Long-Acting Injectable PrEP is Here: Frequently Asked Questions (FAQs) for Implementation

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Introduction and Background:

On December 20, 2021, the U.S Food and Drug Administration approved Apretude® (cabotegravir extended-release injectable suspension) for PrEP, making it the first LAI medication option available for the primary prevention of HIV. Apretude® is indicated for adults and adolescents weighing at least 77 pounds who are at risk of sexually acquiring HIV.

The addition of a long-acting form of PrEP to the biomedical intervention tool-box is exciting as it provides another option for primary HIV prevention that is not a daily pill, creating opportunities for patient choice on what would work best for them. LAI PrEP creates new opportunities to support individuals in maintaining adherence, preventing or alleviating pill fatigue, and reducing stigma or privacy concerns associated with taking oral medications. Adolescents, people who use drugs, individuals experiencing homelessness, and others who experience challenges taking daily oral PrEP could benefit from this new PrEP modality.

The following sections include answers to frequently asked questions about implementation of LAIs for PrEP.

LAI Overview:

What are long-acting injectables (LAI)?

Long-acting antiretroviral injectables refers to an antiretroviral drug that is delivered via an injection and lasts in the body for an extended period of time.[1] The goals of injectables are to minimize adherence challenges as daily pills can serve as an adherence challenge. There is now long-acting injectable HIV treatment AND prevention options available. In January 2021 the first long-acting HIV treatment, Cabenuva®, was FDA approved. More long-acting and extended-release HIV prevention products are in the pipeline and currently being evaluated in clinical trials. These include additional injectable methods, vaginal rings, vaginal and rectal gels, and

[1]https://www.avac.org/sites/default/files/infographics/AVAC_Introduction_to_LongActing_Injectables.Dec2016.pdf

other oral pills. This graphic ,developed by AVAC in June 2021, details the research pipeline. Since this graphic the FDA is no longer reviewing Dapivirine by manufacturer International Partnership for Microbicides (IPM). In December 2021 IPM pulled their application for FDA approval.[2]

What is the effectiveness of LAI?

Two large clinical trials have confirmed the safety and efficacy of long acting cabotegravir. HPTN 083 started in December 2016 and studied cisgender gay men and other men who have sex with men, as well as transgender women. A parallel study, HPTN 084, launched in 2017 and examined the safety and efficacy among cisgender women. Both studies demonstrated the superiority of injectable cabotegravir to oral regimens for PrEP for HIV prevention. **Both cabotegravir and oral TDF/FTC have high efficacy for PrEP.**[3] AVAC developed an Advocates' Primer on Injectable Cabotegravir for PrEP, which includes additional information on the HPTN 083 and 084 trials.

Oral PrEP reaches maximum protection from HIV for receptive anal sex at about 7 days of daily use, and receptive vaginal sex at about 21 days of daily use.[4] As opposed to oral PrEP, the time from initiation of Apretude® for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown.[5]

How is LAI administered?

Apretude® is administered through a gluteal intramuscular injection given as few as six times per year and is initiated with a single 600 mg (3 mL) injection given one month apart for two consecutive months. After the second initiation injection, the recommended continuation injection dose is a single 600 mg (3 mL) injection given every two months. Apretude® must be administered by a clinical provider. An initiation dosing infographic has been developed by NASTAD to assist providers and navigators understand the dosing frequency. Access the infographic here.

Is there an oral lead in?

Vocabria® (cabotegravir tablets) is an optional oral lead-in dosing option to assess the tolerability of the medicine before the long-acting formulation is administered. If used, it should be taken for at least 28 days before the first Vocabria® injection. See "How will the optional lead-in medication (Vocabria®) be covered?" below.

[2] https://www.medscape.com/viewarticle/967175
[3]https://www.avac.org/sites/default/files/resource-files/CAB_PRIMER_FEB2022_R10.pdf
[4] https://www.cdc.gov/hiv/basics/prep/prep-effectiveness.html
[5]https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Apretude/pdf/APRETUDE-PI-PIL-IFU.PDF

What happens if LAI doses are missed?
It is recommended to schedule a follow-up appointment at the end of the initial or follow up appointments as adherence to the injection dosing schedule is strongly recommended. However, sometimes things come up resulting in a missed appointment and missed dose. Recommendations on how to proceed after a missed dose can be broken up by "planned" or "unplanned" missed doses.

Planned:
If an individual plans to miss a scheduled every-2-month continuation injection visit by more than 7 days, take daily oral cabotegravir (Vocabria) for a duration of up to 2 months to replace 1 missed scheduled every-2-month injection. The recommended oral daily dose is one 30-mg tablet of Vocabria. The first dose of oral PrEP should be taken approximately 2 months after the last injection dose of Apretude®.

Unplanned:
If a scheduled injection visit is missed or delayed by more than 7 days and oral dosing (Vocabria®) has not been taken in the interim, clinically reassess the individual to see if resuming Apretude® remains appropriate[5].

The time after missing a dose determines appropriate follow-up procedures. The following table shares dosing recommendations after missed injections. This table and more recommendations on responding to missed doses are on pages 4 and 5 of Apretude's® full prescribing information.[5]

Table 3. Injection Dosing Recommendations after Missed Injections

Time since Last Injection	Recommendation
If second injection is missed and time since first injection is:	
Less than or equal to 2 months	Administer 600-mg (3-mL) gluteal intramuscular injection of APRETUDE as soon as possible, then continue to follow the every-2-month injection dosing schedule.
Greater than 2 months	Restart with 600-mg (3-mL) gluteal intramuscular injection of APRETUDE, followed by a second 600-mg (3-mL) initiation injection dose 1 month later. Then continue to follow the every-2-month injection dosing schedule thereafter.
If third or subsequent injection is missed and time since prior injection is:	
Less than or equal to 3 months	Administer 600-mg (3-mL) intramuscular injection of APRETUDE as soon as possible, then continue with the every-2-month injection dosing schedule.
Greater than 3 months	Restart with 600-mg (3-mL) gluteal intramuscular injection of APRETUDE, followed by the second 600-mg (3-mL) initiation injection dose 1 month later. Then continue with the every-2-month injection dosing schedule thereafter.

What are some considerations for stopping LAI usage?
Patients discontinuing Apretude® injections, who may be at ongoing risk of sexual and injection HIV exposure, should be provided with another highly effective HIV prevention method during the months following their last injection, such as oral PrEP (generic TDF/FTC, Truvada® or Descovy®). If PrEP is indicated, prescribe daily oral PrEP

beginning within 8 weeks after last injection. Apretude® is a long-acting medicine and its active ingredient may stay in the body for up to three years in men and four years in women after the last injection.[6] This time is considered the pharmacokinetic (PK) "tail". If someone contracts HIV while still in the PK "tail" phase following discontinuation of Apretude®, drug resistance to cabotegravir and other integrase strand transfer inhibitors can occur. This can have significant implications for HIV treatment regimen selection.

It is important for clients to keep their follow up appointments even if they have decided to stop receiving injections. Educating clients regarding the long PK "tail" and discussing the potential need for continued oral PrEP to minimize risk of contracting HIV upon discontinuing Apretude® is strongly recommended. Additionally, when helping patients discontinue CAB PrEP safely, clinicians should: Educate about nPEP, continue follow-up visits quarterly for 12 months and conduct HIV-1 RNA tests at each quarterly follow-up visit after discontinuing CAB injections.

Injections can be restarted at any point after determining HIV status with HIV-1 RNA testing. More information about discontinuing or restarting Apretude® can be found on pages 52 and 53 of CDC's 2021 PrEP Clinical Guidelines.

What are the lab requirements for LAI?

Table 7 Timing of CAB PrEP-associated Laboratory Tests

Test	Initiation Visit	1 month visit	Q2 months	Q4 months	Q6 months	Q12 months	When Stopping CAB
HIV*	X	X	X	X	X	X	X
Syphilis	X			MSM^/TGW~ only	Heterosexually active women and men only	X	MSM/TGW only
Gonorrhea	X			MSM/TGW only	Heterosexually active women and men only	X	MSM/TGW only
Chlamydia	X			MSM/TGW only	MSM/TGW only	Heterosexually active women and men only	MSM/TGW only

* HIV-1 RNA assay
X all PrEP patients
^ men who have sex with men
~ persons assigned male sex at birth whose gender identification is female

Before initiating long-acting cabotegravir, an individual must have a negative HIV-1 RNA test. If an antigen/antibody-specific test is used and provides negative results, results should be confirmed using an RNA-specific assay.[5] Due to the long duration of drug exposure following a cabotegravir injection, exclusion of acute HIV infection is necessary. An HIV-1 RNA assay should be used as it is the most sensitive test available.[7] Unlike oral PrEP, creatine screening is not indicated prior to starting Apretude®

[6] https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(20)30165-X/fulltext
[7] https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf

injections. The following table details the recommended lab schedule for long-acting cabotegravir. More information about initiation and monitoring labs can be found on pages 48-52 of CDC's 2021 PrEP Clinical Guidelines.

What are the benefits of LAI?

As mentioned earlier, the introduction of long-acting cabotegravir for PrEP creates another option for patients to choose from, while also addressing adherence challenges coming from daily oral PrEP, such as pill fatigue. LAI can greatly address suboptimal adherence and can benefit many individuals, especially the following groups:

- Individuals experiencing homelessness/houselessness
- Adolescents
- Individuals who use drugs
- Individuals with kidney disease
- Individuals seeking privacy (don't want to be seen with medication)
- Individuals with challenges taking oral medications

Ensuring Apretude® is accessible to priority populations is essential. The following sections discuss cost and coverage considerations.

Coverage and Implementation:

How much does Apretude® cost?

The Wholesale Acquisition Cost (WAC) for Apretude® is $3,700 per 3 mL dosing kit. This translates into an annual cost of approximately $22,200 (the estimated annual cost for the first year of Apretude® is $25,900, taking into consideration seven possible injections).

As Apretude® is a provider-administered drug product, additional costs are expected to apply. These include clinic/office visit and administration costs.

How can patients access Apretude®?

Because Apretude® is approved for gluteal intramuscular use only, it should be administered by a licensed medical provider. In turn, it will not be available through retail community pharmacies, but rather through a limited distribution system involving either specialty distributors or specialty pharmacies. Apretude® can be procured by health care providers through "buy-and-bill", "white bagging", or "clear bagging" mechanisms. Learn more about these mechanisms in the table below.

Distribution Mechanisms	
Buy-and-Bill	Provider or clinic purchases Apretude® from a specialty distributor and maintains an inventory of the drug for use on an as-needed basis. Following administration of the drug to a patient, the provider submits a reimbursement claim to the patient's public or private insurance carrier.
White Bagging	Provider submits prescription for Apretude® to a specialty pharmacy within ViiV's specialty pharmacy network. The specialty pharmacy processes the claim and ships the product to the provider. Once the Apretude® is received by the provider, it can only be administered to the patient who was prescribed the drug.
Clear Bagging	A health system's internal specialty pharmacy maintains inventory of Apretude®, processes the claim when a prescription is received from a health system provider, and then delivers the medication in time for the patient's drug administration appointment.

Apretude® is currently available via buy-and-bill from the following **specialty distributors:** ASD Specialty Healthcare, Besse Medical, Cardinal Health Specialty, Curascript Specialty Distribution, McKesson Plasma and Biologics, McKesson Specialty Health, McKesson Medical-Surgical, and Oncology Supply.

Apretude® is currently available via white-bag mechanisms from the following **specialty pharmacies**: Accredo Health Group, Inc, AHF Pharmacy, Coordinated Care Network, Curant Health, CVS Specialty, Diplomat (Optum), Fairview Specialty, Humana Specialty Pharmacy, Kroger Specialty Pharmacy, Longs/Avita Specialty, Mail-Meds Clinical Pharmacy, Meijer Specialty, Optum/Avella, and Walgreens/AllianceRx Prime.

How will the medication and administration be covered by insurers?

Due to the need for Apretude® to be administered in a clinical setting, health insurers are likely to cover it as a medical benefit. Insurers may also cover it as a pharmacy benefit, or as both a medical and pharmacy benefit. Cost-sharing requirements will depend on how Apretude® is covered:

- Drugs covered as a medical benefit by private insurance plans often require a flat co-insurance rate (e.g., 20% of the total cost of the medication), typically after the plan deductible requirement has been met.
- State **Medicaid** programs must cover Apretude®, but cost-sharing and utilization management (e.g., prior authorization or step therapy) requirements may vary by state. Cost-sharing is typically nominal.

- For **Medicare** clients, Apretude® is expected to be covered under Part B as a provider-administered drug. Under Medicare Part B, the beneficiary may be responsible for up to 20% of the medication cost after the deductible requirement has been met; supplemental insurance coverage, Medicaid dual-eligibility, or enrollment in the Qualified Medicare Beneficiary (QMB) program may defray cost-sharing requirements. Some Medicare Advantage plans that include prescription drug coverage (Part D) may opt to cover it as a pharmacy benefit.

How will the optional lead-in medication (Vocabria®) be covered?

Vocabria® is being provided free-of-charge by ViiV Healthcare. It can be accessed via ViiVConnect and is being shipped by a contracted non-commercial pharmacy (TheraCom Pharmacy) once insurance coverage for Cabenuva® has been verified and/or authorized. Oral lead-in doses can also be procured directly from TheraCom Pharmacy (General Phone: 1-877-654-7812; General Fax: 1-844-773-1422; ViiV Specific Team Phone: 1-844-276; ViiV Specific Team Fax: 1-833-904-1881).

How can individuals without insurance access Apretude®?

Through the ViiVConnect assistance program, ViiV Healthcare is providing access to Apretude® at no cost to HIV-negative patients who meet all of the following criteria:

- Reside in one of the 50 states, the District of Columbia, or Puerto Rico
- Have a household income ≤500% of the Federal Poverty Level (example: income that does not exceed $91,550 in a household of two in 2022). Federal Poverty Guidelines can be accessed here.
- Not eligible for Medicaid (or Mi Salud, Puerto Rico's government-funded health plan)

And either:

- Have no prescription drug coverage, or
- Have a Medicare Part B, Medicare Part D, or Medicare Advantage Plan, and have spent at least $600 or more on out-of-pocket prescription expenses during the current calendar year, or
- Have a private insurance plan limited to generic-only coverage, outpatient use only, or therapeutic class exclusion (non-coverage) of a drug

Enrollment in ViiVConnect is required to verify eligibility for the assistance program. Once approved, Apretude® (and Vocabria®, if recommended) will be shipped to the provider from TheraCom. Providers will not be able to use their own inventory of Apretude® for patients enrolled in the ViiVConnect assistance program.

Apretude® is not expected to be available via the Ready, Set, PrEP initative.

How do clinics stock and store Apretude®?

Apretude® does not require cold-chain storage, though it can be refrigerated to a temperature as low as 36 degrees Fahrenheit. If Apretude® is refrigerated, the vial should be brought to room temperature prior to administration (not to exceed 86 degrees Fahrenheit). Providers should not use any heating methods – other than the warmth of their hands – to bring Apretude® to room temperature.

Providers and clinics will need to store Apretude® received for specific patients via white bagging from specialty pharmacies separately from their own inventories received from specialty distributors for buy-and-bill purposes.

What are the 340B Drug Pricing Program implications for Apretude®?

Section 340B of the Public Health Service Act requires pharmaceutical manufacturers participating in Medicaid to sell outpatient drugs at discounted prices to health care organizations that care for many uninsured and low-income patients. As Apretude® is an outpatient prescription drug, it is subject to discounted pricing under the 340B Drug Pricing Program. It is also subject to the same organization eligibility, patient definition, and diversion prohibition requirements as those in place for oral medications not administered directly by a licensed medical provider.

While Apretude® is being sold through a limited distribution network, ViiV Healthcare is expected to provide the same opportunity for 340B covered entities and non-340B purchasers to procure the drug through its selected specialty distributors and specialty pharmacies (see HRSA's Clarification of Non-Discrimination Policy, 340B Drug Pricing Program Notice Release No. 2011-1.1). 340B covered entities may be able to take advantage of 340B-discounting pricing via the following mechanisms:

340B Patient Definition

In order to be eligible, the patient must receive health care services other than drugs from the 340B covered entity, including routine HIV testing and counseling. To meet this standard, the patient must have an established relationship with the 340B entity, which maintains records of that patient's health care, and must be seen in an eligible location for the covered entity. The patient must also receive health care services from a health care professional employed by the 340B entity or one who provides health care by an arrangement (such as a referral) in which the responsibility for care still rests with the 340B entity. Finally, the patient must receive health care services that are consistent with the scope of the grant used for 340B covered entity eligibility (e.g., HIV prevention or STI services). If the patient meets all of these criteria, they qualify for the discounted pharmaceutical products.

- **Direct purchasing from a specialty distributor.** 340B covered entities may procure Apretude® at a price point that does not exceed the statutorily required

340B ceiling price from a contracted specialty distributor in ViiV Healthcare's distribution network for Apretude®, plus any applicable supplemental 340B discounts and additional discounts provided by the distributor. Apretude® purchased at a 340B-discounted price can only be administered to 340B Drug Discount Program-eligible patients and it will be important for the covered entity to develop and maintain policies and procedures to prevent diversion. See the 340B patient definition in the text box above.

Of note, the Apexus 340B Prime Vendor Program has developed a network of specialty distributors, including several ViiV Healthcare's specialty/limited distribution network for Apretude®.

- **White bagging from a specialty pharmacy.** In cases where the patient's insurance carrier requires prescriptions for Apretude® to be submitted to, and filled by, a specialty pharmacy – or the provider prefers white-bagging over buy-and-bill purchasing and the patient's insurance carrier allows for specialty pharmacy fills as a medical or pharmacy benefit – 340B-discounting purchasing will depend on whether there is a 340B contract in place with the specialty pharmacy. Similar to 340B contracts with retail community pharmacies for oral medications, 340B covered entities may arrange for ship to/bill to replenishments with contracted specialty pharmacies to take advantage of discounted purchasing and program savings.

How does the June 2019 United States Preventive Services Task Force (USPSTF) Grade A recommendation for PrEP impact Apretude® coverage and cost sharing?

The Affordable Care Act (ACA) requires most private insurance plans and Medicaid expansion programs to cover select preventive services – including any service with a Grade A or B from the USPSTF – without cost sharing, which means that these services must be covered before any deductible and without coinsurance or a copayment. With a Grade A recommendation for PrEP from USPSTF issued in June 2019, most private insurance plans and Medicaid expansion programs must now cover PrEP without cost sharing.

In July 2021, the Departments of Labor, Treasury, and Health and Human Services released a set of Frequently Asked Questions clarifying the requirements for plans to cover PrEP, including the oral medications approved at the time: emtricitabine/tenofovir disoproxil fumarate (Truvada® and therapeutically equivalent generic formulations) and emtrictabine/tenofovir alafenamide fumarate (Descovy®). The guidance notes that "plans and issuers may cover a generic version of PrEP without cost sharing and impose cost sharing on an equivalent branded version," but they must also "accommodate any individual for whom a particular PrEP medication (generic or brand name) would be medically appropriate, as determined by the individual's health

care provider, by having a mechanism for waiving the otherwise applicable cost sharing for the brand or non-preferred brand version."

The federal guidance does not mention Apretude®, and Apretude® (or any long-acting injectable modality for PrEP) has not been evaluated by the USPSTF. Because long-acting products are not discussed in either the current USPSTF recommendation or federal guidance, it is possible that plans will apply cost sharing to Apretude® or employ utilization management techniques that prefer other PrEP options unless there is a clinical justification for Apretude®. The USPSTF has finalized a research plan to guide the systematic review of evidence required for an update to the current recommendations for PrEP. The potential benefits of newer PrEP regimens, including long-acting injectable cabotegravir, are to be assessed as part of this systematic review. This USPSTF review process will likely lead to a proposed updated USPSTF recommendation to incorporate new PrEP medications approved since 2019; however, the timing of when this updated recommendation could be released is unclear. In the meantime, there is likely to be variation in coverage and cost sharing for Apretude® across public and private payers.

Because the current federal USPSTF recommendation likely does not automatically apply to Apretude®, several states are enacting their own statutes and regulations to require plans regulated by the state to cover all FDA-approved medications for PrEP without cost sharing. States only regulate a portion of the private insurance market, so even within states with these laws on the books, there is still likely to be variation in coverage and cost sharing for Apretude® until there is an updated USPSTF recommendation or additional federal guidance. Please consult NASTAD's PrEP coverage brief published July 2021 for more information regarding the CMS sub-regulatory guidance addressing PrEP services to be covered with no cost sharing.

For questions about long-acting injectable PrEP, please contact NASTAD's PrEP Access team at PrEP@NASTAD.org.