Lenacapavir (SUNLENCA®, YEZTUGO®)
National Drug Monograph
Update November 2025

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[1]

Description/Mechanism of Action[1,2]

- Lenacapavir (LEN), a first-in-class capsid inhibitor, inhibits HIV-1 capsid function by binding to capsid protein (p24) subunits
    - LEN inhibits HIV-1 replication by interfering with multiple HIV replication process, including capsid-mediated uptake of HIV-1 proviral DNA, assembly and release, and capsid core formation

Indication(s) Under Review in This Document[1]

- On 12/22/2022, the FDA approved LEN, in combination with other antiretrovirals (ARVs), for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral treatment (ART) regimen due to resistance, intolerance, or safety considerations
- On 6/18/2025, the FDA approved LEN for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg who are at risk for HIV-1 acquisition.

Dose and Dosage Form(s)[1,2,3]

- LEN extended-release injectable suspension for subcutaneous (SQ) administration. The product is administered with two vials of 463.5mg (1.5 mL per vial) for each maintenance dose
- The recommended dose of LEN is an initiation dosing with oral LEN outlined below, followed by a maintenance dose of 927 mg (3 mL = 2 vials) SQ injection every 26 weeks (±2 weeks) from the date of the last SQ injection
    - **Initiation Dosing Option #1[3] For HIV treatment and HIV PrEP:**
        - **Day 1: 927 mg SQ injection with 600 mg oral tablets (2 x 300 mg tablets)**
        - **Day 2: 600 mg oral tablets**
    - **Initiation Dosing Option #2[2] For HIV treatment ONLY** (dosing used in phase-3 trial):
        - **Day 1: 600 mg oral tablets**
        - **Day 2: 600 mg oral tablets**
        - **Day 8: 300 mg oral tablets**
        - **Day 15: 927 mg SQ injection**
- If more than 28 weeks have elapsed since the last injection, then the dosing series must be restarted with initiation dosing from Day 1, using Option #1 (HIV or PrEP) or #2 (HIV) outlined above

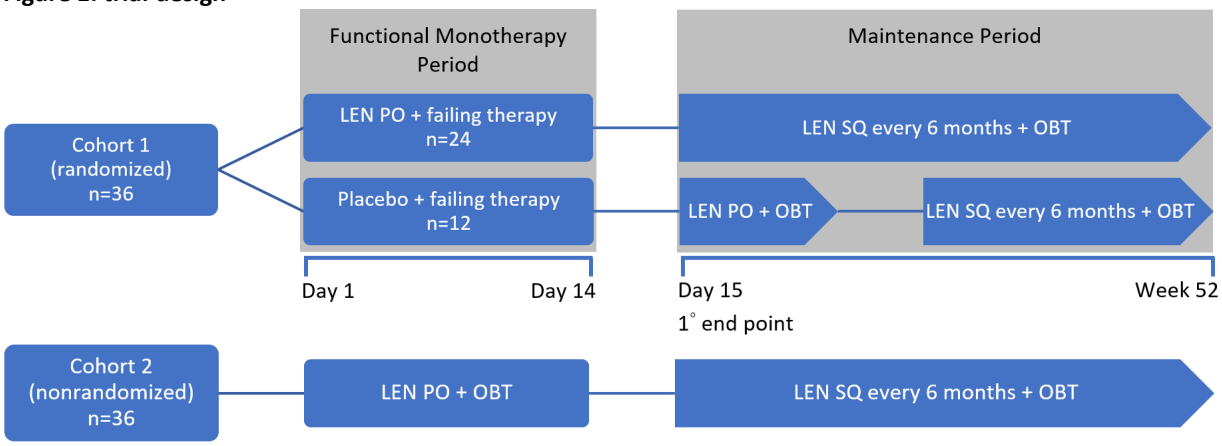
Clinical Evidence Summary

Efficacy for HIV Infection[1,2]

Approval of LEN was based on the results of a single phase 3, multi-cohort, multicenter clinical trial (NCT04150068; CAPELLA trial) in 72 highly treatment-experienced patients with multidrug resistant (MDR) HIV-1 infection.[2]

- **Inclusion criteria:**
    - Individuals 12 years and older who had received stable failing ART (indicated by HIV-1 RNA level ≥400 copies/mL at initial screening) for at ≥8 weeks.
    - Documented resistance to ≥2 ARVs from each of ≥3 of the 4 main classes of medications [nucleoside reverse-transcriptase inhibitors (NRTI), non-nucleoside reverse-transcriptase inhibitors (NNRTI), protease inhibitors (PI), and integrase inhibitors (INSTI)], except for M184V/I mutation.
    - ≤2 fully active ARVs remaining from the 4 main classes to formulate a viable regimen.
- **The trial was composed of 2 cohorts (Figure 1)**
    - **Cohort 1:** Patients with a stable viremia (indicated by a decrease of **<**0.5 $\log_{10}$ copies/mL between the screening and cohort-selection visits**,** 14-30 days apart) and HIV-1 RNA level of ≥400 copies/mL.
        - **Functional monotherapy (FM) period:** Patients were given oral LEN (with initiation dosing option #2) or matching placebo while continuing their failing therapy.
        - **Maintenance period:** Patients were given LEN and optimized background therapy (OBT)
            - Patients given oral LEN during the FM period were transitioned to LEN SQ injection every 6 months on day 15
            - Patients given placebo during FM period were initiated with the LEN initiation dosing option #2 on day 15
    - **Cohort 2**: Patients with a decrease of ≥0.5 $\log_{10}$ copies/mL between the screening and cohort-selection visits, HIV-1 RNA level <400 copies/mL at screening visit, or both; patients who meet the cohort 1 enrollment criteria after cohort 1 enrollment ended

Figure 1: trial design



- **Study endpoints:**
    - **Primary endpoint (functional monotherapy period):**
        - Cohort 1: Percentage of patients in LEN and placebo groups with a reduction of ≥0.5 $\log_{10}$ copies/mL in the plasma HIV-1 RNA viral load by day 15.
    - **Secondary endpoints (maintenance period):**
        - Cohort 1: Percentage of patients in LEN and placebo groups with a HIV-1 RNA viral load <50 or < 200 copies/mL at week 26
    - **Statistics:**
        - **Efficacy analysis was performed on all subjects in cohort 1 who received at least one dose of the study drug**
        - Safety data based on all patients from cohort 1 and 2 who received at least one dose of drug
- **Results:**
    - Seventy-two subjects were enrolled in the study with 36 patients enrolled for each cohort
        - All patients received at least one dose of medication, including the first LEN SQ injection

- **In cohort 1, 24 received LEN and 12 received placebo during FM period**
- In cohort 2, 3 patients were enrolled due to not meeting the criteria for cohort 1

Table 1: Baseline characteristics

Characteristic	Cohort 1	
	LEN (n=24)	Placebo (n=12)
Median age (range) – years	55 (24-71)	54 (27-59)
Female sex – no. (%)	7 (29)	3 (25)
Race		
Black	10 (42)	6 (55)
White	12 (50)	4 (36)
Viral load		
Mean – log_{10} copies/mL	**3.97±0.92**	**4.87±0.39**
>100,000 copies/mL – no. (%)	**1 (4)**	**6 (50)**
CD4+ count		
Mean – cells/mm^3	**199±166**	**85±63**
<200 cells/mm^3	**16 (66)**	**11 (92)**
Resistance to ≥2 drugs in major class – no. (%)		
NRTI	23 (96)	12 (100)
NNRTI	22 (92)	12 (100)
PI	20 (83)	8 (67)
INSTI	**20 (83)**	**7 (58)**
All 4 major classes	**14 (58)**	**3 (25)**
Resistance to entry inhibitor – no./total no. (%)		
Enfuvirtide	2/23 (9)	3/10 (30)
Fostemsavir	**5/23 (22)**	**5/10 (50)**
Ibalizumab	8/23 (35)	3/10 (30)
Maraviroc	19/24 (79)	8/11 (73)
Composition of OBT – no. (%)		
NRTI	23 (96)	9 (75)
INSTI	16 (67)	9 (75)
PI	**12 (50)**	**9 (75)**
NNRTI	6 (25)	4 (33)
Ibalizumab	9 (38)	3 (25)
Maraviroc	**2 (8)**	**4 (33)**
Fostemsavir	3 (12)	0
Enfuvirtide	1 (4)	2 (17)
Median overall susceptibility score* of OBT	**2.0**	**1.3**
Number of fully active agents in OBT – no. (%)		
0	4 (17)	2 (17)
1	**7 (29)**	**7 (58)**
≥2	**13 (54)**	**3 (25)**

* Full susceptibility = 1.0; partial susceptibility = 0.5; no susceptibility = 0

- Similar baseline demographic characteristics between cohort 1 and 2, except for younger age and higher CD4+ count from cohort 2

- Primary Endpoint:
  - By day 15, **21 of 24 patients (88%) from the LEN group and 2 of 12 patients (17%) from the placebo group achieved HIV-1 RNA reduction by ≥0.5 log_{10} copies/mL**
    - Absolute difference 71%; 95% confidence interval (CI) 0.35 – 0.90, p <0.001
    - The between-group difference in percentage remained significant with adjustment for the baseline viral load (88% vs. 17%; p<0.001)

- Secondary Endpoints:
  - **By week 26, 29 of 36 patients (81%) achieved viral load <50 copies/mL and 32 of 36 patients (89%) achieved viral load <200 copies/mL**
    - Although only cohort 1 was evaluated for all efficacy-related endpoints, similar HIV suppression was noted from cohort 2 as 30 of 36 patients (83%) achieved HIV-1 RNA <50 copies/mL and 31 of 36 patients (86%) achieved HIV-1 RNA <200 copies/mL
    - Characteristics of cohort 1 and 2 patients with virologic response (viral load <50 copies/mL) at week 26 is shown in Table 2
      - The percentage of patients with virologic response (viral load of <50 copies/mL) at week 26 was higher among women, among those with age <50 years, and among those with a baseline viral load ≤100,000 copies/mL
      - The efficacy of LEN was generally consistent regardless of the activity of the OBT or resistance to INSTI
- Ad-hoc analysis:
  - **At week 26, an increase in CD4+ count by an average of 75 (95% CI, 0.4 – 1.1) in cohort 1 and 104 (95% CI, 0.69 – 139) in cohort 2 was achieved**
    - Percentage of patients with a CD4+ count of < 50 decreased from 25% to 0%

Table 2: Secondary endpoint – virologic response and baseline characteristics

Variable	Cohort 1	Cohort 2	All patients
Age			
<50 yr.	100%	84%	**89%**
≥50 yr.	74%	82%	**77%**
Sex			
Male	77%	79%	**78%**
Female	90%	100%	**94%**
Baseline CD4+ count			
<200 cells/mm3	78%	84%	80%
≥200 cells/mm3	89%	82%	85%
Baseline viral load			
≤100,000 copies/mL	86%	86%	**86%**
>100,000 copies/mL	57%	71%	**64%**
Overall OBT susceptibility score			
0 to <1	67%	80%	73%
1 to <2	92%	91%	91%
≥2	78%	80%	79%
Number of fully active antiretroviral agent			
0	67%	83%	75%
1	86%	92%	89%
≥2	81%	76%	79%
INSTI resistance			
Yes	85%	87%	86%
No	62%	75%	70%
Use of dolutegravir or darunavir			
Both dolutegravir and darunavir	83%	67%	75%
Dolutegravir only	83%	83%	83%
Darunavir only	78%	100%	90%
Neither	78%	86%	81%
Use of ibalizumab			
Yes	75%	60%	71%
No	83%	87%	85%

- **Resistance analysis[2,4,5]:**
  - Genotypic and phenotypic resistance analysis was performed in 19 patients (11 in cohort 1 and 8 in cohort 2) who met any of the four definitions of virologic failure.
  - **LEN-associated capsid substitutions developed in 8 patients (4 in cohort 1 [1 in the LEN group] and 4 in cohort 2) during the maintenance period**
    - All the mutations occurred at amino acid residues that had previously been identified during selections for in vitro resistance[5]
      - 6 patients with M66I mutations (1 patient with M66I and N74D), 1 with Q67H and K70R and 1 patient with K70H
  - **4 of the 8 patients did not achieve HIV-1 RNA level re-suppression (<50 copies/mL)**
    - **2 patients continued to have viremia**
      - Patient with M66I mutation was on dolutegravir, darunavir/cobicistat, emtricitabine, and ibalizumab for OBT with no fully active agents in OBT
      - Patient with K70H mutation was on dolutegravir and darunavir/cobicistat for OBT with 2 fully active agents (dolutegravir and darunavir) in OBT
      - No emergent resistance to PI, NNRTI/NRTI, or INSTI in the two patients
    - 1 death at week 10 and 1 patient discontinued from LEN during post-week 4 at the investigator's discretion because of nonadherence to the regimen
  - The other 4 patients achieved HIV-1 RNA re-suppression
    - **2 patients achieved re-suppression without a fully active OBT, and none had confirmed emergent resistance mutation**
  - Additionally, L56I and K70N variants are identified as resistance-associated mutations in vitro. However, most variants, except for Q67H, are associated with reduced replication capacity.[2,4]
- In a 104-week follow up of the CAPELLA study, 55 of the original 71 participants were evaluated:[11]
  - 62% (44/71) had HIV-1 RNA < 50 copies and 63% (45/71) had HIV-1 RNA < 200 copies
  - From 55 participants, mean CD4 count increase was 122 cells/mcl
  - 14 patients developed LEN related mutations although all had suboptimal adherence

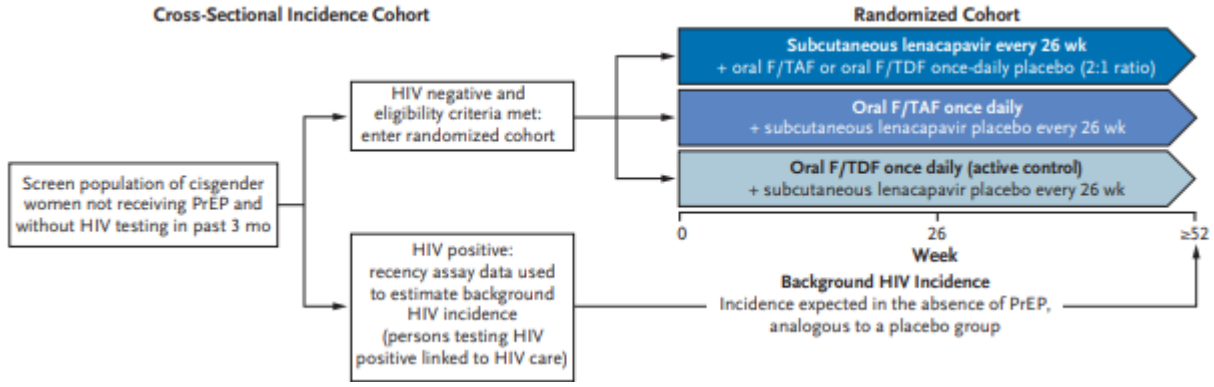
Efficacy for HIV PrEP [6,7]

Approval of LEN was based on the results of two randomized, double-blind, active-controlled trials, PURPOSE 1 and PURPOSE 2, in which a total of 8616 adult and adolescent participants received subcutaneous lLEN (N=4323) every 26 weeks, emtricitabine [FTC]/tenofovir alafenamide [TAF] (N=2135) once daily, or FTC/tenofovir disoproxil fumarate [TDF] (N=2158) once daily for HIV-1 PrEP. Purpose 1 was conducted in South Africa and Uganda and Purpose 2 was conducted in the US, South America, South Africa and Thailand.

Purpose 1[6]

- **Inclusion criteria:**
  - Adolescent girls and young women (16 to 25 years of age) who were sexually active (≥2 vaginal intercourse encounters) with male partners, were not using PrEP, and had unknown HIV status and no HIV testing within the previous 3 months (to avoid biasing the cross-sectional incidence cohort toward persons less likely than the local population to have HIV infection)
- **Study Design (Figure 2)**
  - HIV negative participants were randomized 2:2:1 to receive subcutaneous lenacapavir (n=2,134) every 26 weeks, daily oral FTC/TAF (n=2,136) or daily oral FTC/TDF (n=1,068). Participants in the lenacapavir group received oral loading doses of two 300-mg tablets of lenacapavir each on days 1 and 2. All groups received the alternate subcutaneous or oral placebo. Background HIV incidence was a cross-sectional estimate derived during the screening period.

Figure 2: PURPOSE 1 Trial Design



- **Study endpoints:**
  - **Primary endpoint:**
    - Incident HIV infection
  - **Secondary endpoint:**
    - Incidence rate ratio comparing HIV incidence with lenacapavir or FTC/TAF with the HIV incidence among those receiving FTC/TAF
  - **Statistics:**
    - Efficacy analysis used a mITT that excluded people adjudicated to have had HIV infection on date of randomization
- **Results:**
  - 5345 participants were randomized and received at least one dose; 7 of these were determined to have had HIV infection at time of randomization and were not included in the mITT analysis.
    - Background HIV incidence was 2.41/100 person-years (PY) (95%CI 1.82 to 3.19)
    - Baseline characteristics between the three treatment groups were similar
  - **Primary Endpoint:**
    - 55 incident HIV infections occurred: 0 in lenacapavir group (0 per 100 PY; 95% CI, 0.00 to 0.19), 39 in the FTC/TAF group (2.02 per 100 PY; 95% CI, 1.44 to 2.76), and 16 in the FTC/TDF group (1.69 per 100 person-years; 95% CI, 0.96 to 2.74)
  - **Secondary Endpoints**:
    - Lenacapavir reduced HIV incidence compared with background HIV incidence and compared with FTC/TDF. HIV incidence with FTC/TAF did not differ from background HIV incidence or from FTC/TDF.
      - Lenacapavir compared to background HIV incidence: incidence rate ratio, 0.00; 95% CI, 0.00 to 0.04; P<0.001
      - Lenacapavir compared to FTC/TDF: incidence rate ratio, 0.00; 95% CI, 0.00 to 0.10; P<0.001
      - FTC/TAF compared to background HIV incidence: incidence rate ratio, 0.84; 95% CI, 0.55 to 1.28; P=0.21
      - FTC/TAF compared to FTC/TDF: incidence rate ratio, 1.20; 95% CI, 0.67 to 2.14)
  - 34/37 participants in the FTC/TAF group and 13/14 in the FTC/TDF group with incident HIV infection had low or no detection of tenofovir diphosphate indicating poor adherence to oral medications.
    - In the FTC/TAF group participants with medium or high adherence had a lower odds of acquiring HIV infection than those with low adherence (odds ratio, 0.11; 95% CI, 0.01 to 0.49)

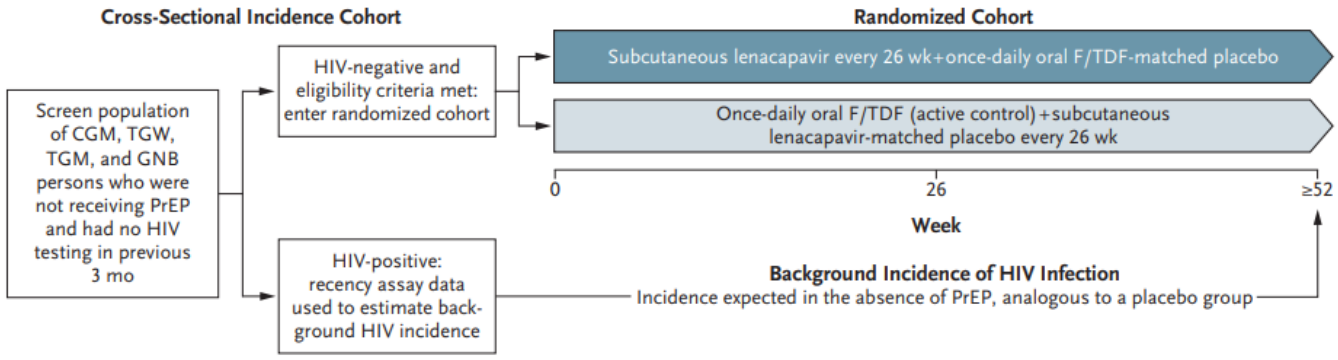
Purpose 2[7]

- **Inclusion criteria:**
  - Sexually active cisgender gay, bisexual and other men, transgender women and men, and gender non-binary individuals who have condomless receptive anal sex with partners assigned male at birth; were at least 16 years of age; had unknown HIV status; and reported no HIV testing or PrEP use in the 3 months before

screening (to avoid biasing the cross-sectional incidence cohort toward persons less likely than the local population to have HIV infection)

- **Study Design (Figure 3)**
  - HIV negative participants were randomized 2:1 to receive subcutaneous lenacapavir (n=2,183) every 26 weeks or daily oral FTC/TDF (n=1,088). Participants in the lenacapavir group received oral loading doses of two 300-mg tablets of lenacapavir each on days 1 and 2. Both groups received the alternate subcutaneous or oral placebo. Background HIV incidence was a cross-sectional estimate derived during the screening period.

Figure 3: PURPOSE 2 Trial Design



- **Study endpoints:**
  - **Primary endpoint:**
    - New HIV infection among randomized participants
  - **Secondary endpoint:**
    - Rate of Incident HIV-1 infections per 100 person-years (PY) with LEN compared to background HIV incidence and compared to FTC/TDF
  - **Statistics:**
    - Efficacy analysis used a mITT that excluded people adjudicated to have had HIV infection on date of randomization
- **Results:**
  - 4807 participants underwent screening and 3271 screened participants with negative HIV tests were randomized and received at least one dose of drug; 6 participants were determined to have had HIV infection at time of randomization and were not included in the mITT analysis.
    - Background HIV incidence was 2.37/100 person-years (PY) (95%CI 1.65 to 3.42)
    - Baseline characteristics between the two treatment groups were similar
  - **Primary Endpoint:**
    - 11 new HIV infections occurred: 2 in lenacapavir group (0.10 per 100 PY; 95% CI, 0.01 to 0.37) and 9 in the FTC/TDF group (0.93 per 100 person-years; 95% CI, 0.43 to 1.77)
  - **Secondary Endpoints**:
    - The incidence of HIV infection with lenacapavir was lower than the background HIV incidence and with FTC/TDF
      - Lenacapavir compared to background HIV incidence: incidence rate ratio, 0.04; 95% CI, 0.01 to 0.18; P<0.001
      - Lenacapavir compared to FTC/TDF: incidence rate ratio, 0.11; 95% CI, 0.02 to 0.51; P<0.002
  - Lenacapavir concentrations in the 2 participants that acquired HIV were within the range of the overall lenacapavir concentrations in the pharmacokinetics cohort
  - All nine participants in the FTC/TDF group who received a diagnosis of HIV infection had evidence of low (n=2) or no adherence (n=6) or had discontinued (n=1) FTC/TDF more than 10 days before diagnosis

Safety Considerations[1,2,6-8, 10]

- **Boxed warnings[1] for HIV PrEP:** Risk of drug resistance with use of LEN for PrEP in undiagnosed HIV-1 infection. Individuals must be tested for HIV-1 infection prior to initiating LEN and with each subsequent injection using a test approved or cleared by the FDA. Drug resistant HIV-1 variants have been identified with the use of LEN in individuals with undiagnosed HIV-1 infection. Do not initiate LEN unless negative infection status is confirmed.
- **Contraindications[1]:** Concomitant administration with strong CYP3A inducers that may result in the loss of therapeutic effect and development of resistance to LEN
- **Drug-drug interaction[1]:**
    - Concomitant administration with moderate CYP3A inducers during LEN treatment is not recommended due to the risk of loss of therapeutic effect and/or development of resistance
    - Concomitant administration with P-gp, UGT1A1, and strong 3A4 inhibitors (including cobicistat and ritonavir) during LEN treatment is not recommended due to risk of increased LEN serum concentration
    - LEN is a moderate CYP3A inhibitor and can increase the exposure of drugs primary metabolized by CYP 3A (i.e. direct oral anticoagulants, corticosteroids, HMG-CoA reductase inhibitors) initiated within 9 months after the last LEN SQ dose
    - As residual concentrations of lenacapavir may remain in the systemic circulation for 12 months or longer, lenacapavir may increase the risk of adverse reactions from drugs metabolized by CYP3A initiated within 9 months after the last dose
- **Other warnings / precautions[1]**:
    - During initial phase for HIV treatment: immune reconstitution syndrome possible
    - If LEN is discontinued, initiate an alternative, fully suppressive ART or PrEP regimen within 28 weeks after last LEN dose. When stopping LEN for PrEP, subtherapeutic serum concentrations may extend beyond 12 months.
    - In clinical trials, lenacapavir resistance-associated capsid substitutions were detected in individuals who acquired HIV while receiving lenacapavir treatment for PrEP.
- **Most common side effects[1,2,6-8]**
    - **LEN-related injection site reaction occurred (swelling, pain, erythema, nodule formation, and induration) in 45 patients (63%) from the CAPELLA trial**
        - 96% of the reported reactions were with grade 1 or 2 severity
        - **While most of the reactions resolved within days, the median duration of nodule and induration were 133 and 102 days, respectively**
    - In a phase 2, randomized open-label trial for LEN with various combinations of ART as initial and maintenance therapy for HIV (NCT04143594; CALIBRATE trial), similar injection site reactions were observed[6]:
        - Of the 103 patients receiving at least 1 dose of LEN SQ injection, 57 (55%) experienced LEN-related injection site reactions
        - 98% of the reported reactions were with grade 1 or 2 severity
    - In phase 3 PrEP trials, adverse events (including grade 3 or higher and serious events) were similar across groups except more injection site reactions (ISRs) occurred with LEN (68.8%-83.2% v. 34.9%-69.5%) including subcutaneous nodules (63.4%-63.8% v. 16.6%-39.2%); 0.2% - 1.2% discontinued due to ISRs in LEN groups
- **Other safety consideration[2]**
    - LEN was discontinued in 2 patients (3%) due to an adverse event (grade 1 injection-site nodule at week 62) and death (cancer-related death at week 10)
    - Improper administration (intradermal injection) has been associated with serious injection site reactions such as necrosis or ulcers.

Other Considerations

Storage and Handling[1]

- LEN oral formulations are supplied in 2 different packages depending on the initiation dosing options

  - Tablets must be dispensed only in original blister pack and should be stored at 20 – 25 °C.
- LEN SQ injection dosing kit contains 2 single-dose vials of LEN solution
  - Injection kit must be stored at 20 °C – 25 °C
  - Vials must be maintained in the original carton until prior to preparation of the injections to protect from light
  - Injection should be administered as soon as possible once solutions are drawn into the syringes

Pharmacokinetics / Pharmacodynamics[1,3]

- Half-life
  - Oral: 10 – 12 days
  - SQ: 8 to 12 weeks
- LEN trough concentration of 15.5 ng/mL, a 4-fold greater than the in vitro protein adjusted 95% effective concentration, has been associated with high rates of virologic suppression
  - In a phase 1, open-label study, 45 individuals were enrolled to compare Option #1 (14 patients) and #2 (31 patients) based on the mean LEN plasma trough concentration
  - Both Option #1 and #2 groups achieved mean plasma concentration and their lower bound 90% CI exceeded the target threshold of 15.5 ng/mL from 2 hours post-dose on Day 2
  - The median time to maximal concentration occurred on day 70 in Option #1 group versus on day 85 in Option #2 group

Formulary Alternative Therapeutic Options -- Treatment[7]

Drug	Clinical Guidance	Other Considerations
Lenacapavir (SUNLENCA) **PA-F, restricted to HIV/ID providers**	• Given as a SC injection every 26 weeks (after initial load) • Effective in reducing viral load and maintaining suppression in a large % of heavily treated patients with highly resistant HIV • No to limited cross-resistance with other antiretrovirals	• Requires in-office visit for administration • May need to be given in combination with alternatives below in order to form an effective regimen • Main adverse events were injection site reactions • Drug-drug interactions (moderate CYP3A inhibitor)
Ibalizumab-uiyk injection (TROGARZO) **PA-F with CFU**	• Entry inhibitor, preventing HIV-1 entry into CD4+ T cell • Effective in reducing viral load and maintaining suppression in a large % of heavily treated patients with highly resistant HIV • Dosed as a loading dose of 2000 mg (10 vials) on day 1, followed by 800 mg (4 vials) IV on day 14 and every 2 weeks thereafter	• Requires in office administration every 2 weeks infusion and need for maintaining IV access • Diarrhea, dizziness, nausea, and rash and laboratory abnormalities (increased serum creatinine, hyperbilirubinemia, leukopenia, and/or neutropenia) • May need to be given in combination with alternatives in this table in order to form an effective regimen
Fostemsavir **PA-F, restricted to HIV/ID providers**	• Dosed as 600mg PO twice daily – no special handling or storage • No significant cross-resistance with other antiretrovirals • No dose adjustment for renal or hepatic dysfunction	• Common AE: diarrhea, nausea, headache, possible QT prolongation • Drug interactions with CYP3a inducers • May need to be given in combination with alternatives in this table in order to form an effective regimen
Enfuvirtide (FUZEON) **T-20**	• Approved in 2003 for HIV salvage in combination with an optimized background regimen	• Extremely difficult to tolerate due to painful and long-lasting nodules at injection site and need for continual injection twice daily • Despite availability for over 20 years, very low usage

PA-F, restricted to HIV/ID providers		• May need to be given in combination with alternatives in this table in order to form an effective regimen

Formulary Alternative Therapeutic Options – PrEP

Drug / Formulary Status	Dose	Other Considerations
Lenacapavir (YEZTUGO) - **PA-F with CFU**	• 927mg (2 vials) given as a SC injection every 26 weeks (and initial oral loading dose of 600mg day 1 and 2)	• Requires in-office visit for administration • Main adverse events were injection site reactions • Drug-drug interactions (moderate CYP3A inhibitor)
Emtricitabine/Tenofovir disoproxil (TRUVADA) **PA-F, restricted to experienced providers**	• One tablet (emtricitabine 200mg / tenofovir disoproxil 300mg) once daily	• Initiation restricted to patients with CrCl >60mL/min. Mentoring of renal function during therapy is recommended. • Per USPSTF, kidney adverse events were primarily grade 1 due to creatinine level elevations and generally resolved following PrEP cessation
Emtricitabine/Tenofovir alafenamide (DESCOVY) - **PA-F with CFU**	• One tablet (emtricitabine 200mg / tenofovir alafenamide 25mg) once daily	• No dose adjustment required if CrCl > 30mL/min • Not recommended in patients who have receptive vaginal sex or IV drug use
Cabotegravir (APRETUDE) **PA-F with CFU**	• 600mg IM on month 1 and 2, then every two months thereafter	• Requires in-office visit for administration • Main adverse events were injection site reactions • Drug-drug interactions (contraindicated in with moderate to strong UGT1A1 inducers)

Projected Place in Therapy -- Treatment

LEN is the first-in-class capsid inhibitor that binds to capsid protein subunits and inhibits viral replication at both early and late stage of the life cycle, including capsid-mediated translocation of proviral DNA, assembly and release, and capsid core formation. LEN may be considered as salvage treatment of HIV-1 infection in patients with multi-drug resistant HIV infection who are heavily treatment experienced and failing their current ART regimen, assuming the following expectations can be met:

- Unable to formulate a viable suppressive regimen with two fully active agents due to predicted resistance by genotypic or phenotypic resistance tests, drug intolerance, drug-drug interactions or, in the case of maraviroc, dual-mixed or CXCR4-tropism. Co-administer LEN with OBT composed of at least one fully active antiretroviral
- Patients must understand and commit to receive LEN SQ injection every 26 weeks (± 2 weeks), administered by a healthcare provider. Patient must also understand that dosing cycle must be restarted with either initiation dosing option #1 or #2 if more than 28 weeks have elapsed since the last injection.
    - Healthcare providers should make every reasonable effort to facilitate removal of barriers to administration, when LEN is clinically indicated, including logistics, such as transportation and psychosocial barriers (e.g., co-existing mental health and substance use disorders that may contribute to difficulty adhering to the requirement for SC injection)

Projected Place in Therapy -- PrEP

LEN demonstrated statistical superiority to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in reducing incident HIV infections among high-risk populations, including cisgender women, men who have sex with men, and gender-

diverse individuals. Based on efficacy and safety demonstrated by the two RCTs, the CDC PrEP Guidelines Work Group strongly recommends lenacapavir injections as an HIV PrEP option. LEN should be reserved for individuals with contraindications, intolerance, or inability to adhere to oral TDF/FTC, with daily oral TDF/FTC remaining the preferred first-line PrEP agent for most patients. LEN's unique biannual dosing may offer adherence advantages in select populations, but its formulary placement should reflect its role as an alternative for those unable to use oral TDF/FTC for PrEP.

References

1. SUNLENCA (lenacapavir) injection, [prescribing information online]. Gilead Sciences, Inc. Approved Dec 2022. Accessed 3/31/23.
2. Segal-Maurer S, DeJesus E, Stellbrink HJ, et al. Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection. N Engl J Med. 2022;386(19):1793-1803.
3. Jogiraju V, et al. Pharmacokinetics of a simplified subcutaneous lenacapavir regimen versus phase 2/3 regimen. Poster presented at: AIDS 2022; Montreal, Quebec, Canada; July 29-August 2, 2022. Poster PESUB22.Sdf
4. Dvory-Sobol H, Shaik N, Callebaut C, Rhee MS. Lenacapavir: a first-in-class HIV-1 capsid inhibitor. Curr Opin HIV AIDS. 2022;17(1):15-21.
5. Link JO, Rhee MS, Tse WC, et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. Nature. 2020;584(7822):614-618. doi:10.1038/s41586-020-2443-1
6. Bekker L. G., Das M., Abdool Karim Q., et al. Twice-yearly lenacapavir or daily F/TAF for HIV prevention in cisgender women. N Engl J Med 2024;391(13):1179-92. (PURPOSE-1) https://www.nejm.org/doi/10.1056/NEJMoa2407001
7. Kelley C. F., Acevedo-Quiñones M., Agwu A. L., et al. Twice-yearly lenacapavir for HIV prevention in men and gender-diverse persons. N Engl J Med 2025;392(13):1261-76. (PURPOSE-2)
8. Gupta SK, Berhe M, Crofoot G, et al. Lenacapavir administered every 26 weeks or daily in combination with oral daily antiretroviral therapy for initial treatment of HIV: a randomised, open-label, active-controlled, phase 2 trial. Lancet HIV. 2023;10(1):e15-e23.
9. TROGARZO (ibalizumab-uiyk) injection, [prescribing information online]. Theratechnologies Inc. Revised Oct 2022. Accessed 3/31/23.
10. FDA. Yeztugo (lenacapavir) tablets, for oral use; injection, for subcutaneous use. 2025 Jun. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf
11. Onyema Ogbuagu, Jean-Michel Molina, Ploenchan Chetchotisakd, Moti N Ramgopal, William Sanchez, Jason Brunetta, Francesco Castelli, Gordon E Crofoot, Chien-Ching Hung, Sylvie Ronot-Bregigeon, Nicolas A Margot, Hui Wang, Hadas Dvory-Sobol, Martin S Rhee, Sorana Segal-Maurer, Efficacy and Safety of Long-Acting Subcutaneous Lenacapavir in Heavily Treatment-Experienced People with Multidrug-Resistant HIV-1: Week 104 Results of a Phase 2/3 Trial, Clinical Infectious Diseases, Volume 80, Issue 3, 15 March 2025, Pages 566–574, https://doi.org/10.1093/cid/ciae423
12. 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;74:541–549.

Original: June 2023
Update: Sept 2025

Prepared by Pam Belperio, PharmD, BCPS.
Contact person: Mary Cole PharmD, National PBM Clinical Pharmacy Program Manager – Formulary, Pharmacy Benefits Management Service