Cabotegravir (APRETUDE)
National Drug Monograph
June 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Cabotegravir (CAB) is the first injectable HIV-1 integrase strand transfer inhibitor (INSTI)

Indication(s) Under Review in This Document

- CAB injection is indicated in at-risk adults and adolescents for Pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Patients must have a negative HIV-1 test prior to initiating CAB (with or without an oral lead-in with oral CAB) for HIV-1 PrEP.
- CAB for PrEP was approved by the FDA on 12/20/2021.

Dosage Form(s) Under Review / Dosage

- Cabotegravir extended-release injectable suspension for intramuscular (IM) administration. The product is a 600mg single dose vial (200 mg/mL).
- Dose = 600mg IM, repeated 4 weeks later, then every 8 weeks.
    - An oral cabotegravir lead-in for 4 weeks is OPTIONAL if there are concerns about adverse events
    - Procurement of oral cabotegravir would be through the specialty medications process, with a national waiver in place for free oral lead in.

Clinical Evidence Summary

Efficacy Considerations[1-5]

- Guidelines from the U.S. Public Health Service (PHS) recommend HIV PrEP for sexually active adults who report sexual behaviors that place them at substantial ongoing risk of HIV acquisition and for persons who inject drugs (PWID) who report injection practices that place them at ongoing risk for HIV acquisition.
- Oral options for PrEP include Truvada (FTC/TDF) and its generic preparations for all 3 of those populations. Descovy (FTC/TAF) is recommended for all except those at risk of HIV through vaginal receptive intercourse. Both must be taken as a daily oral pill. FTC/TDF can be given to those with CrCl ≥ 60 mL/min, while FTC/TAF those with CrCl≥ 30 mL/min
- CAB for PrEP was approved by the FDA on the basis of two Phase 3 double-blind, randomized controlled trials comparing CAB with emtricitabine + tenofovir disoproxil fumarate (TRUVADA or FTC/TDF), in addition to supportive Phase 1 and 2 safety, pharmacokinetic and dose ranging trials. In the Phase 3 trials, CAB was given as a 600mg injection at 0 and 1 month, and then every 2 months through the trials. In both trials, a 30mg oral CAB lead-in was given for 5 weeks. (See Table 1)
    - ***Note: the FDA product information states the oral lead-in is optional***

- The primary efficacy data are from the Phase 3 trials HPTN 083 and HPTN 084 with the primary outcome of new HIV infection.[1-3]
    - HPTN 083 compared CAB to FTC/TDF in cisgender men who have sex with men (MSM) and transgender women (TGW) at high risk for acquiring HIV.[1,2]
    - HPTN 084 compared CAB to FDC/TDF in cisgender women at high risk for HIV acquisition.[1,3]
    - Superiority of CAB vs. FTC/TDF was demonstrated in both studies at preventing incident HIV infection.
    - No data exist that compare CAB with emtricitabine + tenofovir alafenamide (Descovy or FTC/TAF).

Table 1: Efficacy results from clinical trials: CAB for PrEP[1-4]

Study	Design	Demographics	Efficacy Results
HTPN 083[1-3] Randomized, double-blind, Phase 3, placebo controlled trial in MSM and TGW	**Step 1**: Oral CAB 30mg or FTC/TDF (with matching placebos) for 5 weeks (oral lead-in) **Step 2***: CAB 600mg IM q4wk x 2 doses, then q8wk plus oral placebo vs. FTC/TDF daily (with placebo CAB IM) **Step 3**: all participants receive open-label FTC/TDF for up to 48 weeks (tail) **Key inclusion:** • Adult MSM and TGW • High-risk for HIV (i.e., any of the following in 6 months prior to study: any condom-less receptive anal intercourse, > 5 sex partners, any stimulant drug use, rectal/urethral gonorrhea, or chlamydia) • HIV uninfected just prior to randomization • CrCl ≥ 60 mL/min • Relatively normal liver tests, Hgb>11 g/dL, ANC > 750, platelets > 100K/mm^3 **Exclusion:** • One or more reactive + HIV test • Active/recent illicit drug use • Significant history of CV disease, chronic liver disease, prohibited medications, seizure disorder, anything that would preclude IM administration **Primary endpoints:** • HIV incident infection in steps 1&2 in all subjects with at least 1 dose medication (mITT) • Grade 2 or higher adverse events (AE)	**mITT population:** **CAB: n=2,282** **FTC/TDF: n=2,284** MSM: 88.2% CAB vs. 86.6% FTC/TDF Median age 26 yrs. (both groups), 0.3% ≥ 60 yrs. 67% some college education 85% SEXPRO score ≤16** **Median adherence by pill count 97%, with 72% TDF concentrations consistent with at least 4 doses per week** 92% adequately "covered" by CAB = delay less than 2 weeks after scheduled dose	**52 new HIV acquisitions during trial follow-up:** - **12 with CAB (0.37/100PY)** - **39 with TDF (1.22/100PY)** **HR 0.31 (95% CI 0.16 to 0.58), p=0.0003** HR consistent across subgroups, but only statistically superior in those <30 years old, MSM, black race and U.S. geographic location Most FTC/TDF HIV infections in patients with low TDF concentrations in preceding visit. *INSTI resistance identified in 4 of 9 cases incident cases on CAB* **Bottom line**: Over course of 3 years, averted 27 HIV infections in a cohort of 4600 patients at high-risk for HIV Largest number of TGW in any PrEP trial with similar HR although nonsignificant HR
HTPN 084[1,4] Randomized, double-blind, Phase 3, placebo controlled trial, carried out in 3 steps in CISGENDER women	**Dosing as in HPTN 083** **Inclusion:** • Cisgender women 18-45 years, sexually active • HIV uninfected at screening and randomization • Modified VOICE score≥ 5*** • Willing to use reliable contraception **Exclusion** • Pregnancy or breastfeeding • Hepatic / renal insufficiency • History of seizures	**MITT population:** **CAB: n=1614** **FTC/TDF: n=1610** Median age 25 yrs., 51% ≥ 2 sex partners, 41% transactional sex, 34% partner HIV+/unknown **62% had detectable TDF, with 46% levels indicating daily use**	**Overall: 39 new HIV acquisitions during the trial follow-up:** **3 with CAB (0.15 per 100PY)** **36 with TDF (1.85 per 100PY)** HR 0.10 (95% CI 0.04 to 0.27), p<0.0001 Only 2 CAB infections occurred during the injection phase, vs. majority of

	Primary endpoints: • HIV incident infection in steps 1&2 in all subjects with at least 1 dose (MITT) and AE	In CAB arm, 89-94% 'adequate' coverage at various time points	TDF/FTC infections (98% of FTC/TDF incident HIV cases had concentrations consistent with < 2 doses/wk.)

**Step 2 duration was event driven and continued until the required number of HIV infections occurred*
***Sexpro score ≤ 16 in MSM is indicative of high risk for HIV acquisition (includes number of sex partners, frequency of anal sex and frequency of condom use, use of stimulants or alcohol, and bacterial sexually transmitted infection in 6 months prior*
****VOICE score is ≥ 3 is indicative of high-risk for HIV acquisition based on age, partner characteristics and alcohol use*

Efficacy Summary

PHTN 083 and 084 found CAB long-acting injection, every 8 weeks was associated with a 66% lower rate of HIV infection than TDF/FTC in high-risk MSM/TGW and an 90% reduction in HIV in high-risk cisgender women.

As in previous studies, serum levels of TDF suggested adherence was an issue with TDF/FTC, while over 90% of CAB subjects were within an appropriate injection window to be considered adherent. Studies have suggested poor adherence to be less forgiving in cisgender women at high risk for HIV infection, which the data from HTPN 084 supports, suggesting this may be an important population to target.

MSM make up the majority of patients at high-risk for HIV acquisition and the majority of the VHA population currently receiving or eligible to receive PrEP. Superiority of CAB over FTC/TDF was demonstrated with an incidence of HIV infections across the study period of 1.7% for FTC/TDF vs. 0.57% for CAB over 161 weeks (median 1.2 years / patient).

Safety Considerations

Safety Results from Clinical Trials:

- The safety data on cabotegravir comes from PHTN 083 and 084, as well as PHTN077, ÉCLAIR and Phase 1 trials.
- Of note, both phase 3 studies used a 5-week lead-in with 30mg of ORAL cabotegravir, primarily to identify adverse events prior to administration of a long-acting injectable preparation. Although no data is available for PreP, the FLAIR study in patients infected with HIV, did not show any difference in tolerability with and without oral cabotegravir and rilpivirine, leading the FDA to state the oral lead in is optional when CAB IM is used for PrEP.

Table 2: Safety results from clinical trials

Study	Results	Comments

PHTN 083	• Over 92% of subjects in both groups had any grade 2 or higher AE, and 32% CAB and 34% of FTC/TDF had an AE ≥ grade 3 which were largely well-balanced.
	• 6% CAB and 4% FTC/TDF discontinued due to AEs
	• **Pyrexia:** 4% vs. < 1%
	• **Fatigue:** 4% vs. 2%
	• **Nausea:** 3% vs. 5%
	• **Weight gain** of 2.1 kg from baseline, vs. 1.2 kg with FTC/TDF by week 97
	• **Injection site reactions (ISR)** (CAB vs. FTC/TDF)
	  ○ 82% vs. 35%
	  ○ Most mild-moderate (41% mild, 56% moderate, 3% severe), led to DC in 3% of CAB patients
	  ○ Besides pain in vast majority, other ISRs significantly higher with CAB were nodules (15% vs. 2%, induration (15% vs. < 1%), and swelling (12% vs. 1%)
	  ○ Duration: median 4 days
	• **Increased creatinine (>1.8 x ULN or ≥ 1.5 X baseline)** (3% CAB and 3% FTC/TDF)
	• **Cholesterol** increased 1 mg/dL with CAB and decreased 10 mg/dL with FTC/TDF by wk. 57 (LDL was +1 vs. -6 mg/dL)
		No difference in hepatotoxicity events leading to discontinuation
		
		ISRs much more common with CAB than placebo FTC/TDF inj. but most were mild-moderate and did not lead to DC
		
		Slightly greater increases in weight and lipid parameters with CAB
		
		Very little difference in renal adverse events and did not lead to DC

PHTN 084	• Over 92% of subjects in both groups had any grade 2 or higher AE.
	• **Pyrexia:** <1% vs. < 1%
	• **Fatigue:** 3% vs. 3%
	• **Nausea:** 4% vs. 8%
	• **Injection site reactions (ISR)**
	  ○ 38% CAB vs. 11% FTC/TDF
	  ○ Maximum severity in HPTN 084 (mild 66%, moderate 34%, severe < 1%) with a median duration **8 days**
	  ○ More common early on and decreased over time
	  ○ Besides pain in vast majority, other ISRs significantly higher with CAB were nodules (14% vs. 2%, induration (12% vs. 2%), and swelling (18% vs. 3%). Pruritis less common (6% vs. 11%)
	• **Weight gain**: median of 4 kg from baseline with CAB vs. 3 kg with FTC/TDF by week 97
	• **Increased creatinine (>1.8 x ULN or ≥ 1.5 X baseline)** (5% CAB and 4% FTC/TDF)
	• **Cholesterol** increased 0.2 mg/dL with CAB and decreased 3.9 mg/dL with FTC/TDF by wk. 57 (LDL was -1 vs. -5 mg/dL)
		ISRs still most common AE but less frequent than in MSM study and did not lead to DC
		
		ISRs decreased over time
		
		Weight gains more pronounced with CAB than in MSM population
		
		Lab changes uncommon with similar changes in renal function and liver enzymes.
		
		As expected, lipids improved on FTC/TDF

Boxed warnings:

- **Risk of drug resistance with use as PrEP in undiagnosed HIV infection: individuals must be tested for HIV-1 infection with an FDA cleared test prior to initiating oral or injectable cabotegravir and with each subsequent injection. Drug-resistant variants have been identified with use in individuals with undiagnosed HIV**.

Contraindications:

- Unknown or positive HIV status
- Previous hypersensitivity to CAB
- Co-administration with drugs where significant decreases in CAB plasma concentrations may occur

Other warnings / precautions:

- **Comprehensive management to reduce HIV-1 resistance:**
  - Healthcare providers should carefully select individuals who agree to the required injection dosing and testing schedules, and counsel individuals about the importance of adherence to reduce the risk of acquiring HIV. Comprehensive management to reduce HIV-1 risk should be used with CAB (see PI for details).
  - The time from initiation of CAB for HIV PrEP to maximal protection is unknown.
- **Potential risk for resistance if an individual acquires HIV-1 while on CAB.**
  - All patients should be confirmed to be HIV negative as monotherapy in undiagnosed HIV-1 infection may result in INSTI resistance
  - In patients with recent high-risk behaviors, providers should evaluate for clinical symptoms compatible with acute HIV infection and if present use a test cleared or approved by FDA to aid diagnosis of acute HIV.
  - Testing should be repeated prior to EACH dose and upon diagnosis of other STIs and
  - Patients found to be HIV positive should immediately be transitioned to a full antiretroviral regimen to treat HIV.
- **Long-acting properties and potential associated risks with CAB residual concentrations**
  - Residual concentrations of CAB may remain in circulation for up to 12 months or longer.
  - **Providers should carefully select individuals who agree to required every other month injections.**
  - Healthcare providers should take the prolonged release characteristics into consideration when deciding to use CAB for PrEP.
  - **If CAB is discontinued, alternative PrEP should be considered for those who remain at high-risk beginning within 2 months of the last injection.**
  - In HPTN 077, the median time to undetectable concentrations was 43.7 weeks for males and 67.3 weeks for females. At 76 weeks, 13% of males and 42% of females had detectable CAB.
- **Hypersensitivity reactions**
  - Has been reported with other integrase inhibitors and oral lead in may help identify those at risk for hypersensitivity prior to administration of long-acting CAB injection.
- **Hepatotoxicity**
  - Has been reported in a limited number of patients on CAB with or without pre-existing hepatic disease or risk factors.
  - Clinical and lab monitoring should be considered, and CAB discontinued if hepatotoxicity is suspected.
- **Depressive disorders**
  - Has been reported with CAB (including depression, suicide ideation and attempt)

Adverse reactions (see table 2)

- **Common (≥ 3% in either trial)**
  - Injection site reactions (ISR)
  - Diarrhea
  - Headache
  - Nausea
  - Pyrexia
  - Fatigue
  - Sleep disorders
  - Dizziness
- **Laboratory abnormalities:**
  - Elevations in AST or ALT: uncommon and similar to placebo
  - Elevations in serum creatinine: similar between CAB and FTC/TDF
  - Fasting lipid changes: favored FTC/TDF as previously described
- **Special populations:**
  - **Pregnancy**
    - Per CAB prescribing information, insufficient data available in pregnancy, but neural tube defects have been associated with dolutegravir, another INSTI.
      - In animal reproduction studies, a delay in the onset of parturition and increased stillbirths and neonatal deaths were observed in a rat pre-and postnatal development study at >28 times the exposure at the recommended human dose (RHD). No evidence of adverse developmental outcomes was observed with oral cabotegravir in rats or rabbits (>28 times or similar to the exposure at the RHD, respectively) given during organogenesis
    - Given concentrations may persist for > 12 months, this should be considered in women of childbearing potential
    - A pregnancy registry exists for women exposed to CAB during pregnancy
  - **Lactation**
    - Unknown if CAB is present in human breast milk, affects human milk production, or has effects on the breastfed infant. Was present in milk in lactating rats. Since concentrations may persist for > 12 months, it is recommended women breast feed only if expected benefits outweigh the risks.
  - **Geriatric use:**
    - No dose adjustment required but very limited data in patients 65 years and older
  - **Renal insufficiency:**
    - No dosage adjustment with mild or moderate renal impairment.
    - With severe renal impairment (creatinine clearance 15 to 29 mL/min) or end-stage renal disease (creatinine clearance <15 mL/min), increased monitoring for adverse effects recommended Dialysis is not expected to alter exposures of cabotegravir
  - **Hepatic insufficiency:**
    - No dose adjustment needed for mild-moderate hepatic impairment (CTP A or B).
    - Impact of severe hepatic impairment on pharmacokinetics is unknown

Other Considerations

- **Pharmacokinetics/Pharmacodynamics**
  - **Absorption**
    - T_{max} = 7 days
    - C_{max} at steady state (after 2nd or later injection) = 4 mcg/mL
  - **Distribution**
    - 99% protein-bound
  - **Metabolism**

        - Hepatic through UGT1A1 (major) and UGT1A9 (minor)
    - **Excretion**
        - 27% eliminated in urine (none unchanged), 59% eliminated in feces (47% unchanged)
        - C_{min} = 1.6 mcg/mL
        - **Half-life = 5.6 – 11.5 weeks**
    - **Pharmacodynamic considerations**
        - Results from the phase 2 ÉCLAIR study suggested that a dose of 800mg IM every 12 weeks resulted in 15-30% of subjects having concentrations below the protein-adjusted 90% inhibitory concentration (PA-IC_{90}).
        - In contrast, simulation based on data from ÉCLAIR, LATTE-2 (in HIV infected patients) and HPTN 077 suggested a dose of 600mg IM given monthly x 2, followed by every other month (8 weeks) maintained concentrations > 4 X PA-IC_{90} in over 90% of patients. Both studies used an oral lead in of CAB PO 30mg daily x 4 weeks.

- **Dosing / administration issues**
    - The oral cabotegravir lead-in can be used but is optional as safety data was similar with and without the oral lead-in in studies of CABENUVA (cabotegravir with rilpivirine) injection. Facilities should follow the process outlined by PBM to obtain oral cabotegravir if needed for an oral lead-in.
        - If an oral lead-in is used, the dose is 30mg daily by mouth for 28 days, and the injection should be started on the last day of oral (or within 3 days thereafter)
    - Dosing of the injectable is 600mg (3 mL) IM monthly for 2 months, and then every 2 months, and can be given up to 7 days before or after the date it is due.
        - Injectable CAB must be given by a health care professional
        - A negative HIV-1 test **MUST be completed and negative prior to each dose**
    - ***Individuals who miss a scheduled dose by more than 7 days should be clinically reassessed to ensure resumption remains appropriate. In addition, the dosing schedule may need to be adjusted depending on the length of time since the prior injection was given, which may include restarting with 2 monthly doses prior to restarting an every-2-month injection schedule.***
    - Oral cabotegravir can also be used for known, scheduled plans to miss an injection by taking oral 30mg CAB for up to 2 months to replace one scheduled every 2-month injection. The first oral dose should be taken approximately 2 months after the previous injection dose.
- Use in special populations

Drug-drug interactions

- CAB is not an inhibitor of CYPA or P-gp or most other enzymes/transporters.
- In vitro, CAB inhibited renal OAT1, and modeling suggests it may increase substrate concentrations by up to 80%.
- All drug-drug interaction studies completed with ORAL CAB. No data on drug interactions with CAB injection.
- CAB is contraindicated with moderate-strong inducers of UGT1A1 due to potential for loss of CAB efficacy with decreased CAB concentrations (see contraindications).

Guidelines and requirements:

PrEP Guidelines USPSTF 2021: US Public Health Service: PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE, A CLINICAL PRACTICE GUIDELINE (cdc.gov)

- Conditioned on a PrEP indication approved by FDA, PrEP with intramuscular cabotegravir (CAB) injection is recommended for HIV prevention in adults and adolescents who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition. (1A recommendation)

Other Therapeutic Options

Alternative treatments for HIV Pre-exposure Prophylaxis are listed in table 3 below

Table 3 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
Cabotegravir (APRETUDE)	TBD	Indicated as every two-month injection for HIV PrEP in MSM/ TGW and cisgender women Can be used with any degree of renal dysfunction Was more effective at prevention of HIV than FTC/TDF	Requires logistics for injections Real world impact of adherence unknown As concentrations last for a long time, risk of resistance due to suboptimal concentrations during the "tail" Higher acquisition cost than generic FTC/TDF
FTC/TDF (TRUVADA)	F	Strong data to support use as PrEP in MSM and cisgender women Recommended in CDC guidelines for at risk patients Is available in a low-cost generic formulation	Efficacy is tied to adherence, which is often suboptimal with PrEP Associated with small changes in renal function markers and bone mineral density when used in PrEP Cannot be used if CrCl < 60 mL/min Does not have adverse impact on weight or lipid parameters
FTC/TAF (DESCOVY)	F	Non-inferior to FTC/TDF for HIV PrEP in MSM/TGW No data in cisgender women In VA limited to those at risk for renal dysfunction / nephrotoxic drugs or osteopenia/osteoporosis	Associated with weight gain but less impact on BMD / renal function although not Cannot be used if CrCl < 30 mL/min CDC guidelines mention that most patients should not need to be switched as differences in biomarkers is of unclear significance Higher acquisition cost vs. generic FTC/TDF

Projected Place in Therapy

- Approximately 36,400 people acquired HIV in the U.S. in 2018. HIV PrEP in patients at high risk for acquisition is an important part of a multipronged approach to eliminate HIV in the United States. It was estimated that in 2018, only 18% of those with an indication for PrEP received a prescription.
- **TRUVADA** (FTC/TDF) daily has been the mainstay of HIV PrEP for many years in both MSM/TGW and cisgender women, as well as those at risk due to injection drug use and has been shown to reduce the incidence of HIV infection 44-84% in MSM, and up to 65% in cisgender women.
    - **FTC/TDF is the workhorse PrEP product on the VA National Formulary and should be used as the primary therapy in those able to take it**
    - DESCOVY (FTC/TAF) received FDA approval as an option for PrEP in 2019 based on the DISCOVER trial which showed non-inferiority of FTC/TDF to FTC/TAF in MSM and TGW. It should not be used in those at risk for vaginal acquisition of HIV.
    - Efficacy of FTC/tenofovir preparations is dependent on adherence, which has been shown to be suboptimal in many studies. In the DISCOVER trial, 15 of 17 new HIV acquisitions (88%) occurred in those with dried blood spot concentrations consistent with < 2 doses / week.
- APRETUDE (CAB) was shown in two large, double-blind, placebo-controlled trials to be superior to FTC/TDF in MSM/TGW (HPTN 083) and cisgender women (HPTN 084).
    - In HPTN 083, the incidence of HIV was 1.22 / 100 person years in the FTC/TDF arm vs. 0.34 /100 PY with CAB. This contrasts with an incidence of 0.34 / 100 PY with FTC/TDF in the DISCOVER trial (and 0.16 / 100 PY with FTC/TAF), which may be a reflection of a younger, less adherent population in HPTN 083
    - In HPTN 084 – only 3 of 39 cases of HIV in cisgender women were in the CAB arm in HPTN 084. Of note, this was a very high-risk patient with 54% having 2 or more sex partners and 41% engaging in transactional sex in the prior X months. Approximately 1/3 reported sex with a partner who was HIV positive or had an unknown HIV status. Median VOICE score was 6.

- **CAB is an important addition to the VA National Formulary. It should be prescribed by Infectious Diseases, HIV or other PrEP providers who have training or experience in managing patients on HIV PrEP. In addition, additional criteria for use have been developed to target those populations most likely to benefit from the CAB over FTC/TDF or FTC/TAF**
    - **FTC/TDF is the workhorse product for those patients with CrCl ≥60 mL/min**
    - Given the long half-life and prolonged duration of subtherapeutic concentrations when CAB is discontinued, patients should be carefully selected who agree to reliably come to clinic visits. If a patient does not show up for an injection visit, they should be reassessed for continued use of CAB. Also, in the event CAB is discontinued, additional oral PrEP should be started within 4 weeks after the last dose of CAB in those continuing to engage in high-risk behaviors.
    - Patient started on CAB should receive adherence counseling and support and be educated on side effects, particularly during the first month of therapy.
    - CAB may be particularly beneficial in patients with:
        - CrCl < 30 mL/min or multiple risk factors for nephrotoxicity (e.g., comorbidities and medications)
        - Osteoporosis or osteopenia when FTC/TAF is not appropriate
        - Those unable to adhere to oral daily dosing for reasons such as, but not limited to:
            - Patients with cognitive dysfunction impacting medication adherence
            - Those with unstable housing or homelessness
            - Patients with gastrointestinal dysfunction where absorption may be impaired
            - Patients with previous medication non-adherence where efforts to improve compliance have been unsuccessful but who regularly adhere to clinic visits
            - Those with mental illness or substance abuse impacting compliance
            - Patients who have concerns about stigma or discovery of the use of HIV PrEP by family or friends

        - Given the greater efficacy demonstrated in HPTN 083 and HPTN 084, those at the highest risk of HIV infection may be most likely to derive an efficacy benefit, and consideration for CAB may be appropriate, even in the absence of other indication, but this should be assessed on a case-by-case basis. Example of this may include patients with frequent condom-less sexual encounters, unprotected sexual encounters in partners with known or at high-risk for HIV, and frequent needle/equipment sharing with IDU.
    - CAB should not be used in those receiving contraindicated medications (strong CYP inducers).
    - HIV should be excluded at baseline, and at least every 2 months while on therapy (See USPSTF 2021 Guidelines for this and additional monitoring recommendations)

References

1. APRETUDE, Cabotegravir injection Prescribing information, December 2021. Accessed 3/8/22.
2. APRETUDE, Cabotegravir injection. AMCP Dossier. 2022
3. Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. *N Engl J Med* 2021;385:595-608.
4. Delany-Moretlwe S, Hughes J, Bock P, et. al., Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3 randomized clinical trials. *Lancet* 2022. Online ahead of print. https://doi.org/10.1016/S0140-6736(22)00538-4
5. Mysexpro.org. Risk calculator for MSM and risk of HIV-1 acquisition.
6. Landovitz R, Li S, Brinsztejn B, et al. Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV uninfected individuals. HPTN 077, a Phase 2a randomized, controlled trials. *PlosMedicine* 2018. https://doi.org/10.1371/ournal.pmed.1002690 18 November 2018.
7. Markowitz M, Frank I, Grant R, et al. Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ÉCLAIR): a multicentre, randomised, placebo-controlled, phase 2a trial. *Lancet HIV* 2017;4:e331-40. http://dx.doi.org/10.1016/S2357-3018(17)30068-1 .
8. U.S. Public Health Service Clinical Practice Guideline: Pre-exposure prophylaxis for the prevention of HIV infection in the United States – 2021 update. *US Public Health Service: PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE, A CLINICAL PRACTICE GUIDELINE (cdc.gov)*
9. Mayer K, Molina JM, Thompson M, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet* 2020;396:239-54.
10. Medical Practice Evaluation Center. Ordering of patient simulation in CEPAC. Massachusetts General Hospital.Flowcharts-cepac50c.pdf (massgeneral.org)

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