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

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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. For persons receiving lenacapavir subcutaneous injections (LEN-SQ), on-site visits are required every 6 months for LEN-SQ injections in the clinic. Additional interactions are advised to follow-up for laboratory testing and review of possible adverse effects; for additional interactions that do not require in clinic visits, off-site options can be used.[1]

- **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

Monitoring with Oral HIV PrEP

Frequency of Visits for 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.[2] 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.[2] 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.[2]

Laboratory Monitoring for 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).[2] 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.[2] 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 for 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).[2] 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.[2] 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. Monitoring with a lipid panel is recommended every 12 months due to minor elevations in serum lipids that may occur with TAF-FTC.[2][Q] Monitoring for HCV While on TAF-FTC

Monitoring with Cabotegravir

Frequency of Visits for 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 CAB-LA injections.

Laboratory Monitoring for 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 HIV testing every 2 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.[2] The following summarizes recommendations in the 2021 CDC HIV PrEP Guidelines for laboratory monitoring of persons receiving CAB-LA for HIV PrEP (Figure 3).[2][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 (Figure 4). Likewise, the same 7-day before and after window exists when administering the 1-month second initiation dose. When patients are scheduled for an 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 (Figure 5). 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 6). 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 7). 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.

Monitoring with Lenacapavir

Frequency of Visits for Persons Receiving LEN-SQ

After the first injection of LEN-SQ, the next injection should be given 6 months (26 weeks) later. All subsequent injections should be given every 6 months (26 weeks). The first injection is referred to as an initiation phase injection and follow-up injections are referred to as continuation phase injections. For persons receiving LEN-SQ for HIV PrEP, the timing of longitudinal follow-up is linked to the timing of the in-clinic injections and the need for regular HIV and STI testing. Regular monitoring of persons who are receiving LEN-SQ 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 LEN-SQ injections.

Laboratory Monitoring for Persons Receiving LEN-SQ

Since persons receiving LEN-SQ require in-clinic injections every 6 months, the typical laboratory monitoring in persons receiving LEN-SQ continuation phase injections is every 3 month testing. Routine renal or lipid monitoring is not indicated for persons receiving LEN-SQ since this medication does not cause nephrotoxicity or hyperlipidemia. In addition, LEN-SQ can safely be administered to persons without renal insufficiency without a need for dose adjustment. The following summarizes recommendations in the 2025 CDC LEN-SQ HIV PrEP Guidelines for laboratory monitoring of persons receiving LEN-SQ for HIV PrEP (Figure 8).[2]

Scheduling and Tracking LEN-SQ Dosing

Clinics providing LEN-SQ should ideally have a mechanism and designated clinic personnel for scheduling and tracking all persons receiving LEN-SQ. When administering every 6-month CAB-LA, the acceptable dosing window is 2 weeks before or 2 weeks after the scheduled dose, which would be 6 months (26 weeks) from the last LEN-SQ injection (Figure 9). When patients are scheduled for the every 6-month injections, it is optimal to schedule the next injection as close as possible to the exact 6-month interval. From a practical standpoint, this timing of scheduling close to the exact time 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 6 months apart from the prior injection, and they miss the clinic visit for the injection, this will allow the clinic staff 2 weeks to contact, reschedule, and administer LEN-SQ and still have the injection given within the acceptable 2-week late window.

Oral Bridge Dosing for Planned Missed Continuation Phase Injection

For individuals who plan to miss a scheduled every 6-month LEN-SQ injection (perhaps due to travel or other conflicts) by more than 2 weeks, oral HIV PrEP bridging medication should be used (Figure 10). The recommended strategy is to use oral lenacapavir 300 mg every 7 days for the oral bridge for up to 6 months. The planned oral bridge should be based on the last LEN-SQ dose, ideally starting 26 weeks after the last LEN-SQ dose and no later than 28 weeks from the last LEN-SQ dose. When the individual is able to resume LEN-SQ, the dose should be administered within 7 days of the last oral dose to ensure lenacapavir levels remain adequate. If oral lenacapavir cannot be used for the bridge, daily oral TDF-FTC or daily oral TAF-FTC can be used, as long as they are indicated for HIV PrEP in the person receiving LEN-SQ. If oral TDF-FTC or TAF-FTC is used for the oral bridge, restarting LEN-SQ requires repeating the initiation phase lenacapavir dosing: day-1 LEN-SQ injections (927 mg total) and lenacapavir oral doses 600 mg total), followed by day-2 oral lenacapavir doses (600 mg total). If TDF-FTC or TAF-FTC is used for the oral bridge, it is important to have a current (or recent) estimated creatinine clearance and to evaluate hepatitis B virus status—to ensure that TDF-FTC or TAF-FTC is appropriate.

Restarting LEN-SQ After Unplanned Missed Continuation Phase Injection

When starting LEN-SQ after an unplanned missed continuation injection dose (more than 2 weeks late with no oral lenacapavir bridge dosing), the recommendation is to use initiation phase lenacapavir dosing: day-1 LEN-SQ injections (927 mg total) and lenacapavir oral doses 600 mg total), followed by day-2 oral lenacapavir doses (600 mg total) (Figure 11).

Discontinuing HIV PrEP

At each HIV PrEP follow-up visit, HIV risk and the appropriateness of continuing HIV PrEP should be reassessed.[2] 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.[3] 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 restarting HIV PrEP and found the risk of acquiring HIV was significant for many persons who stop HIV PrEP (Figure 12).[4] 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.[4]

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.[2] 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.[5] The investigators concluded that a high level of protection against HIV acquisition may persist for several days after stopping oral TDF-FTC.[5] 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.[6,7] 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.[2] 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).[8,9,10]

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.[11] 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 13).[12] 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.[13] 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.[14]

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. 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 a very 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 14).[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.[17,18] 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.[2,19] They should remain on oral HIV PrEP until the risk of HIV acquisition is no longer present.(Figure 15)
- Individuals without an ongoing risk of HIV acquisition who decide to stop CAB-LA (and do not require continuation of HIV PrEP) should receive counseling about restarting 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 ideally have follow-up visits quarterly for 12 months after discontinuation of CAB-LA to reassess HIV risk, potential indications to restart HIV PrEP, and to undergo HIV testing.[2] 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] Transitioning to Oral HIV PrEP from CAB-LA

Discontinuing LEN-SQ HIV PrEP

Risk of Acquiring HIV After Stopping LEN-SQ

Similar to HIV acquisition that can occur after stopping oral HIV PrEP or CAB-LA, individuals can acquire HIV after stopping LEN-SQ, with the risk beginning roughly 28 weeks after the last LEN-SQ dose. If a person misses or stops receiving LEN-SQ, the risk of HIV acquisition should be assessed and resumption of some type of HIV PrEP should be discussed.

How Long Does Lenacapavir Remain in the Body After Discontinuation?

Lenacapavir injected subcutaneously has an extremely long half-life of 8–12 weeks.[20] After a 927 mg SQ dose of LEN-SQ, levels of lenacapavir typically remain detectable for at least 1 year. Protection against HIV acquisition is for approximately 28 weeks. The half-life of a 600 mg oral dose of lenacapavir is approximately 10–12 days.[20]

Recommendations for Persons Discontinuing LEN-SQ

- At the time of LEN-SQ discontinuation, it is important to document the individual's HIV status, reason for stopping, as well as current and future risk for HIV acquisition.
- If an individual decides to stop LEN-SQ, the clinician should counsel the individual about the very long lenacapavir tail phase (and the risk of developing HIV drug resistance if HIV is acquired after stopping LEN-SQ), as well as the potential for lenacapavir-related drug interaction to occur long after lenacapavir is discontinued.
- Individuals with an ongoing risk of HIV acquisition who decide to stop LEN-SQ should transition to another appropriate HIV PrEP regimen that is started within 28 weeks after the last LEN-SQ injection (Figure 16).
- Individuals without an ongoing risk of HIV acquisition who decide to stop LEN-SQ (and do not require continuation of HIV PrEP) should receive counseling about restarting HIV PrEP if they anticipate future activities that might carry a risk of HIV acquisition.
- Persons who discontinue LEN-SQ should ideally have quarterly follow-up visits for 12 months after discontinuation of LEN-SQ to reassess HIV risk, potential indications to restart HIV PrEP, and to undergo HIV testing.[2] 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).

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.
[Activity] A. Timing of Potential HIV Acquisition in People Prescribed HIV PrEP

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.[2,21,22] A retrospective review in England evaluated persons diagnosed with HIV who were taking or had recently taken oral HIV PrEP and found that 87% (45 of 52) of these individuals reported a significant problem with medication adherence.[23] 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).[24,25,26,27,28,29] There are rare, but clearly documented, cases of HIV acquisition in persons with good oral medication adherence.[23] In addition, in one clinical trial with oral HIV PrEP, there were several suspected cases of baseline HIV infection that was not originally detected.[26]

CaseS of HIV Acquisition in Persons Receiving 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. 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). 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.

CaseS of HIV Acquisition in Persons Receiving LEN-SQ

Because LEN-SQ has been extremely effective as HIV PrEP, there is very little known about HIV acquisition in persons taking LEN-SQ. In the PURPOSE 1 trial, there were no cases of HIV acquisition among the women in the LEN-SQ study arm.[29] In the PURPOSE 2 trial, there were 2 cases of HIV among men in the LEN-SQ study arm and neither of these individuals reported symptoms consistent with acute (primary) HIV.[28] Both of the participants who acquired HIV had lenacapavir concentrations that were within the range of the overall lenacapavir concentrations in the pharmacokinetics cohort, which was considered protective.[28] For the two participants who acquired HIV, one was diagnosed at the week 13 study visit and the other at week 26.[28] The participant diagnosed at week 13 had positive rapid and laboratory-based HIV antigen–antibody tests, an indeterminate HIV antibody differentiation test, and an HIV-1 RNA level of 934,000 copies/mL).[28] The participant diagnosed at week 26 had a negative rapid HIV antigen–antibody test, a positive laboratory-based HIV antigen–antibody test, an antibody differentiation test that was indeterminate for HIV-1 and negative for HIV-2, and an HIV-1 RNA level of 14,100 copies/mL.[28] Additional retrospective standard HIV-1 RNA and HIV-1 RNA single-copy testing of samples obtained at baseline were all negative, except for the participant diagnosed with HIV at week 13 had a positive week 8 HIV-1 RNA single-copy test (4.8 copies/mL).[28] Both participants who acquired HIV had the N74D capsid resistance mutation detected on blood samples drawn at the time of their HIV diagnosis.[28] It was hypothesized the capsid mutations emerged in both participants who acquired HIV as a result of lenacapavir monotherapy.[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 17).[30,31,32] 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.[18,21,33] 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.[18,34] 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.[18,34] 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. 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 for significant diagnostic delays when only using HIV-1/2 antigen-antibody immunoassay for HIV screening in persons receiving oral HIV PrEP or CAB-LA, 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 oral HIV PrEP or CAB-LA.[2] In the PURPOSE 2 trial, the two participants in the LEN-SQ arm who acquired HIV during the study did not have a delay in the HIV diagnosis and both had positive laboratory-based HIV antigen-antibody tests at the time of the HIV diagnosis.[28] For persons receiving LEN-SQ, a blood-based antigen-antibody assay, without HIV-1 RNA testing, is recommended for routine follow-up HIV testing.[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.[35,36] 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.[37,38,39,40,41] 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.[42,43,44] 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 persons with Ambiguous HIV Test Results

The management of persons who are receiving or have recently 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.[45]

- 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.[17,46,47,48] Nevertheless, drug resistance can occur with oral HIV PrEP, CAB-LA, and LEN-SQ, 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.[49,50,51] 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.[52] 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.[52]
- Although infrequent, it is possible the person taking HIV PrEP can acquire drug-resistant HIV while taking HIV PrEP, even with excellent medication adherence.[33,53,54,55] 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 and lenacapavir can persist for longer than 1 year after discontinuation of CAB-LA or LEN-SQ.

- Acquisition of HIV after HIV PrEP has been stopped will typically involve 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 *polymerase* gene in the regions that code for the reverse transcriptase protein. 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.[47] 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.[47] Overall, the M184V/I mutation (FTC resistance) was the most commonly detected mutation.[47] Resistance to TFV involved K65R and K70E mutations.[47]
- 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.[21] 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).[21]
- 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.[56] 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.[56] 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%).[56] 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.[56]

HIV Drug Resistance with Injectable Cabotegravir

If an individual acquires HIV just before starting CAB-LA, while receiving CAB-LA, or after discontinuing CAB-LA, antiretroviral drug resistance may occur.[57] The resistance occurs as a result of mutations in the HIV *polymerase* gene in the region that codes for the HIV integrase protein. integrase resistance may impact future antiretroviral regimen choices, since 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 of integrase resistance in persons receiving CAB-LA.[34]

- There are 37 documented cases of HIV in persons who acquired HIV after receiving cabotegravir where integrase resistance testing was successfully performed. For these HIV cases, major integrase resistance mutations were identified in 11 (30%) of 37 patients.[58]
- Diagnosis of HIV in persons receiving CAB-LA can be complicated and delayed by long-acting viral inhibition (LEVI) syndrome.[59] In this setting of delayed HIV diagnosis, INSTI resistance emerges early.[18,34] In addition, prolonged delays in diagnosis of persons receiving CAB-LA has been associated with the accumulation of integrase resistance mutations.[58]

- There are 37 documented cases of HIV in persons who acquired HIV after receiving cabotegravir where integrase resistance testing was successfully performed. For these HIV cases, major integrase resistance mutations were identified in 11 (30%) of 37 patients.[58]

HIV Drug Resistance with Injectable Lenacapavir

If an individual acquires HIV just before starting LEN-SQ, while receiving LEN-SQ, or after discontinuing LEN-SQ, antiretroviral drug resistance may occur.[57] Resistance to lenacapavir occurs as a result of mutations in the HIV *gag* gene, in the region that codes for the HIV capsid (p24) protein. At this time, there is only one FDA-approved capsid inhibitor (lenacapavir). There are two reported cases of HIV acquisition among persons receiving LEN-SQ for HIV PrEP and both individuals had the N74D capsid resistance mutation detected on blood samples drawn at the time of their HIV diagnosis.[28] Lenacapavir does not have a high genetic barrier to resistance. Lenacapavir resistance is not known to have a significant impact on HIV susceptibility to other classes of HIV antiretroviral medications.

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. There are no commercially available tests to detect capsid resistance mutations (resistance to lenacapavir).
- **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.[2,60] 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 19).[60]

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.[60] The addition of the third medication should not be delayed while the HIV drug resistance testing is pending.[2,60] 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.[19]

- **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.[60]
- **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.[61,62,63]
- **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.[64,65] 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.[60] 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.[60] 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

Choosing an Antiretroviral Therapy Regimen in Persons Who Received LEN-SQ

If a person acquires HIV and has received one or more doses of LEN-SQ for HIV PrEP, the initial choice of antiretroviral therapy is straightforward and the choice of initial antiretroviral therapy would not be impacted by receipt of LEN-SQ. In this situation, the Adult and Adolescent ARV Guidelines recommend using an initial antiretroviral regimen that consists of 2 NRTIs (typically TAF-FTC or TDF-FTC) plus an INSTI (bictegravir or dolutegravir).[60]

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.[2] 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 20). 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.
NOTE: The HIV PrEP Tools for Clinicians is in the process of revision to include lenacapavir as an option for HIV PrEP.

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 taking oral HIV PrEP , every 2 months in persons receiving CAB-LA injections, and every 6 months in persons receiving LEN-SQ injections.
- For persons receiving HIV PrEP, regular STI testing is indicated, with more frequent testing recommended for MSM. 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 and MSM.
- 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 and lenacapavir have a very long half-life when administered as CAB-LA and LEN-SQ. Thus, special counseling should be given regarding the risk of HIV acquisition after stopping CAB-LA or LEN-SQ.
- 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 can occur 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 or LEN-SQ, 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).

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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	Initial visit	Q 3 months	Q 6 months	Q 12 months	When stopping
HIV Antigen/ Antibody*	ALL†	ALL			ALL
HIV-1 RNA	If indicated‡	ALL			ALL
Renal Function (eCrCl)	ALL		Age ≥50 years ***OR*** baseline eCrCl <90 mL/min§	Age <50 years ***AND*** baseline eCrCl ≥90 mL/min§	ALL
Syphilis Serology	ALL	MSM	MSW WSM		MSM
Gonorrhea	ALL	MSM	MSW WSM		MSM
Chlamydia	ALL	MSM	MSW WSM		MSM
Hepatitis B Serology	ALL¶				
Hepatitis C Serology	ALL¶			MSM and/or PWID	
Pregnancy Test	ALL#	ALL#			

ABBREVIATIONS:

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

LEGEND:

*The HIV antigen-antibody test must be a blood-based assay; oral fluid HIV testing is not recommended.

†Perform within 7 days of starting HIV PrEP

‡Not routinely recommended, but order if any of the following apply: (1) received oral HIV PrEP or HIV PEP medications in past 3 months; (2) received cabotegravir injection in the past 12 months; (3) had high-risk exposure to HIV in prior 4 weeks; (4) has symptoms that suggest acute HIV.

§TDF-FTC is not recommended if the estimated creatinine clearance is less than 60 mL/min.

¶One-time screening recommended for all adults in the United States. Give hepatitis B immunization if nonimmune.

#For women with childbearing potential; advised for counseling purposes

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.

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

ABBREVIATIONS:
MSM = men who have sex with men; MSW = men who have sex with women; WSM = women who have sex with men; PWID = persons who inject drugs

LEGEND:
* The HIV antigen-antibody test must be a blood-based assay; oral fluid HIV testing is not recommended.
† Perform within 7 days of starting HIV PrEP
‡ Not routinely recommended, but order if any of the following apply: (1) received oral HIV PrEP or HIV PEP medications in past 3 months; (2) received cabotegravir injection in the past 12 months; (3) had high-risk exposure to HIV in prior 4 weeks; (4) has symptoms that suggest acute HIV.
§ TAF-FTC is not recommended if the estimated creatinine clearance is less than 30 mL/min.
¶ One-time screening recommended for all adults in the United States. Give hepatitis B immunization if nonimmune.
# For women with childbearing potential; advised for counseling purposes

EDITOR'S NOTES
1. Inability to order HIV-1 RNA testing should not preclude the use of TAF-FTC for HIV PrEP.

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	Initial visit	1 month	Q2 months	Q4 months	Q6 months	Q12 months	When stopping
HIV Antigen/ Antibody*	ALL†	ALL†	ALL‡				ALL
HIV-1 RNA	ALL§	ALL§	ALL§				ALL
Syphilis	ALL			MSM	MSW WSM		MSM
Gonorrhea	ALL			MSM	MSW WSM		MSM
Chlamydia	ALL			MSM	MSW WSM		MSM
Hepatitis B Serology	ALL¶						
Hepatitis C Serology	ALL¶					MSM and/or PWID	
Pregnancy Test	ALL#			ALL			

ABBREVIATIONS:

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

LEGEND:

* The HIV antigen-antibody test must be a blood-based test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. Two testing options are acceptable: (1) a laboratory blood-based HIV-antigen antibody test, or (2) a rapid, point-of-care blood HIV antigen-antibody test. Oral fluid HIV testing should not be used.

† Perform within 7 days of starting HIV PrEP. Confirm negative HIV status prior to giving the first dose of cabotegravir. If an oral cabotegravir lead-in is used, the initial HIV testing should be done within 7 days of starting the oral lead-in, repeated within 7 days of the first cabotegravir initiation injection dose, and repeated again prior to the second initiation injection dose given 1 month later. If a rapid blood-based HIV antigen-antibody test is used to document the negative HIV test, a supplemental laboratory blood-based HIV antigen-antibody test should also be obtained; the cabotegravir can be started if the laboratory blood-based HIV antigen-antibody test result is pending.

‡ Confirm negative HIV status prior to giving cabotegravir continuation doses. If a rapid blood-based HIV antigen-antibody test is used to document the negative HIV test, a supplemental laboratory blood-based HIV antigen-antibody test should also be obtained; the cabotegravir dose can be given if the laboratory blood-based HIV antigen-antibody test result is pending.

§ An HIV-1 RNA should be obtained prior to the first dose of cabotegravir (oral lead-in and/or first injection) and repeated prior to every cabotegravir injection. Oral cabotegravir lead-in and cabotegravir injections can be given if the HIV-1 RNA result is pending and the blood-based HIV antigen-antibody test result is negative.

¶ One-time screening recommended for all adults in the United States. Give hepatitis B immunization if nonimmune.

For women with childbearing potential; advised for counseling purposes

Figure 4 Acceptable CAB-LA Dosing Schedule Range for Continuation Injections

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

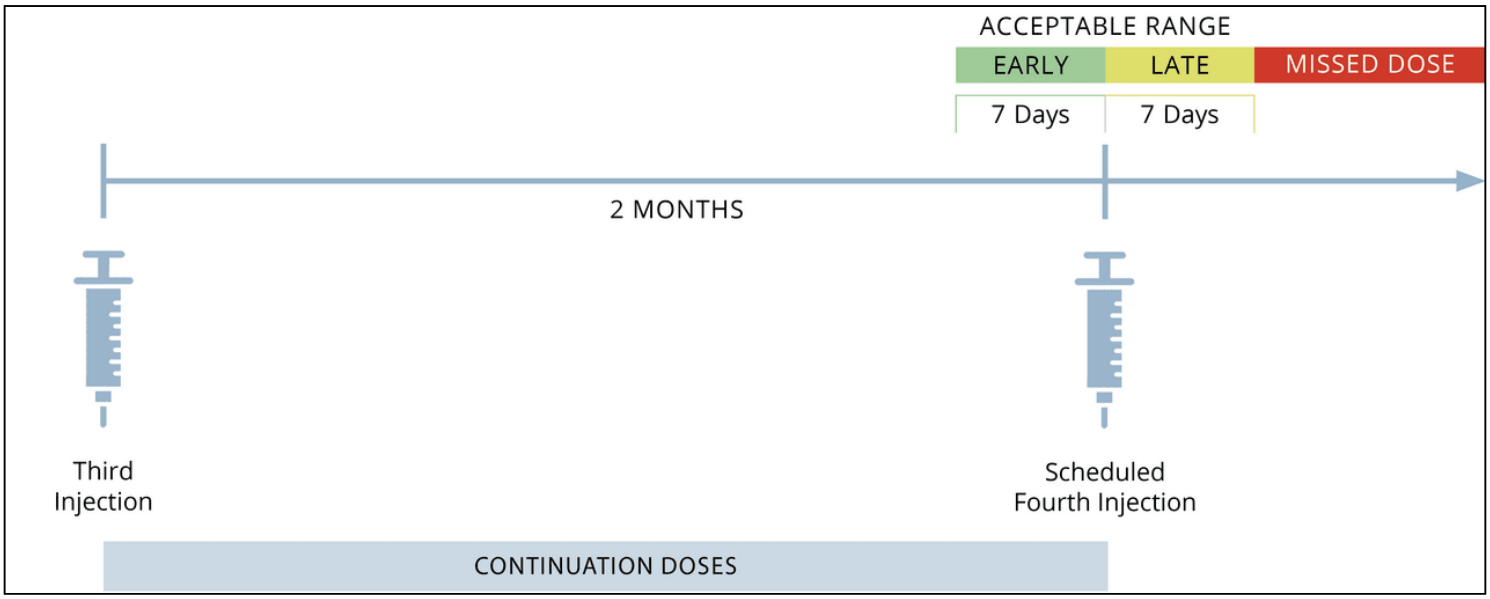

Figure 5 Cabotegravir Oral Bridge for Planned Missed Doses

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

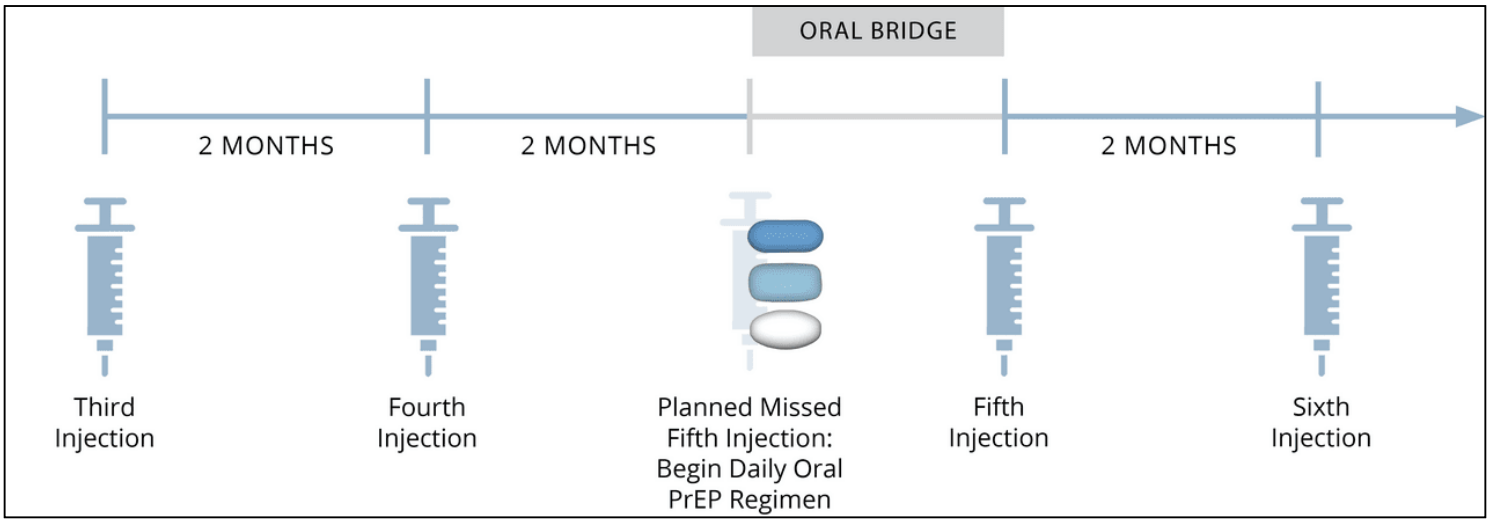

Figure 6 Restarting CAB-LA After Second Missed Injection

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

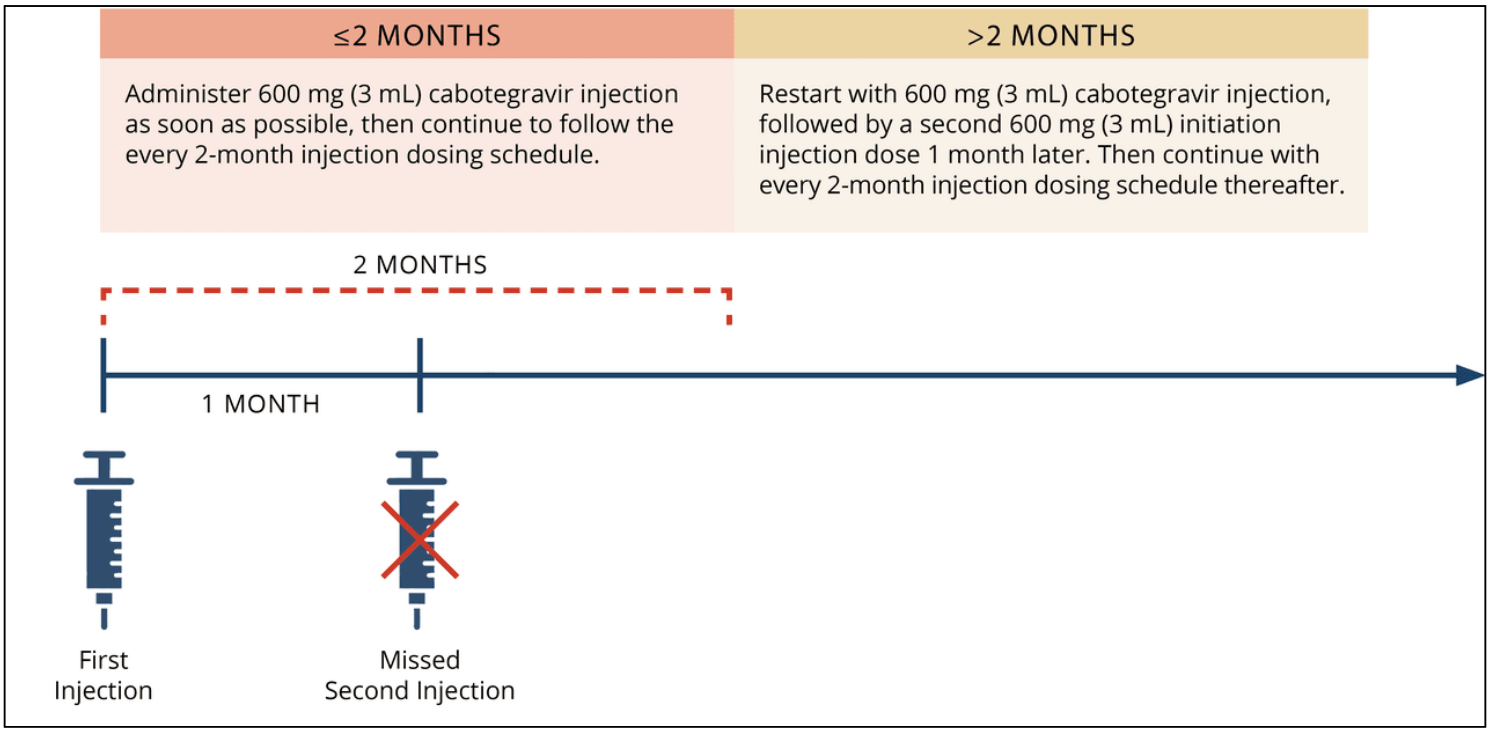

Figure 7 Restarting CAB-LA After Third or Later Missed Injection

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

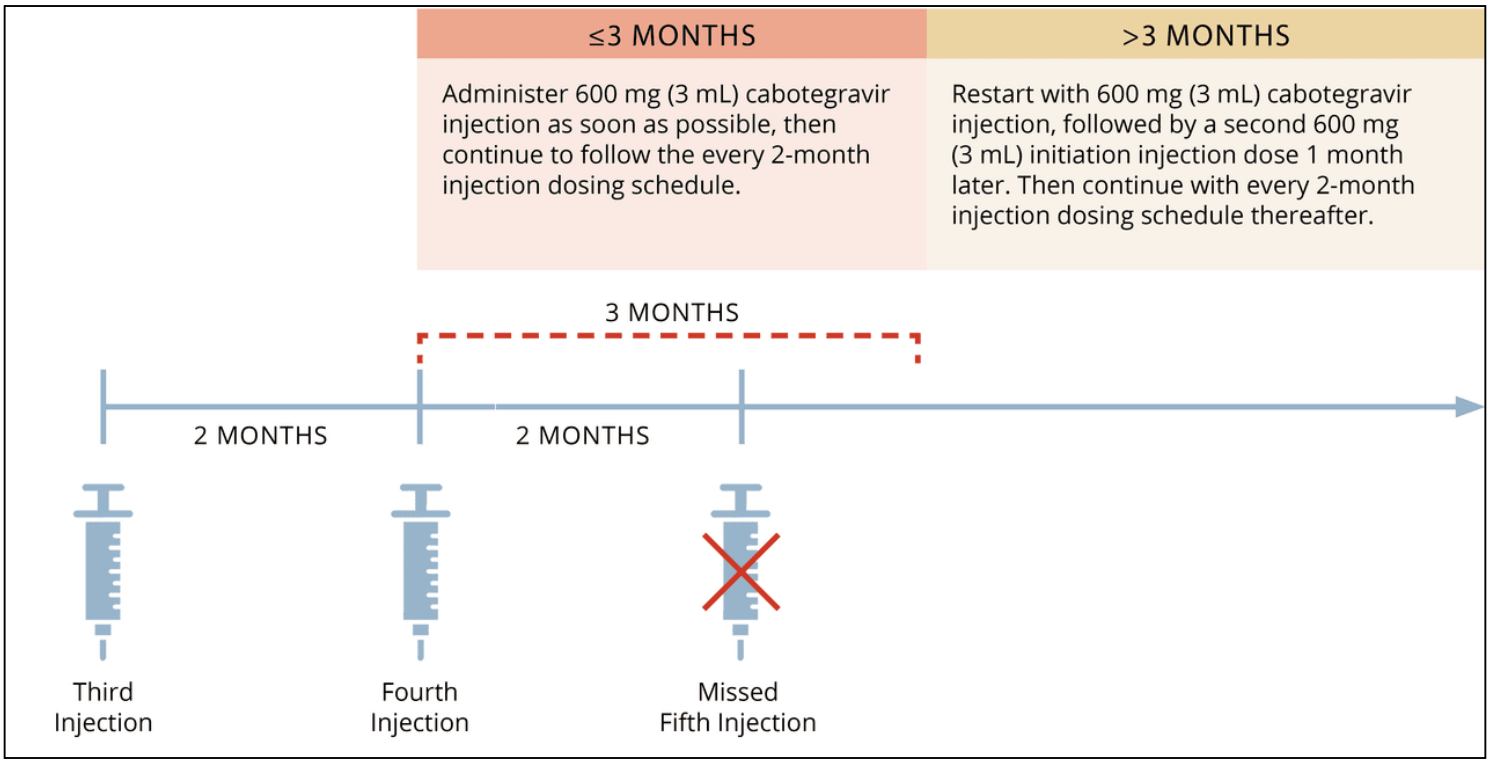

Figure 8 Recommended Laboratory Monitoring in Persons Taking LEN-SQ for HIV PrEP

Source: Patel RR, Hoover KW, Lale A, Cabrales J, Byrd KM, Kourtis AP. Clinical Recommendation for the Use of Injectable Lenacapavir as HIV Preexposure Prophylaxis - United States, 2025. MMWR Morb Mortal Wkly Rep. 2025;74:541-9.

Table based on 2021 CDC Clinical Practice Guidelines for HIV PrEP and Clinical Recommendation for the Use of Injectable Lenacapavir as HIV Preexposure Prophylaxis — United States, 2025

Laboratory Evaluation in Persons Starting or Receiving Lenacapavir for HIV PrEP

Test	Initial visit	Q 6 months	Q 12 months	When stopping
HIV-1 Antigen/ Antibody*	ALL†	ALL‡	ALL‡	ALL
HIV-1 RNA	ALL§			
Syphilis Serology	ALL	MSM¶	ALL	ALL
Gonorrhea	ALL	MSM¶	ALL	ALL
Chlamydia	ALL	MSM¶	ALL	ALL
Hepatitis B Serology	ALL#			
Hepatitis C Serology**	ALL††		MSM and/or PWID	
Pregnancy Test	ALL‡‡	ALL‡‡	ALL‡‡	

ABBREVIATIONS: MSM = Men who have sex with men; PWID = Persons who Inject Drugs

LEGEND:

*The HIV antigen-antibody test must be a blood-based test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. Two testing options are acceptable: (1) a laboratory blood-based HIV-antigen antibody test, or (2) a rapid, point-of-care blood HIV antigen-antibody test. Oral fluid HIV testing should not be used.

†Perform within 7 days prior to starting HIV PrEP. Confirm negative HIV status prior to giving the lenacapavir initiation dose. If a rapid blood-based HIV antigen-antibody test is used to document the negative HIV test, a supplemental laboratory blood-based HIV antigen-antibody test should also be obtained; lenacapavir can be started if the laboratory blood-based HIV antigen-antibody test result is pending.

‡Confirm negative HIV status prior to giving the lenacapavir continuation dose. If a rapid blood-based antigen-antibody test is used to document the negative HIV test, a supplemental laboratory blood-based HIV antigen-antibody test should also be obtained; the lenacapvir continuation dose can be given if the laboratory blood-based HIV antigen antibody test result is pending.

§A blood sample for an HIV-1 RNA test should be drawn within 7 days prior to the initiation dose; the lenacapavir initiation phase dosing can be given if the HIV-1 RNA test result is pending and the blood-based HIV antigen-antibody test is negative. If starting lenacapavir after a switch from another HIV PrEP regimen without any interruption, only a laboratory-based HIV antigen-antibody test is needed before the injection.

¶Testing for MSM is usually done every 3-6 months.

#One-time screening for hepatitis B virus (HBV) recommended for all adults in the United States. Screen with hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb).

**One-time screening for HCV recommended for all adults in the United States.

††Screen with hepatitis C antibody test and, if reactive, reflex to hepatitis C virus (HCV) RNA test.

‡‡For women with childbearing potential; advised for counseling purposes.

Figure 9 Acceptable Dosing Schedule Range with LEN-SQ

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

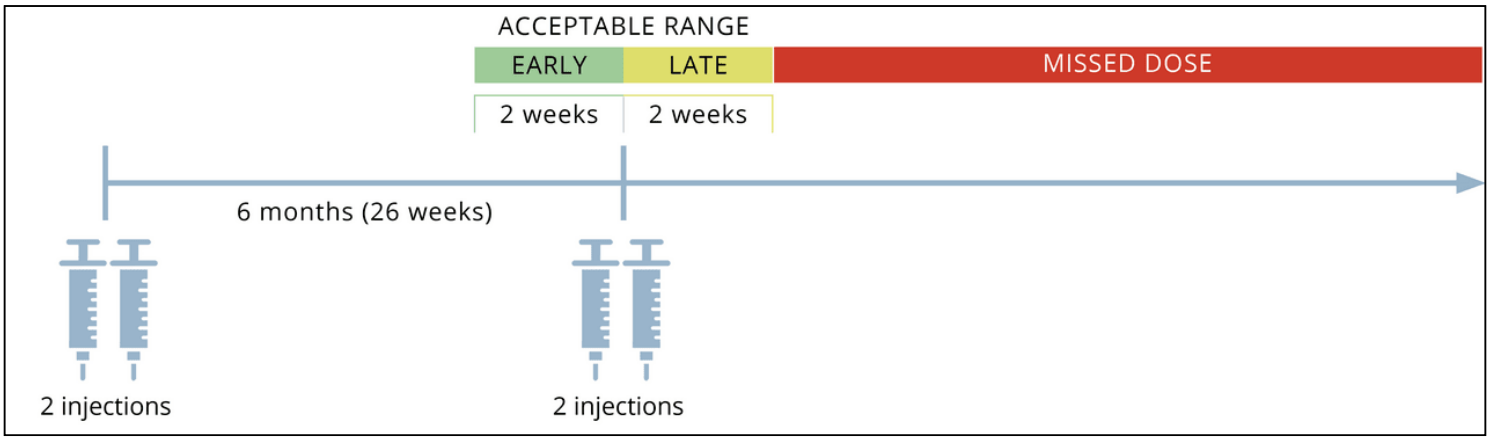

Figure 10 Lenacapvir and Oral Bridge for Planned Missed Doses

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

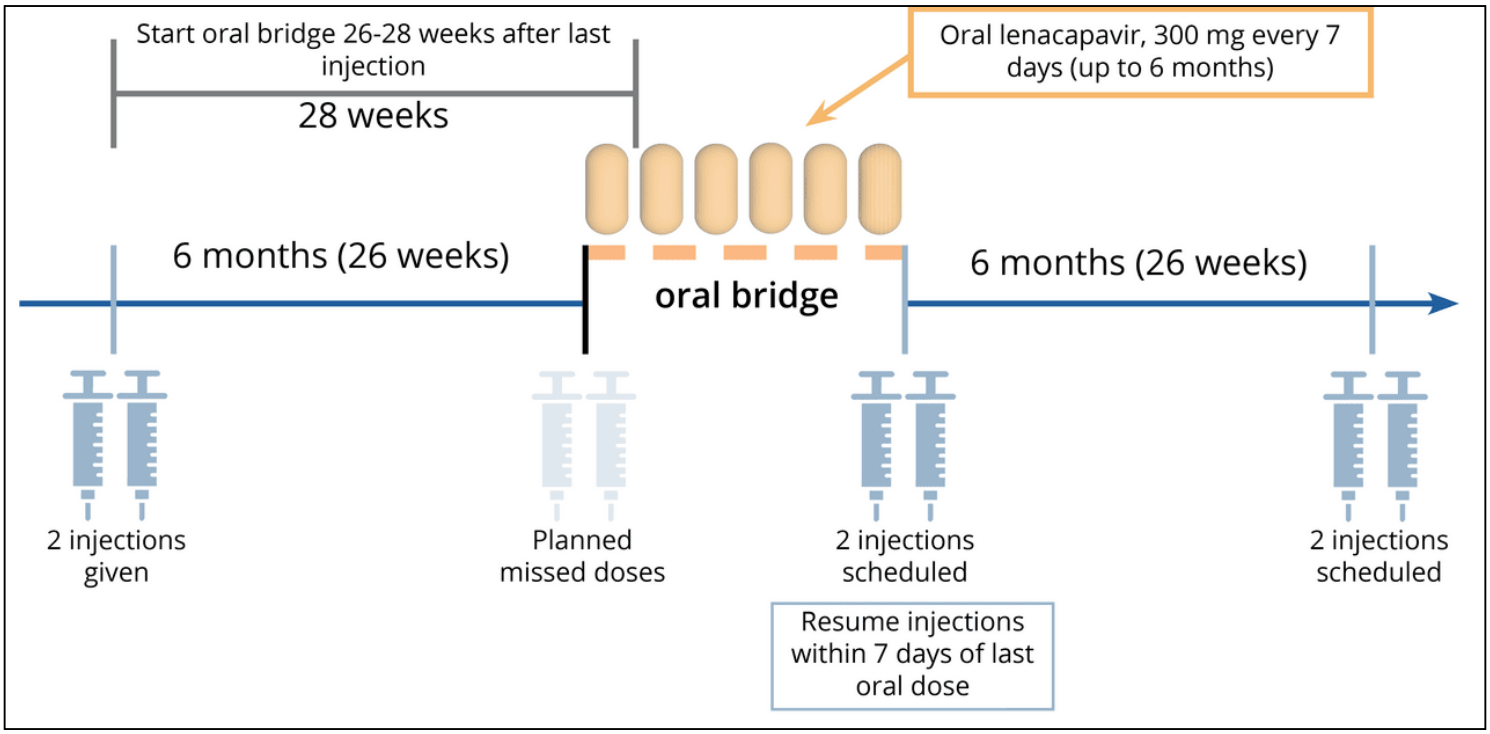

Figure 11 Restarting Lenacapavir After Unplanned Missed Injection Doses

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

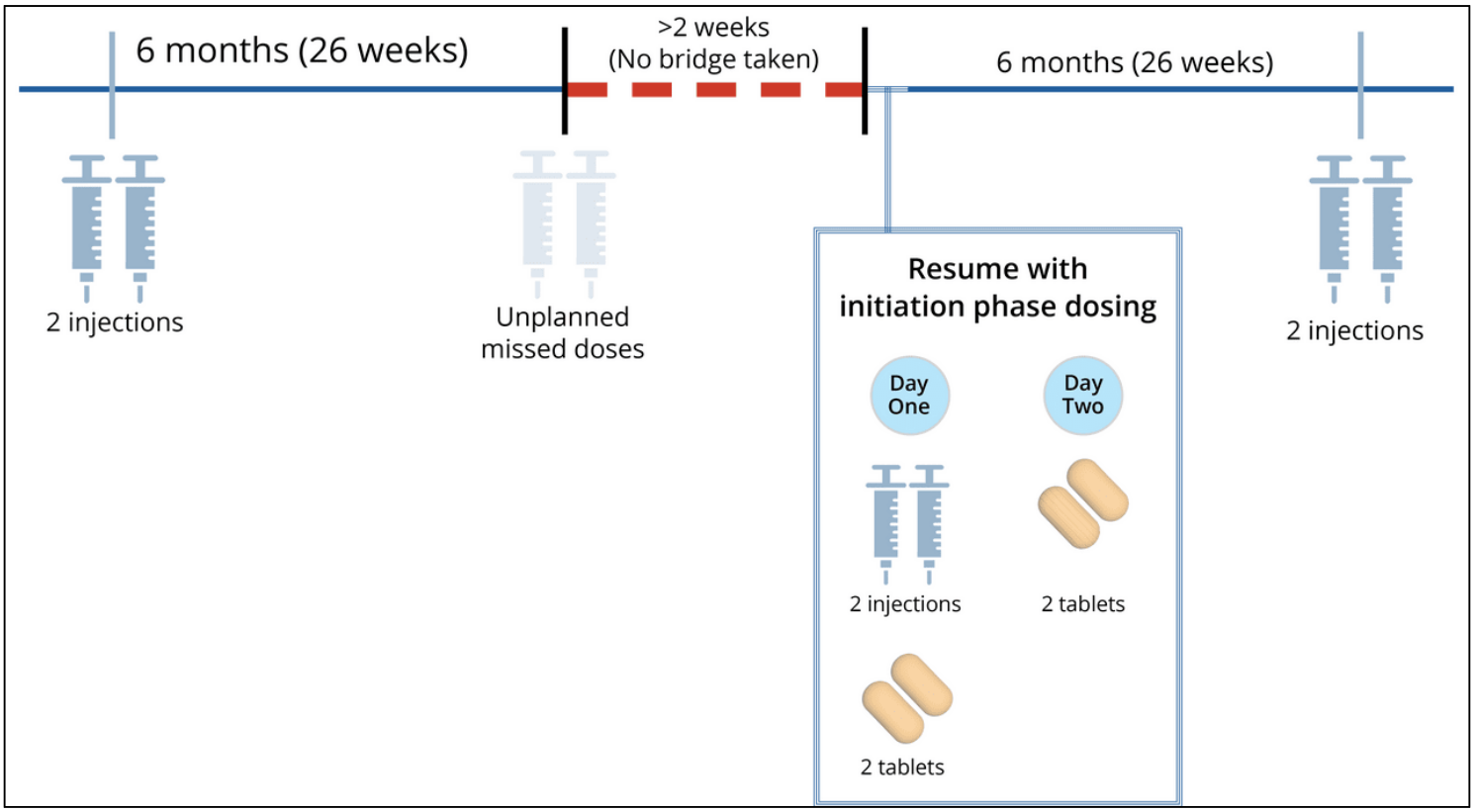

Figure 12 HIV Incidence in MSM Before, While Taking, and After Stopping HIV PrEP

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.

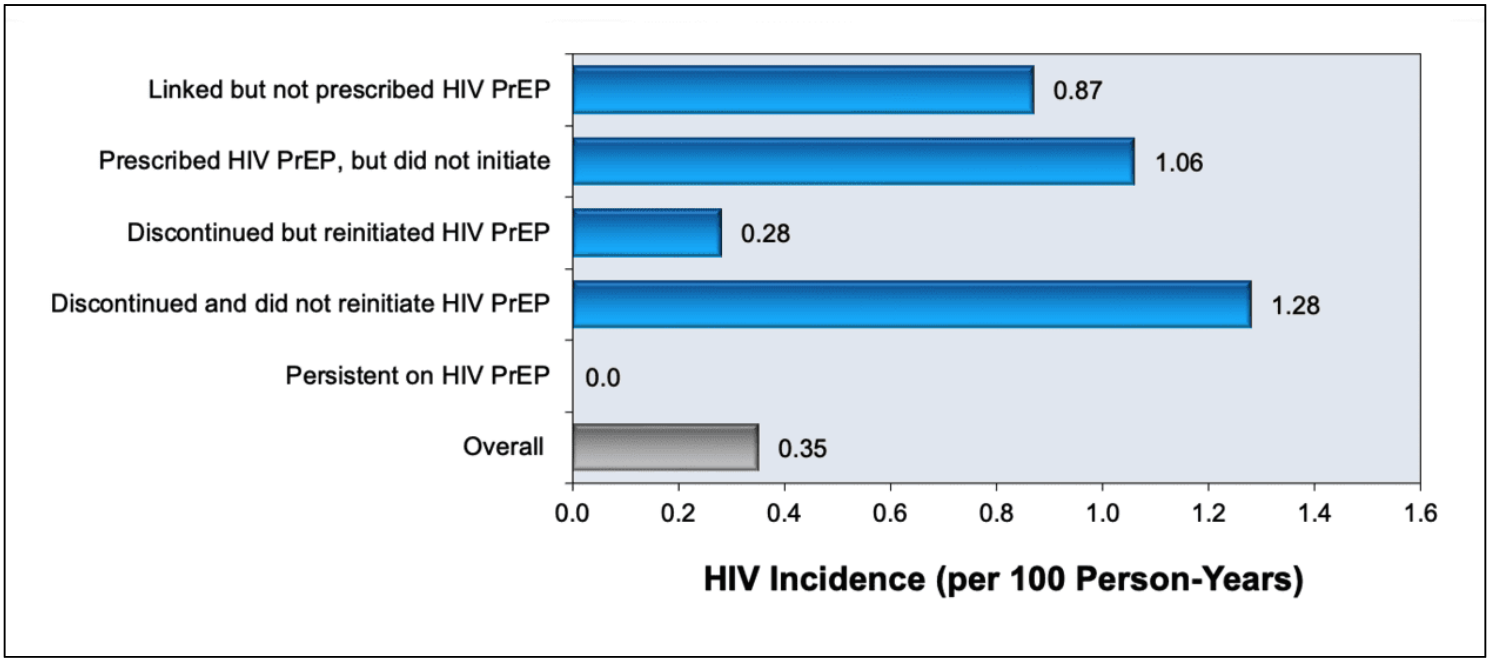

Figure 13 Potential HBV Rebound and Hepatic Flare after Stopping Oral HIV PrEP in Person with Chronic Hepatitis B Virus Infection

Illustration: David H. Spach, MD

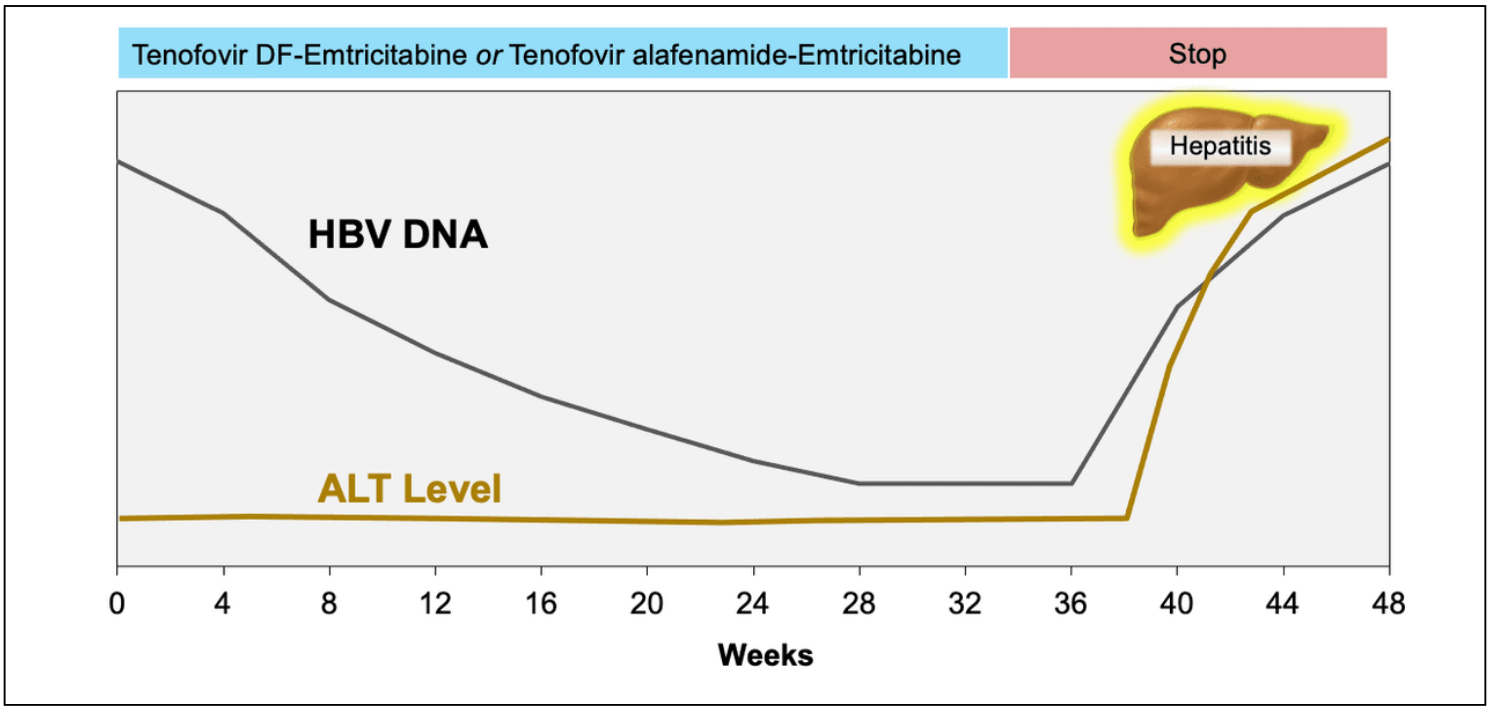

Figure 14 Detectable Cabotegravir Levels Weeks after Last Injection

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.

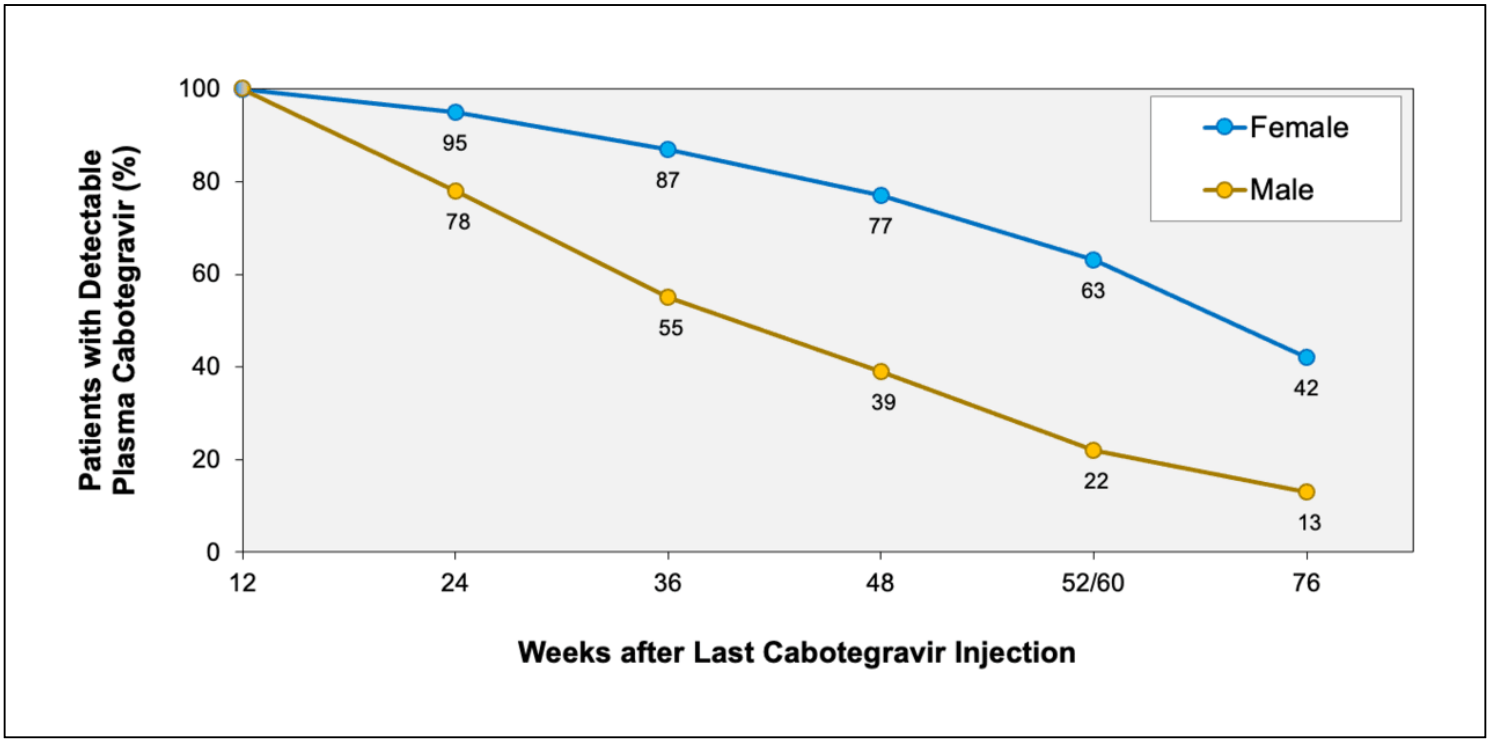

Figure 15 Management when Stopping CAB-LA HIV PrEP

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

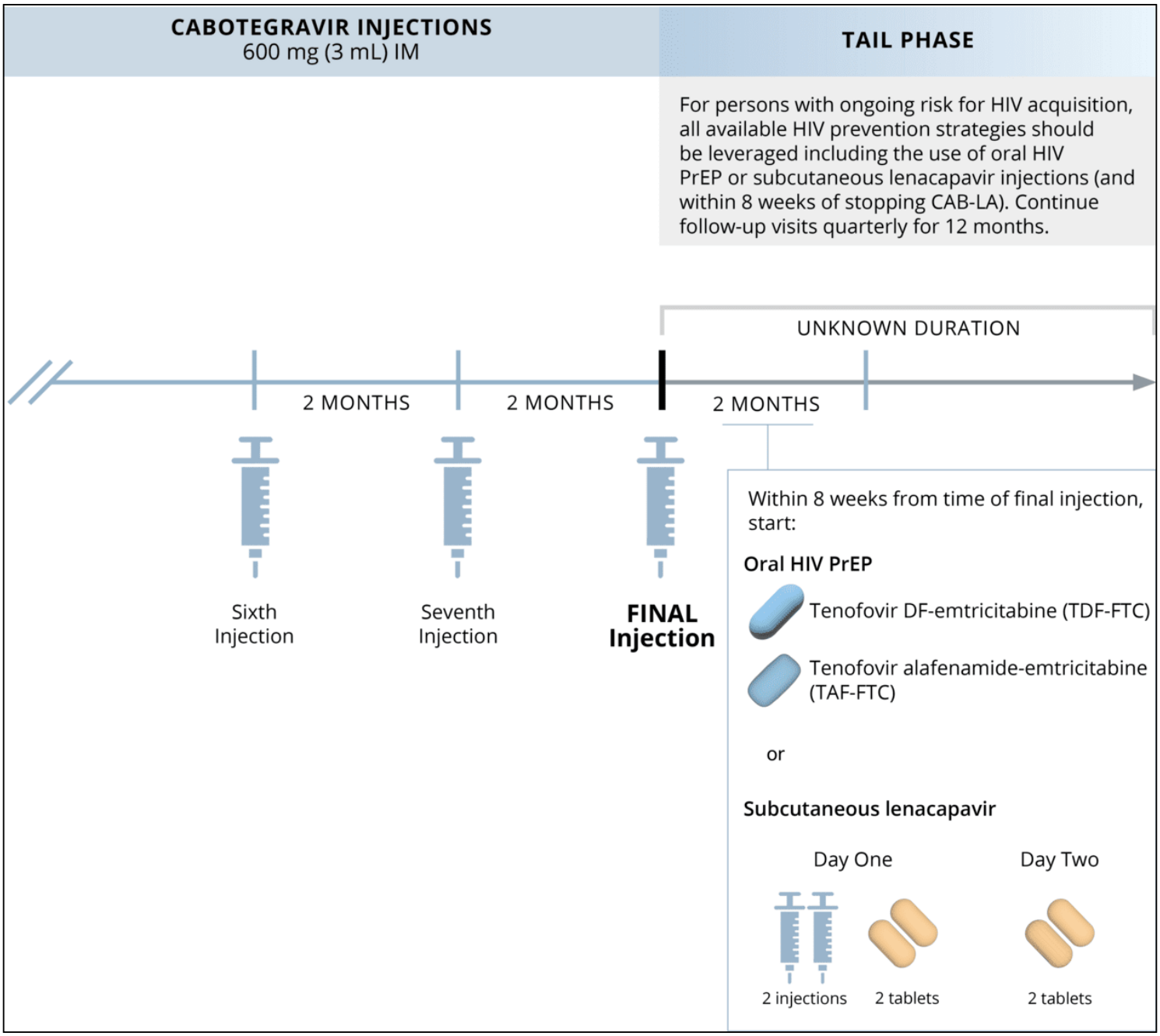

Figure 16 Management when Stopping LEN-SQ HIV PrEP

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

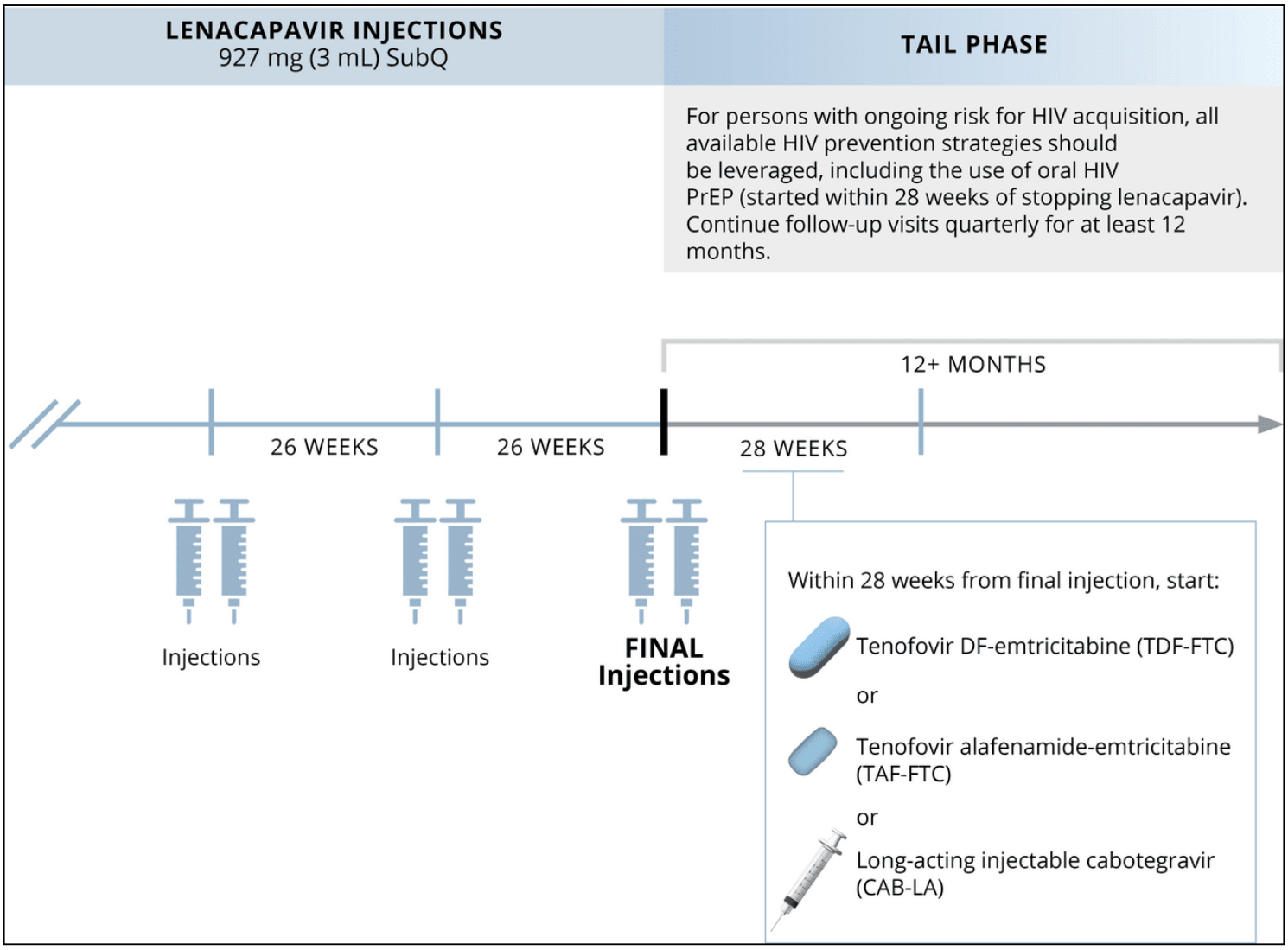

Figure 17 Typical Timing of Laboratory Markers Following Acquisition of HIV in Persons Not on HIV PrEP

Illustration: David H. Spach, MD

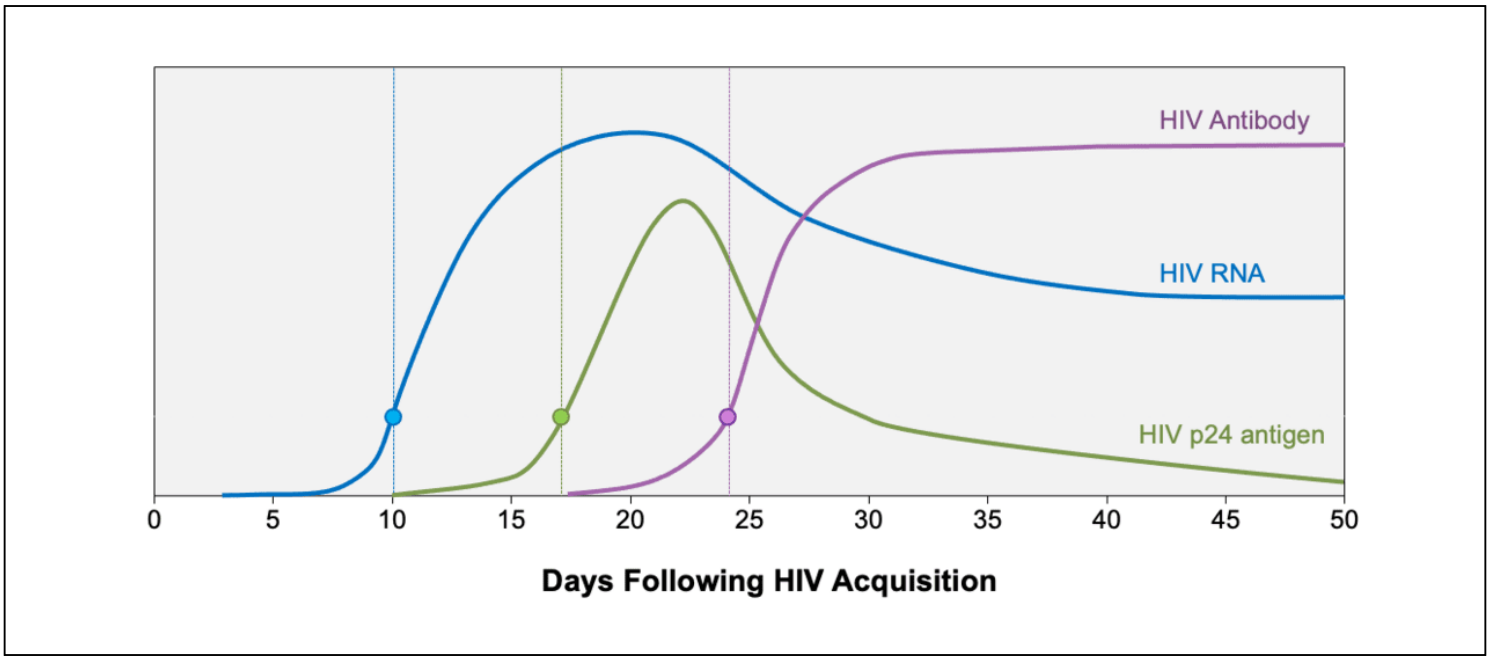

Figure 18 HIV Drug Resistance in Persons Prescribed HIV PrEP

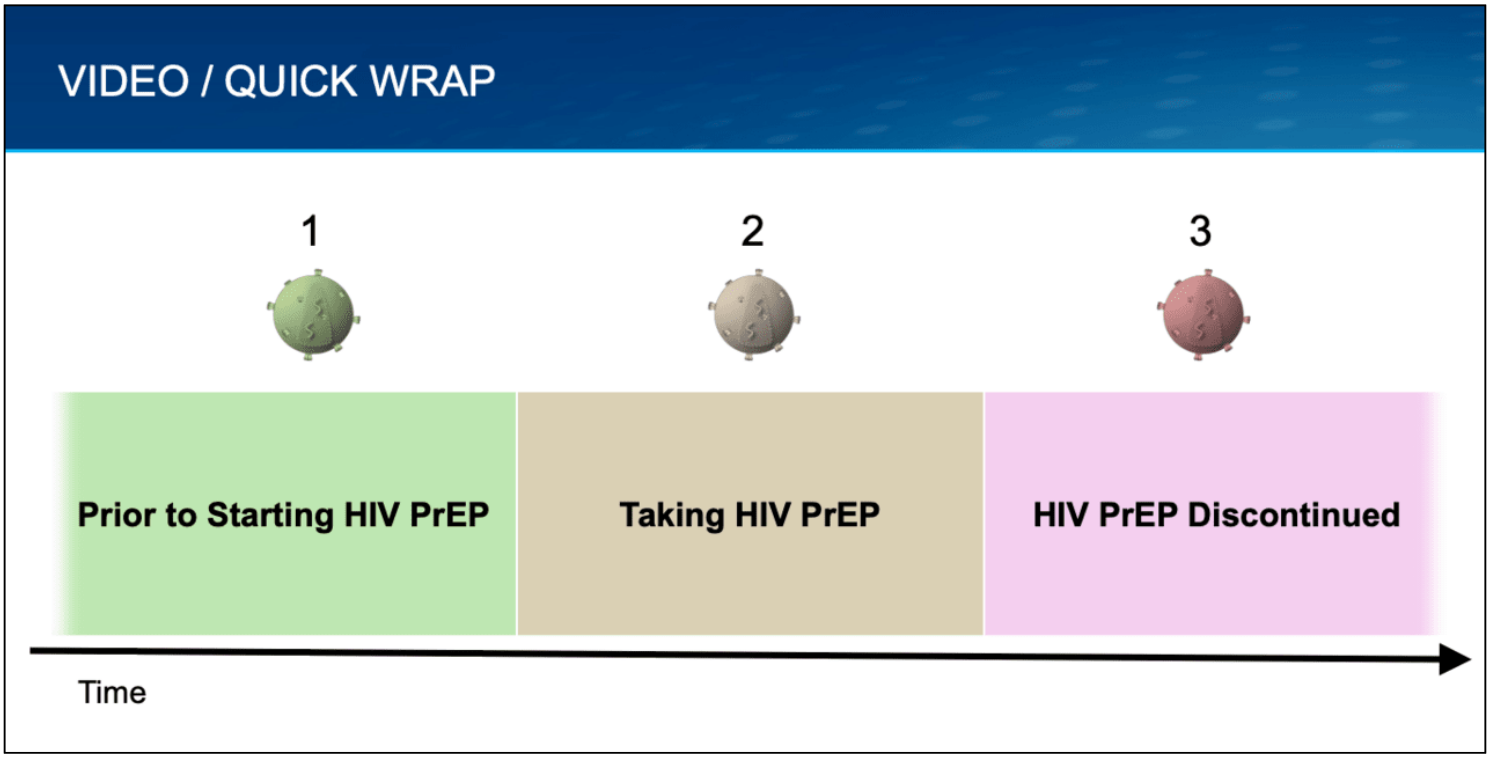

Figure 19 Initiating Antiretroviral Therapy in Person Newly Diagnosed with HIV

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.

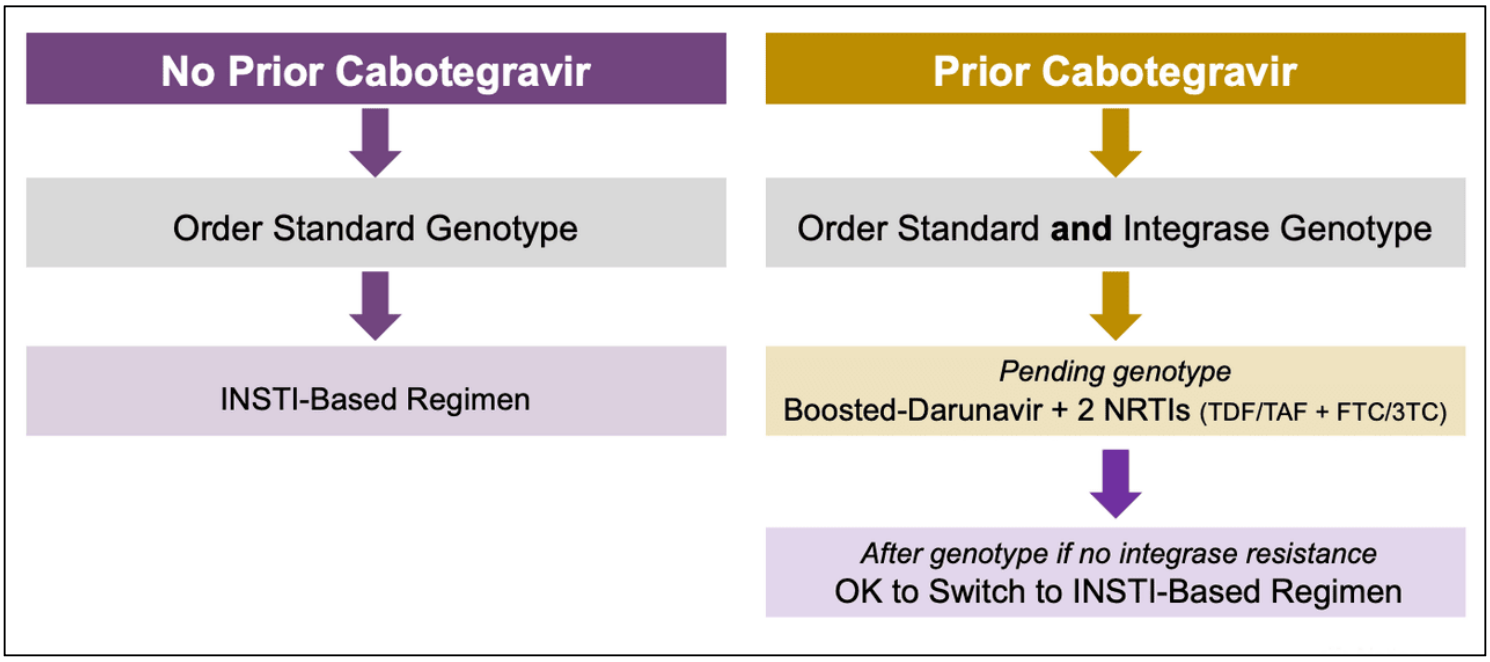

Figure 20 HIV PrEP Tools for Clinicians: Laboratory Tests