhibitors.
- If HIV is acquired in a person who has current or past use of CAB-LA, baseline testing should include standard and integrase HIV drug resistance tests; recommended initial antiretroviral therapy should consist of boosted darunavir plus two nucleoside reverse transcriptase inhibitors (either TAF-FTC or TDF-FTC).

Citations

1. Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. December 2021:1-108.
[CDC] -

2. Krakower D, Maloney KM, Powell VE, et al. Patterns and clinical consequences of discontinuing HIV preexposure prophylaxis during primary care. J Int AIDS Soc. 2019;22:e25250.
[PubMed Abstract] -

3. Hojilla JC, Hurley LB, Marcus JL, et al. Characterization of HIV preexposure prophylaxis use behaviors and HIV incidence among US adults in an integrated health care system. JAMA Netw Open. 2021;4:e2122692.
[PubMed Abstract] -

4. Seifert SM, Glidden DV, Meditz AL, et al. Dose response for starting and stopping HIV preexposure prophylaxis for men who have sex with men. Clin Infect Dis. 2015;60:804-10.
[PubMed Abstract] -

5. Yager JL, Brooks KM, Castillo-Mancilla JR, et al. Tenofovir-diphosphate in peripheral blood mononuclear cells during low, medium and high adherence to emtricitabine/ tenofovir alafenamide vs. emtricitabine/ tenofovir disoproxil fumarate. AIDS. 2021;35:2481-7.
[PubMed Abstract] -

6. Yager J, Castillo-Mancilla J, Ibrahim ME, et al. Intracellular Tenofovir-Diphosphate and Emtricitabine-Triphosphate in Dried Blood Spots Following Tenofovir Alafenamide: The TAF-DBS Study. J Acquir Immune Defic Syndr. 2020;84:323-30.
[PubMed Abstract] -

7. Molina JM, Ghosn J, Assoumou L, et al. Daily and on-demand HIV pre-exposure prophylaxis with emtricitabine and tenofovir disoproxil (ANRS PREVENIR): a prospective observational cohort study. Lancet HIV. 2022;9:e554-e562.
[PubMed Abstract] -

8. Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. N Engl J Med. 2015;373:2237-46.
[PubMed Abstract] -

9. Smith DK, Grohskopf LA, Black RJ, et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. Department of Health and Human Services. MMWR Recomm Rep. 2005;54(No. RR-2):1-20.
[CDC] -

10. Mohareb AM, Larmarange J, Kim AY, et al. Risks and benefits of oral HIV pre-exposure prophylaxis for people with chronic hepatitis B. Lancet HIV. 2022;9:e585-e594.
[PubMed Abstract] -

11. Tseng CH, Chen TH, Wu JL, et al. Serious adverse events after cessation of nucleos(t)ide analogues in individuals with chronic hepatitis B: A systematic review and meta-analysis. JHEP Rep. 2023;5:100617.
[PubMed Abstract] -

12. Solomon MM, Schechter M, Liu AY, et al. The Safety of Tenofovir-emtricitabine for HIV pre-exposure

prophylaxis (PrEP) in individuals with active hepatitis B. J Acquir Immune Defic Syndr. 2016;71:281-6. [PubMed Abstract] -

13. Malahleha M, Ahmed K, Deese J, et al. Hepatitis B virus reactivation or reinfection in a FEM-PrEP participant: a case report. J Med Case Rep. 2015;9:207. [PubMed Abstract] -

14. Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. N Engl J Med. 2021;385:595-608. [PubMed Abstract] -

15. Trezza C, Ford SL, Spreen W, Pan R, Piscitelli S. Formulation and pharmacology of long-acting cabotegravir. Curr Opin HIV AIDS. 2015;10:239-45. [PubMed Abstract] -

16. Landovitz RJ, Li S, Eron JJ Jr, et al. Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial. Lancet HIV. 2020;7:e472-e481. [PubMed Abstract] -

17. Delany-Moretlwe S, Hughes JP, Bock P, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. Lancet. 2022;399:1779–89. [PubMed Abstract] -

18. Gandhi RT, Bedimo R, Hoy JF, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2022 Recommendations of the International Antiviral Society-USA Panel. JAMA. 2023;329:63-84. [PubMed Abstract] -

19. Sivay MV, Li M, Piwowar-Manning E, et al. Characterization of HIV Seroconverters in a TDF/FTC PrEP Study: HPTN 067/ADAPT. J Acquir Immune Defic Syndr. 2017;75:271-9. [PubMed Abstract] -

20. Girometti N, McCormack S, Tittle V, McOwan A, Whitlock G. Rising rates of recent preexposure prophylaxis exposure among men having sex with men newly diagnosed with HIV: antiviral resistance patterns and treatment outcomes. AIDS. 2022;36:561-6. [PubMed Abstract] -

21. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis. 2014;14:820-9. [PubMed Abstract] -

22. To KW, Lee SS. A review of reported cases of HIV pre-exposure prophylaxis failure with resultant breakthrough HIV infections. HIV Med. 2021;22:75-82. [PubMed Abstract] -

23. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363:2587-99. [PubMed Abstract] -

24. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367:399-410. [PubMed Abstract] -

25. Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet. 2020;396:239-54.
[PubMed Abstract] -

26. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012;367:411-22.
[PubMed Abstract] -

27. Marzinke MA, Grinsztejn B, Fogel JM, et al. Characterization of Human Immunodeficiency Virus (HIV) Infection in Cisgender Men and Transgender Women Who Have Sex With Men Receiving Injectable Cabotegravir for HIV Prevention: HPTN 083. J Infect Dis. 2021;224:1581-92.
[PubMed Abstract] -

28. Marzinke MA, Fogel JM, Wang Z, et al. Extended Analysis of HIV Infection in Cisgender Men and Transgender Women Who Have Sex with Men Receiving Injectable Cabotegravir for HIV Prevention: HPTN 083. Antimicrob Agents Chemother. 2023;67:e0005323.
[PubMed Abstract] -

29. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 infection. N Engl J Med. 2011;364:1943-54.
[PubMed Abstract] -

30. Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS. 2003;17:1871-9.
[PubMed Abstract] -

31. Masciotra S, McDougal JS, Feldman J, Sprinkle P, Wesolowski L, Owen SM. Evaluation of an alternative HIV diagnostic algorithm using specimens from seroconversion panels and persons with established HIV infections. J Clin Virol. 2011;52 Suppl 1:S17-22.
[PubMed Abstract] -

32. Hoornenborg E, Prins M, Achterbergh RCA, et al. Acquisition of wild-type HIV-1 infection in a patient on pre-exposure prophylaxis with high intracellular concentrations of tenofovir diphosphate: a case report. Lancet HIV. 2017;4:e522-e528.
[PubMed Abstract] -

33. Stekler JD, Violette LR, Niemann L, et al. Repeated False-Positive HIV Test Results in a Patient Taking HIV Pre-Exposure Prophylaxis. Open Forum Infect Dis. 2018;5:ofy197.
[PubMed Abstract] -

34. Zucker J, Carnevale C, Rai AJ, Gordon P, Sobieszczyk ME. Positive or Not, That Is the Question: HIV Testing for Individuals on Pre-exposure Prophylaxis. J Acquir Immune Defic Syndr. 2018;78:e11-e13.
[PubMed Abstract] -

35. Ariza-Heredia EJ, Granwehr BP, Viola GM, et al. False-positive HIV nucleic acid amplification testing during CAR T-cell therapy. Diagn Microbiol Infect Dis. 2017;88:305-7.
[PubMed Abstract] -

36. Doran TI, Parra E. False-positive and indeterminate human immunodeficiency virus test results in pregnant women. Arch Fam Med. 2000;9:924-9.
[PubMed Abstract] -

37. Gudipati S, Shallal A, Peterson E, Cook B, Markowitz N. Increase in False-Positive Fourth-Generation Human Immunodeficiency Virus Tests in Patients With Coronavirus Disease 2019. Clin Infect Dis. 2023;77:615-9.
[PubMed Abstract] -

38. Hauser JR, Hong H, Babady NE, Papanicolaou GA, Tang YW. False-Positive Results for Human Immunodeficiency Virus Type 1 Nucleic Acid Amplification Testing in Chimeric Antigen Receptor T Cell Therapy. J Clin Microbiol. 2019 Dec 23;58:e01420-19.
[PubMed Abstract] -

39. He JZ, Rezwan M, Arif A, Baroud S, Elhaj M, Khan A. Acute Babesiosis Causing a False-Positive HIV Result: An Unexpected Association. Case Rep Infect Dis. 2023;2023:6271710.
[PubMed Abstract] -

40. de Souza MS, Pinyakorn S, Akapirat S, et al. Initiation of Antiretroviral Therapy During Acute HIV-1 Infection Leads to a High Rate of Nonreactive HIV Serology. Clin Infect Dis. 2016;63:555-61.
[PubMed Abstract] -

41. Donnell D, Ramos E, Celum C, et al. The effect of oral preexposure prophylaxis on the progression of HIV-1 seroconversion. AIDS. 2017;31:2007-16.
[PubMed Abstract] -

42. Kassutto S, Johnston MN, Rosenberg ES. Incomplete HIV type 1 antibody evolution and seroreversion in acutely infected individuals treated with early antiretroviral therapy. Clin Infect Dis. 2005;40:868-73.
[PubMed Abstract] -

43. Smith DK, Switzer WM, Peters P, et al. A Strategy for PrEP Clinicians to Manage Ambiguous HIV Test Results During Follow-up Visits. Open Forum Infect Dis. 2018;5:ofy180.
[PubMed Abstract] -

44. Buskin SE, Lechtenberg RJ, Slaughter FA, et al. A public health approach to monitoring HIV with resistance to HIV pre-exposure prophylaxis. PLoS One. 2022;17:e0272958.
[PubMed Abstract] -

45. Gibas KM, van den Berg P, Powell VE, Krakower DS. Drug Resistance During HIV Pre-Exposure Prophylaxis. Drugs. 2019;79:609-19.
[PubMed Abstract] -

46. Parikh UM, Mellors JW. How could HIV-1 drug resistance impact preexposure prophylaxis for HIV prevention? Curr Opin HIV AIDS. 2022;17:213-21.
[PubMed Abstract] -

47. Naicker CL, Mansoor LE, Dawood H, et al. Importance of early identification of PrEP breakthrough infections in a generalized HIV epidemic: a case report from a PrEP demonstration project in South Africa. BMC Infect Dis. 2020;20:532.
[PubMed Abstract] -

48. Volk JE, Nguyen DP, Hare CB, Marcus JL. HIV Infection and Drug Resistance with Unsupervised Use of HIV Pre-Exposure Prophylaxis. AIDS Res Hum Retroviruses. 2018;34:329-30.
[PubMed Abstract] -

49. Fonner VA, Dalglish SL, Kennedy CE, et al. Effectiveness and safety of oral HIV preexposure

prophylaxis for all populations. AIDS. 2016;30:1973-83.
[PubMed Abstract] -

50. Ambrosioni J, Petit E, Liegeon G, Laguno M, Miró JM. Primary HIV-1 infection in users of pre-exposure prophylaxis. Lancet HIV. 2021;8:e166-e174.
[PubMed Abstract] -

51. Markowitz M, Grossman H, Anderson PL, et al. Newly Acquired Infection With Multidrug-Resistant HIV-1 in a Patient Adherent to Preexposure Prophylaxis. J Acquir Immune Defic Syndr. 2017;76:e104-e106.
[PubMed Abstract] -

52. Cohen SE, Sachdev D, Lee SA, et al. Acquisition of tenofovir-susceptible, emtricitabine-resistant HIV despite high adherence to daily pre-exposure prophylaxis: a case report. Lancet HIV. 2018;S2352-3018(18)30288-1.
[PubMed Abstract] -

53. Colby DJ, Kroon E, Sacdalan C, et al. Acquisition of Multidrug-Resistant Human Immunodeficiency Virus Type 1 Infection in a Patient Taking Preexposure Prophylaxis. Clin Infect Dis. 2018;67:962-4.
[PubMed Abstract] -

54. Misra K, Huang JS, Udeagu CN, Forgione L, Xia Q, Torian LV. Pre-exposure prophylaxis (PrEP) use history in people with antiretroviral resistance at HIV diagnosis: Findings from New York City HIV surveillance and partner services, 2015-2022. Clin Infect Dis. 2023 Nov 17. Online ahead of print
[PubMed Abstract] -

55. Parikh UM, Koss CA, Mellors JW. Long-Acting Injectable Cabotegravir for HIV Prevention: What Do We Know and Need to Know about the Risks and Consequences of Cabotegravir Resistance? Curr HIV/AIDS Rep. 2022;19:384-93.
[PubMed Abstract] -

56. Eshleman SH, Fogel JM, Halvas EK, et al. HIV RNA Screening Reduces Integrase Strand Transfer Inhibitor Resistance Risk in Persons Receiving Long-Acting Cabotegravir for HIV Prevention. J Infect Dis. 2022;226:2170-80.
[PubMed Abstract] -

57. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. What to start: initial combination regimens for the people with HIV. September 21, 2022.
[HIV.gov] -

58. Andreatta K, Willkom M, Martin R, et al. Switching to bictegravir/emtricitabine/tenofovir alafenamide maintained HIV-1 RNA suppression in participants with archived antiretroviral resistance including M184V/I. J Antimicrob Chemother. 2019;74:3555-64.
[PubMed Abstract] -

59. Acosta RK, Willkom M, Andreatta K, et al. Switching to Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) From Dolutegravir (DTG)+F/TAF or DTG+F/Tenofovir Disoproxil Fumarate (TDF) in the Presence of Pre-existing NRTI Resistance. J Acquir Immune Defic Syndr. 2020;85:363-71.
[PubMed Abstract] -

60. Sax PE, Rockstroh JK, Luetkemeyer AF, et al. Switching to Bictegravir, Emtricitabine, and Tenofovir Alafenamide in Virologically Suppressed Adults With Human Immunodeficiency Virus. Clin Infect Dis. 2021;73:e485-e493.
[PubMed Abstract] -

61. Paton NI, Musaazi J, Kityo C, et al. Dolutegravir or Darunavir in Combination with Zidovudine or Tenofovir to Treat HIV. N Engl J Med. 2021;385:330-41.
[PubMed Abstract] -

62. Paton NI, Musaazi J, Kityo C, et al. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. Lancet HIV. 2022;9:e381-e393.
[PubMed Abstract] -

References

- Chernesky MA, Hook EW 3rd, Martin DH, et al. Women find it easy and prefer to collect their own vaginal swabs to diagnose *Chlamydia trachomatis* or *Neisseria gonorrhoeae* infections. Sex Transm Dis. 2005;32:729-33.
[PubMed Abstract] -

- Chou R, Spencer H, Bougatsos C, Blazina I, Ahmed A, Selph S. Preexposure Prophylaxis for the Prevention of HIV: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2023;330:746-63.
[PubMed Abstract] -

- Coy KC, Hazen RJ, Kirkham HS, Delpino A, Siegler AJ. Persistence on HIV preexposure prophylaxis medication over a 2-year period among a national sample of 7148 PrEP users, United States, 2015 to 2017. J Int AIDS Soc. 2019;22:e25252.
[PubMed Abstract] -

- Knox DC, Anderson PL, Harrigan PR, Tan DH. Multidrug-resistant HIV-1 infection despite preexposure prophylaxis. N Engl J Med. 2017;376:501-2.
[PubMed Abstract] -

- Knox J, Tabrizi SN, Miller P, et al. Evaluation of self-collected samples in contrast to practitioner-collected samples for detection of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* by polymerase chain reaction among women living in remote areas. Sex Transm Dis. 2002;29:647-54.
[PubMed Abstract] -

- Marcus JL, Hurley LB, Hare CB, et al. Preexposure Prophylaxis for HIV Prevention in a Large Integrated Health Care System: Adherence, Renal Safety, and Discontinuation. J Acquir Immune Defic Syndr. 2016;73:540-6.
[PubMed Abstract] -

- Marcus JL, Hurley LB, Nguyen DP, Silverberg MJ, Volk JE. Redefining Human Immunodeficiency Virus (HIV) Preexposure Prophylaxis Failures. Clin Infect Dis. 2017;65:1768-9.
[PubMed Abstract] -

- Rhee SY, Parkin N, Harrigan PR, Holmes S, Shafer RW. Genotypic correlates of resistance to the HIV-1 strand transfer integrase inhibitor cabotegravir. Antiviral Res. 2022;208:105427.
[PubMed Abstract] -

- Seifert SM, Chen X, Meditz AL, et al. Intracellular Tenofovir and Emtricitabine Anabolites in Genital, Rectal, and Blood Compartments from First Dose to Steady State. AIDS Res Hum Retroviruses.

2016;32:981-91.
[PubMed Abstract] -

- Sexton ME, Baker JJ, Nakagawa K, et al. How reliable is self-testing for gonorrhea and chlamydia among men who have sex with men? J Fam Pract. 2013;62:70-8.
[PubMed Abstract] -

- Tittle V, Boffito M, McOwan A, Whitlock G. Antiretroviral resistance and management after pre-exposure to prophylaxis. Lancet HIV. 2020;7:e84.
[PubMed Abstract] -

- Zucker J, Carnevale C, Gordon P, Sobieszczyk ME, Rai AJ. Am I Positive? Improving Human Immunodeficiency Virus Testing in the Era of Preexposure Prophylaxis and Immediate Antiretroviral Therapy Using Machine Learning. Open Forum Infect Dis. 2022;9:ofac259.
[PubMed Abstract] -

Figures

Figure 1 Recommended Laboratory Monitoring in Persons Taking TDF-FTC for HIV PrEP

Source: Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. December 2021:1-108.

Table based on 2021 CDC Clinical Practice Guidelines for HIV PrEP

Laboratory Evaluation in Persons Taking Tenofovir DF-Emtricitabine (TDF-FTC) HIV PrEP

Test	Q 3 months	Q 6 months	Q 12 months	When stopping
 HIV-1 RNA	ALL			ALL
 HIV Antigen/ Antibody	ALL¶			ALL¶
 Renal Function (eCrCl)		Age ≥50 years OR baseline eCrCl <90 mL/min	Age <50 years AND baseline eCrCl ≥90 mL/min	ALL
 Syphilis Serology	MSM/TGW	MSW/WSM		MSM/TGW
 Gonorrhea	MSM/TGW	MSW/WSM		MSM/TGW
 Chlamydia	MSM/TGW	MSW/WSM		MSM/TGW
 Hepatitis C Serology			MSM/TGW and/or PWID	
 Pregnancy Test	ALL^			

LEGEND:

¶ Laboratory-based preferred. Point of care blood acceptable but oral fluid testing not recommended.

^ For persons with childbearing potential; advised for counseling purposes

ABBREVIATIONS:

MSM = men who have sex with men; TGW = transgender woman; MSW = men who have sex with women; WSM = women who have sex with men; PWID = persons who inject drugs

EDITOR'S NOTES

1. Inability to order HIV-1 RNA testing should not preclude the use of TDF-FTC for HIV PrEP.
2. These recommendations pertain to persons taking daily oral TDF-FTC or on-demand (2-1-1) TDF-FTC.
3. Individuals who develop symptoms consistent with an STI should undergo prompt STI testing and receive appropriate treatment as clinically indicated; this evaluation should occur regardless of when the next routine STI screening is due.

Figure 2 Recommended Laboratory Monitoring in Persons Taking TAF-FTC for HIV PrEP

Source: Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. December 2021:1-108.

Table based on 2021 CDC Clinical Practice Guidelines for HIV PrEP

Laboratory Evaluation in Persons Taking Tenofovir Alafenamide-Emtricitabine (TAF-FTC) HIV PrEP

Test	Q 3 months	Q 6 months	Q 12 months	When stopping
HIV-1 RNA	ALL			ALL
HIV Antigen/ Antibody	ALL¶			ALL¶
Renal Function (eCrCl)		Age ≥50 years OR baseline eCrCl <90 mL/min	Age <50 years AND baseline eCrCl ≥90 mL/min	ALL
Syphilis Serology	MSM/TGW	MSW/WSM		MSM/TGW
Gonorrhea	MSM/TGW	MSW/WSM		MSM/TGW
Chlamydia	MSM/TGW	MSW/WSM		MSM/TGW
Hepatitis C Serology			MSM/TGW and/or PWID	
Lipid Panel			ALL	
Pregnancy Test	ALL^			

LEGEND:

¶ Laboratory-based preferred. Point of care blood acceptable but oral fluid testing not recommended.

^ For persons with childbearing potential; advised for counseling purposes

ABBREVIATIONS:

MSM = men who have sex with men; TGW = transgender woman; MSW = men who have sex with women; WSM = women who have sex with men; PWID = persons who inject drugs

EDITOR'S NOTES

1. Inability to order HIV-1 RNA testing should not preclude the use of TAF-FTC for HIV PrEP.
2. Individuals who develop symptoms consistent with an STI should undergo prompt STI testing and receive appropriate treatment as clinically indicated; this evaluation should occur regardless of when the next routine STI screening is due.

Figure 3 RecommendedLaboratory Monitoring in Persons Receiving CAB-LA for HIV PrEP

Source: Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. December 2021:1-108.

Table based on 2021 CDC Clinical Practice Guidelines for HIV PrEP

Laboratory Evaluation in Persons Receiving Injectable Cabotegravir (CAB-LA) for HIV PrEP

TEST	1 month visit	Q2 months	Q4 months	Q6 months	Q12 months	When stopping
HIV-1 RNA	ALL	ALL				ALL
HIV Antigen/ Antibody	ALL¶	ALL¶				ALL¶
Syphilis			MSM/TGW	MSW/WSM		MSM/TGW
Gonorrhea			MSM/TGW	MSW/WSM		MSM/TGW
Chlamydia			MSM/TGW	MSW/WSM		MSM/TGW
Hepatitis C Serology					MSM/TGW and/or PWID	
Pregnancy Test			ALL^			

LEGEND:

¶ Laboratory-based preferred. Point of care blood acceptable but oral fluid testing not recommended.

^ For persons with childbearing potential; advised for counseling purposes

ABBREVIATIONS:

MSM = men who have sex with men; TGW = transgender woman; MSW = men who have sex with women; WSM = women who have sex with men; PWID = persons who inject drugs

EDITOR'S NOTES

1. Results for the HIV RNA and Ag/Ab should be available prior to administering the first cabotegravir injection. For all subsequent injections, the laboratory studies can be drawn on the same day the injection is given.
2. Individuals who develop symptoms consistent with an STI should undergo prompt STI testing and receive appropriate treatment as clinically indicated; this evaluation should occur regardless of when the next routine STI screening is due.

Figure 4 Restarting CAB-LA After Second Missed Injection

Illustration: Peter E. Harrison, MPH and David H. Spach, MD Source: Cabotegravir (*Apretude*) Prescribing Information

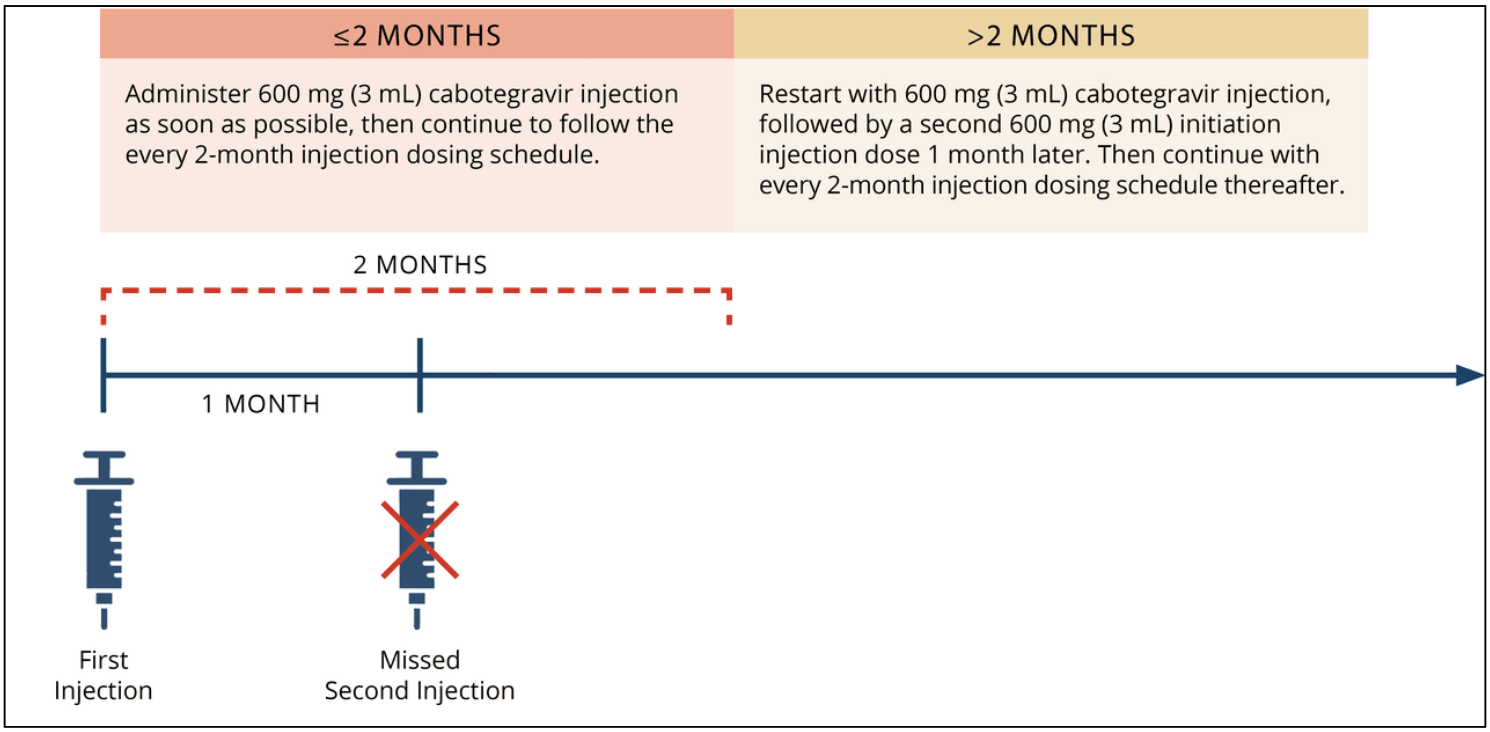

Figure 5 Restarting CAB-LA After Third or Later Missed Injection

Illustration: Peter E. Harrison, MPH and David H. Spach, MD Source: Cabotegravir (*Apretude*) Prescribing Information

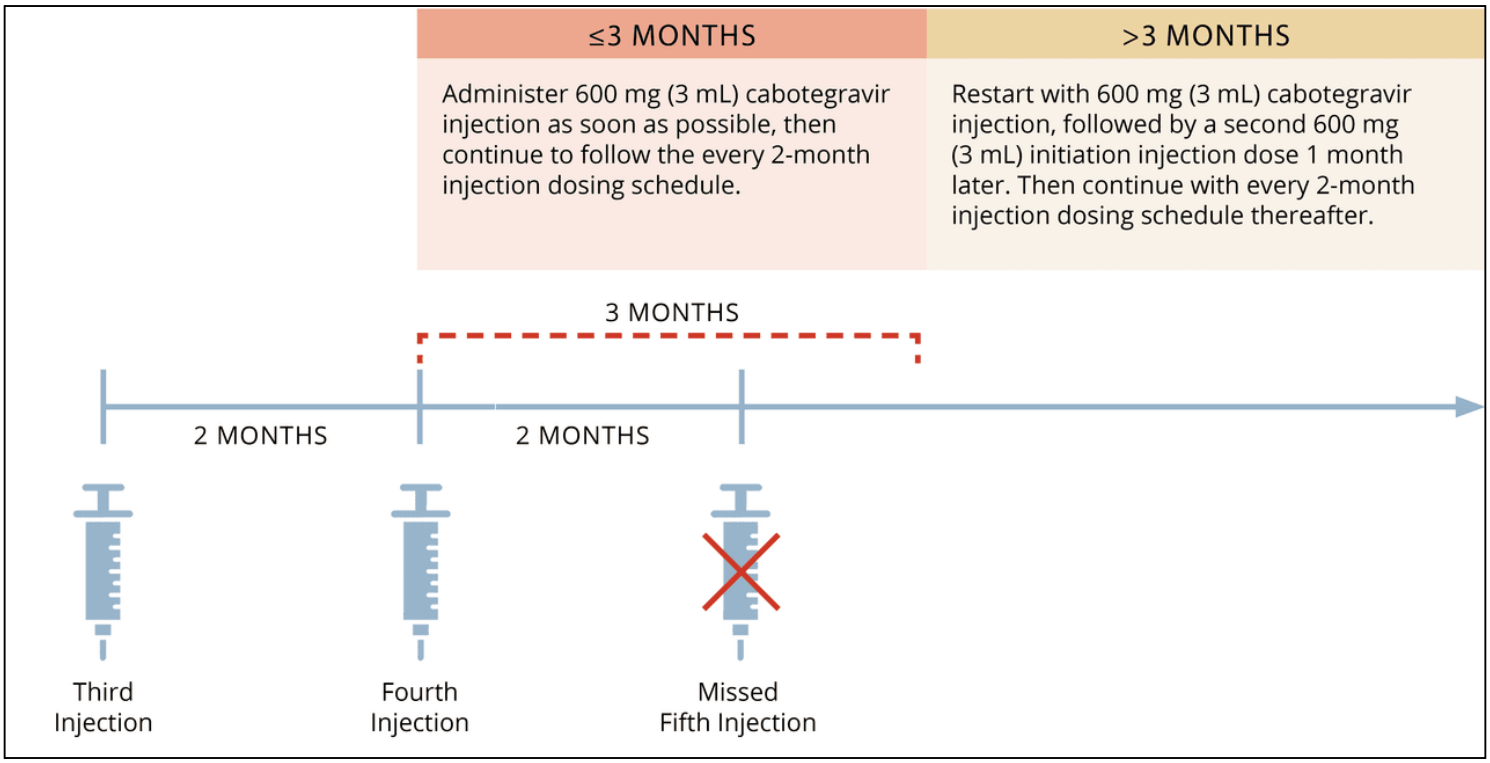

Figure 6 HIV Incidence in MSM Before, While Taking, and After Stopping HIV PrEP

Abbreviations: MSM = men who have sex with men; TDF-FTC = tenofovir DF-emtricitabine

Source: Hojilla JC, Hurley LB, Marcus JL, et al. Characterization of HIV preexposure prophylaxis use behaviors and HIV incidence among US adults in an integrated health care system. JAMA Netw Open. 2021;4:e2122692.

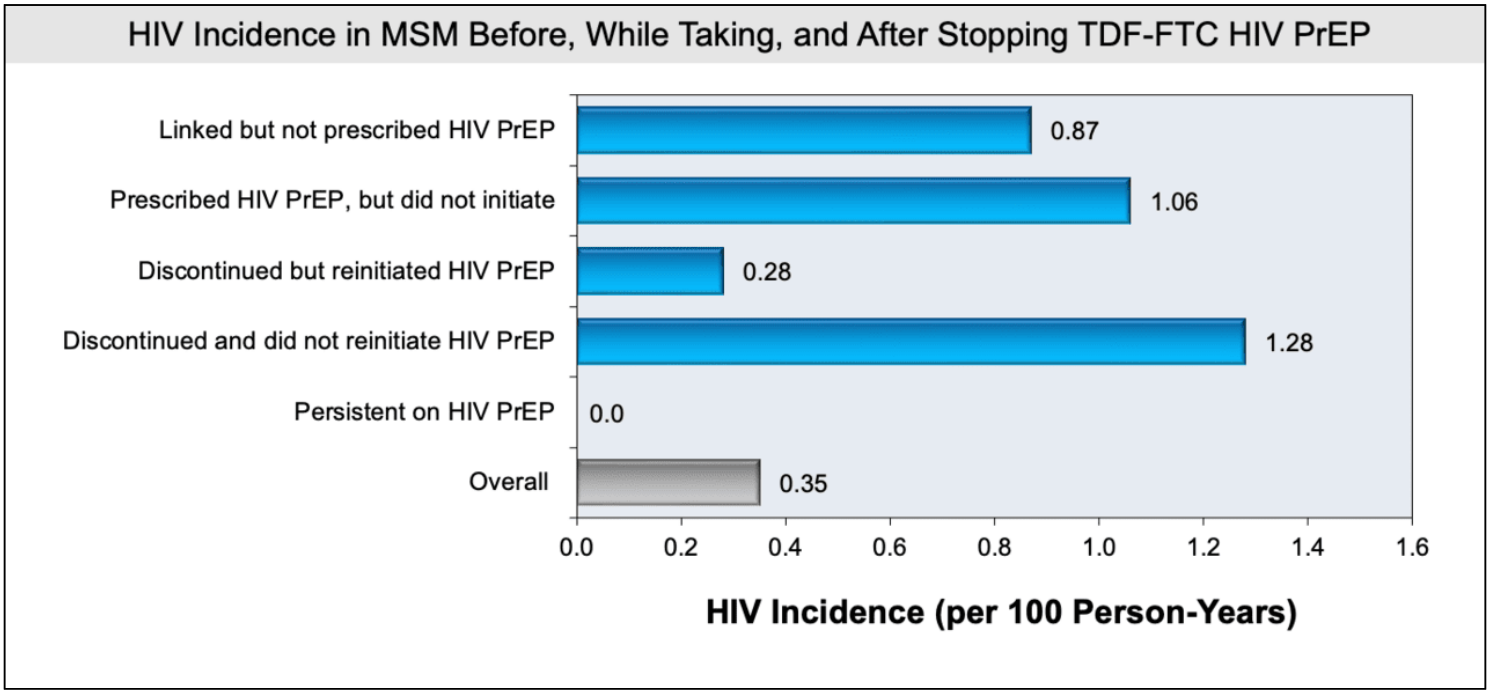

Figure 7 Potential HBV Rebound and Hepatic Flare after Stopping Oral HIV PrEP in Person with Chronic Hepatitis B Virus Infection

Illustration: David H. Spach, MD

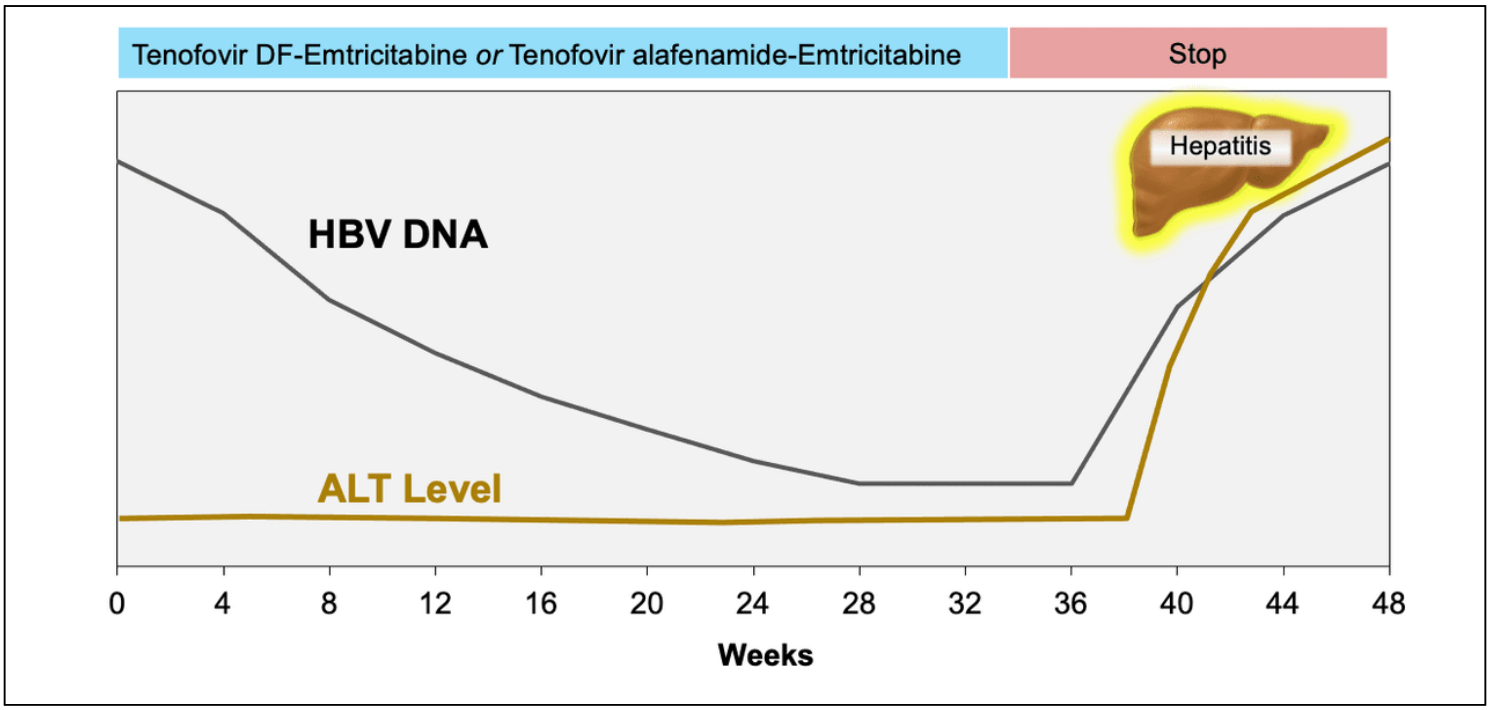

Figure 8 Detectable Cabotegravir Levels Weeks after Last Injection

Note: weeks 52 and 60 were combined as aggregate data

Source: Landovitz RJ, Li S, Eron JJ Jr, et al. Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial. Lancet HIV. 2020;7:e472-e481.

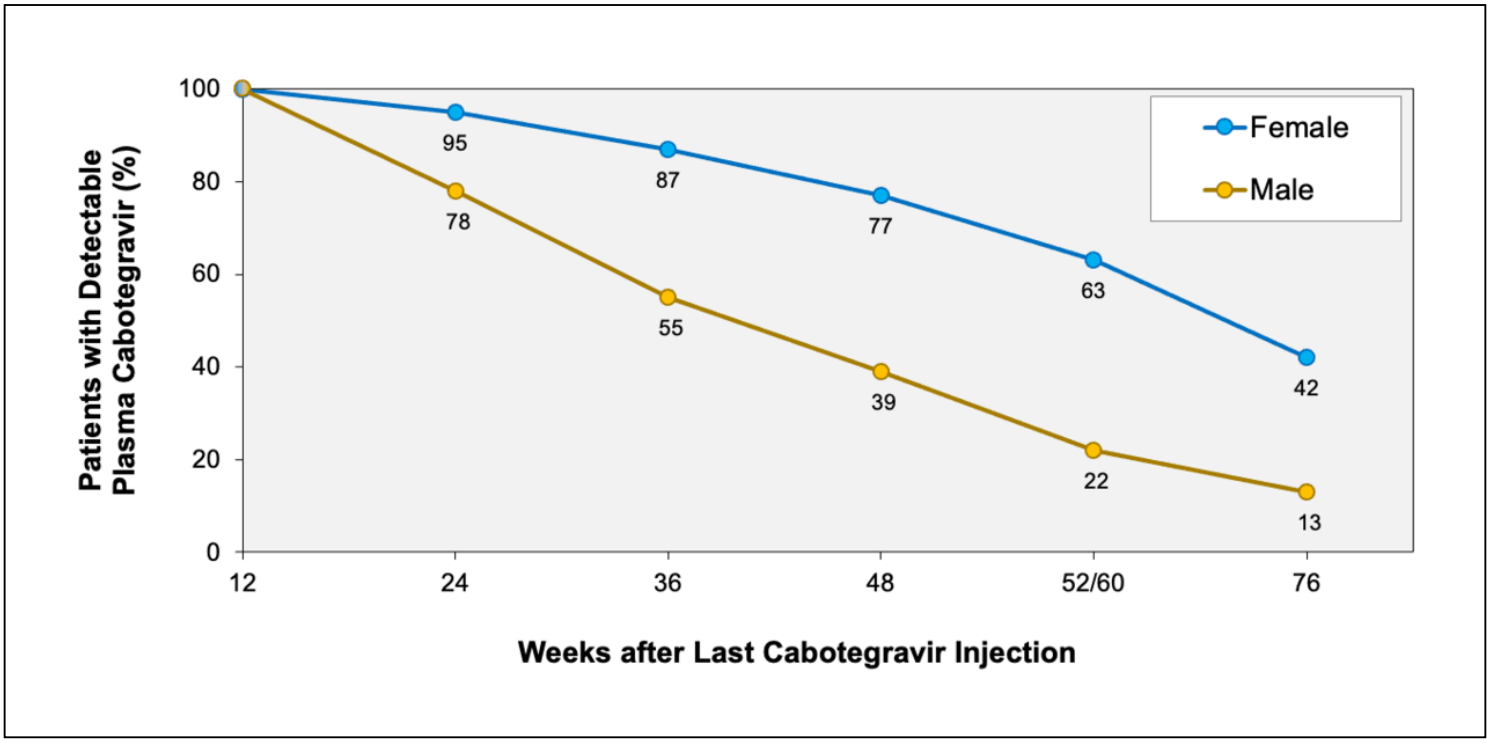

Figure 9 Typical Laboratory Markers Following Acquisition of HIV in Persons Not on HIV PrEP

Illustration: David H. Spach, MD

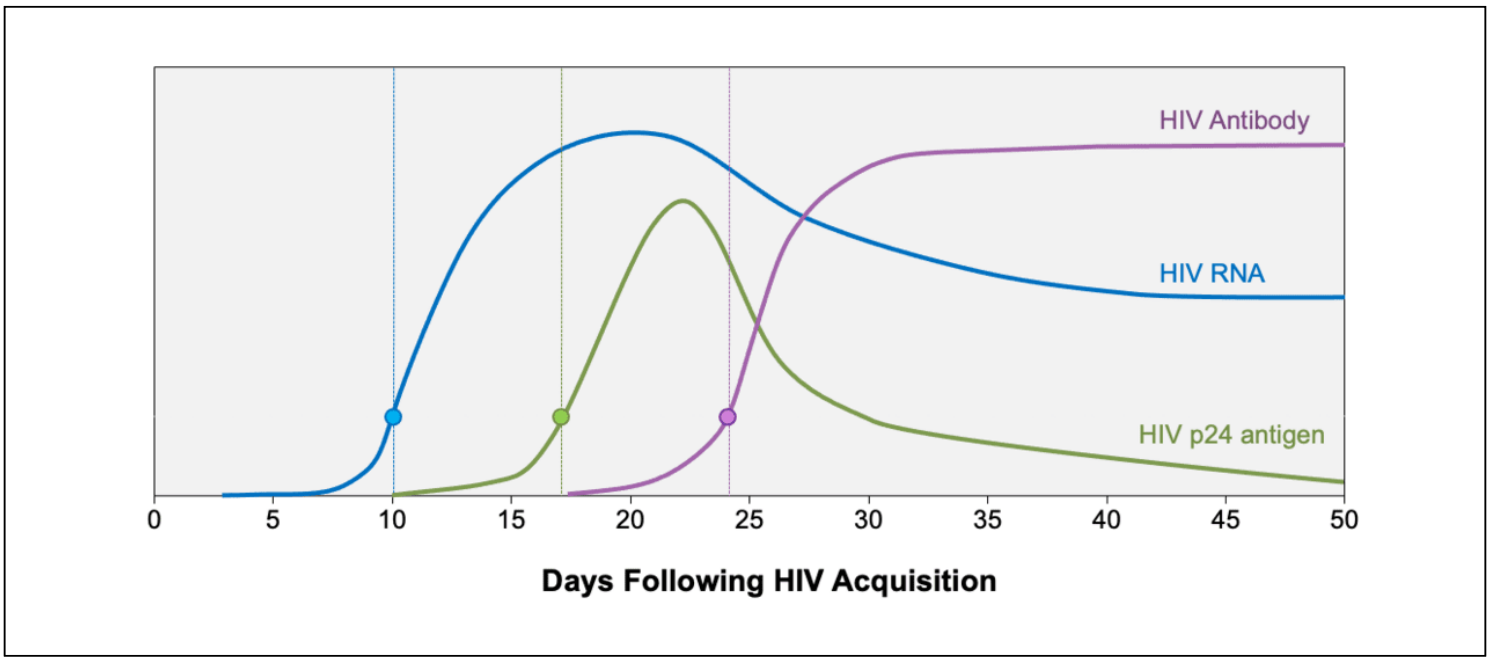

Figure 10 HIV Drug Resistance in Persons Prescribed HIV PrEP

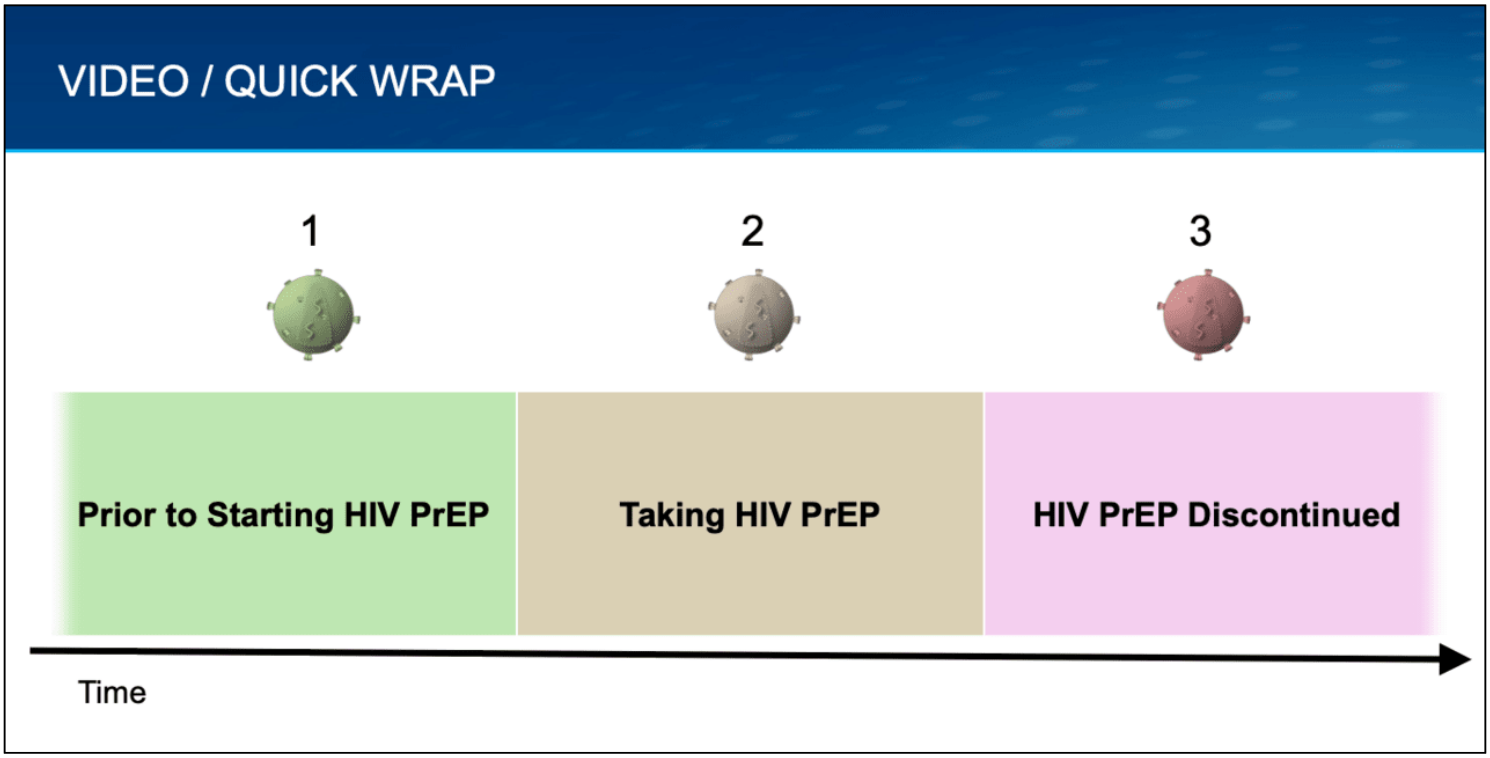

Figure 11 Initiating Antiretroviral Therapy in Person Newly Diagnosed with HIV

Abbreviations: INSTI = integrase strand transfer inhibitor; TDF = tenofovir DF; TAF = tenofovir alafenamide; FTC = emtricitabine; 3TC = lamivudine

Source: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. What to start: initial combination regimens for people with HIV. September 21, 2022.

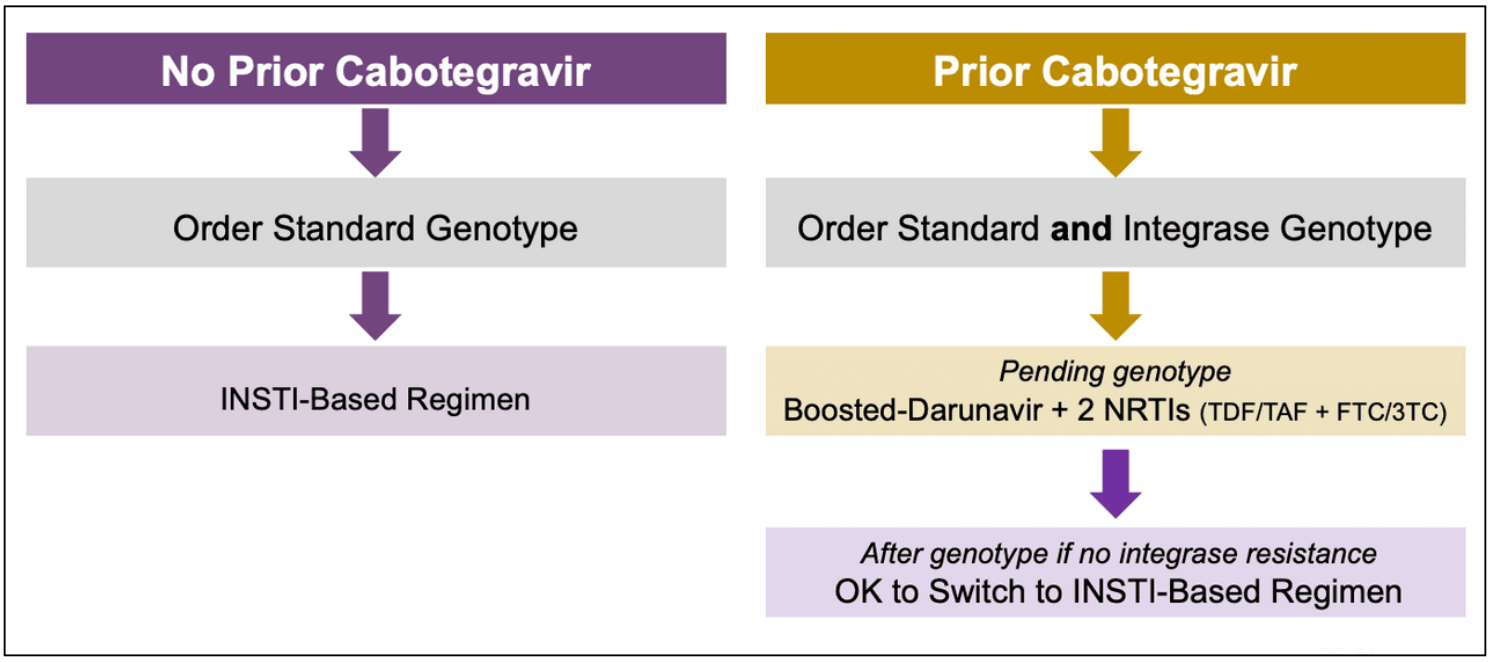

Figure 12 HIV PrEP Tools for Clinicians: Laboratory Tests