HIV Treatment in 2023

Joanne Urban, PharmD, AAHIVP, BCPS
Clinical Pharmacist
University of Florida- Infectious Diseases & Global Medicine
NF AETC Faculty

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Disclosures

- *None.*

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Objectives

1. Describe the need for new antiretroviral medications
2. Discuss antiretroviral medications recently approved by the FDA
   - Cabotegravir/rilpivirine
   - Fostemsavir
   - Lenacapavir
3. Describe the role of newer antiretroviral medications in clinical practice

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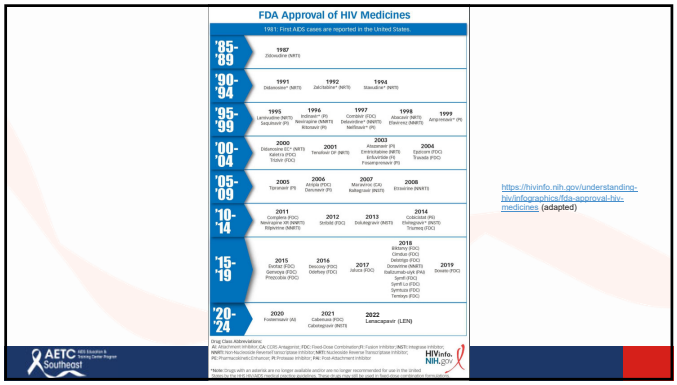
FDA Approval of HIV Medicines
1981: First AIDS cases are reported in the United States.
'85-'89
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'90-'94
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2020
2021
2022
Lenacapavir (LEN)
https://hivinfo.nih.gov/understanding-hiv/infographics/fda-approval-hiv-medicines (adapted)

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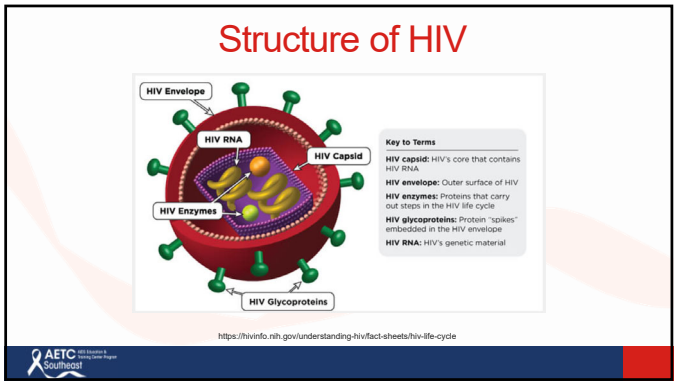
Structure of HIV
HIV Envelope
HIV RNA
HIV Capsid
HIV Enzymes
HIV Glycoproteins
Key to Terms
HIV capsid: HIV's core that contains HIV RNA
HIV envelope: Outer surface of HIV
HIV enzymes: Proteins that carry out steps in the HIV life cycle
HIV glycoproteins: Protein "spikes" embedded in the HIV envelope
HIV RNA: HIV's genetic material
https://hivinfo.nih.gov/understanding-hiv/fact-sheets/hiv-life-cycle

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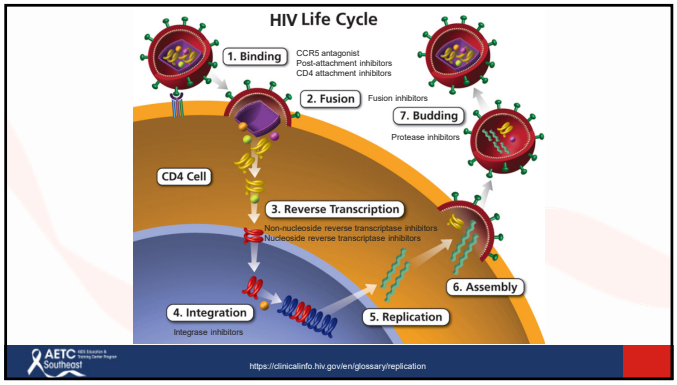
HIV Life Cycle
1. Binding
CCR5 antagonist
Post-attachment inhibitors
CD4 attachment inhibitors
2. Fusion
Fusion inhibitors
7. Budding
Protease inhibitors
CD4 Cell
3. Reverse Transcription
Non-nucleoside reverse transcriptase inhibitors
Nucleoside reverse transcriptase inhibitors
6. Assembly
4. Integration
Integrase inhibitors
5. Replication
https://clinicalinfo.hiv.gov/en/glossary/replication

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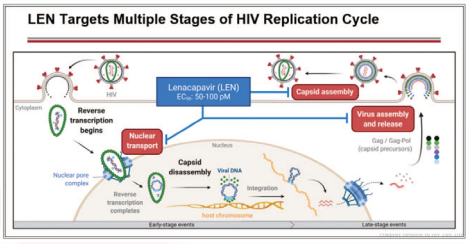
Capsid Inhibitor: Lenacapavir (LEN; Sunlenca)



Dvory-Sobol H, et al. Current Opinion in HIV and AIDS 17(1):15-21, January 2022.

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Recommended Initial Regimens for Most People with HIV

2 NRTI + INSTI
Biktarvy (BIC/TAF/FTC)
Triumeq (DTG/ABC/3TC***only if HLA-B*5701 neg and no HBV infection***
Dolutegravir + (TAF or TDF) + (FTC or 3TC)
1 NRTI + INSTI
Dovato (DTG/3TC) ***except if no genotype, HBV infection, VL > 500,000 copies/mL***

*If on cabotegravir-LA for PrEP, need genotype including integrase before starting antiretroviral therapy (ART) or use boosted darunavir + (TAF or TDF) + (FTC or 3TC)

DHHS. Adult and Adolescent Treatment Guideline Updated 9/21/22. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv

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WHY DO WE NEED NEW ANTIRETROVIRAL MEDICATIONS?

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New Antiretroviral Therapies

- Improved potency/durability (higher barrier to resistance)
- Improved safety and tolerability
- Regimen simplification
  - Lower pill burden
  - Single tablet regimens
  - Long-acting injectable regimen
- Overcome resistance
  - Patients with multi-drug resistant HIV

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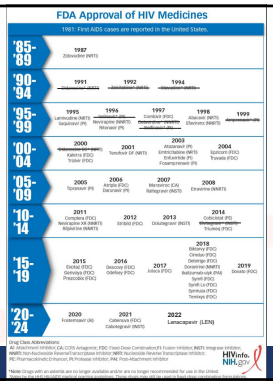

https://hivinfo.nih.gov/understanding-hiv/infographics/fda-approval-hiv-medicines (adapted)

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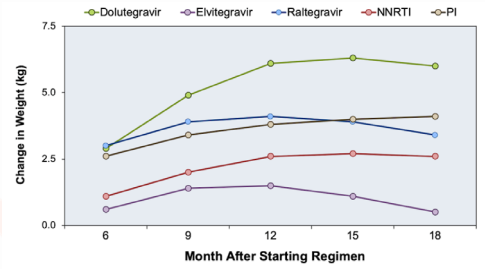
Weight Gain and Antiretroviral Therapy



National HIV Curriculum. 2023. Available at https://www.hiv.uw.edu/go/antiretroviral-therapy/adverse-effects/core-concept/all#integrase-strand-transfer-inhibitors

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Patient Case

- Martin is a 75 year old man with HIV infection who has been in your care for the past 5 years
- His virus has been well-controlled since 2018 on bictegravir/TAF/FTC (Biktarvy)
  - VL not detected, CD 438 on recent labs
- Co-morbidities: Chronic kidney disease, hyperlipidemia, abnormal LFTs (being followed for a liver mass), GERD
- You would like to consider a kidney-sparing regimen

TAF=tenofovir alafenamide, FTC=emtricitabine

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Patient Case (continued)

- Other meds:
  - rosuvastatin 20 mg (2 days per week), ezetimibe 10 mg (5 days per week), famotidine 20 mg once or twice daily
- Prior ART (diagnosed in 1999):
  - zidovudine, stavudine, lamivudine, nevirapine, indinavir, efavirenz/TDF/FTC (Atripla), dolutegravir + TAF/FTC
- Proviral DNA test shows an M184V mutation

TDF=tenofovir disoproxil fumarate FTC=emtricitabine

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Which regimen would you consider?

1. Dolutegravir/lamivudine
2. Dolutegravir + doravirine
3. Cabotegravir/rilpivirine
4. Dolutegravir + darunavir/cobicistat

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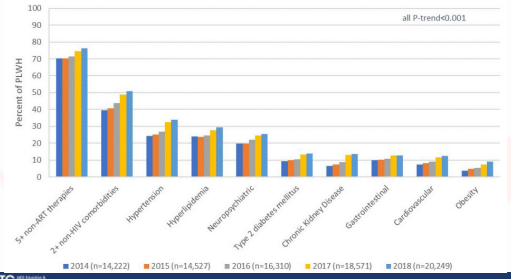
Multimorbidity and Polypharmacy



Paudel M, et al. Abstract 71. Presented at ID Week; September 30, 2021 (Virtual). Https://idweek.org.

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Patient Case

- Melanie is a 46 year old woman being seen for management of HIV infection
  - HIV VL < 20, CD4 561-most recent labs one year ago
- Inconsistent with appts and on and off ART for the past several years
  - Difficulty with transportation to the clinic and lab
  - Diagnosis not shared except with her cousin who lives out of state

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Patient Case (continued)

- History of PJP pneumonia, Candida esophagitis, COPD, myocardial infarction in 2022, depression/anxiety, hiatal hernia/reflux
- Nausea/vomiting daily for the past few months after taking her dolutegravir + TAF/FTC
- Other meds:
  - Pantoprazole, atorvastatin, metoprolol, citalopram, budesonide/formoterol, albuterol, hydroxyzine

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Patient Case (continued)

- Melanie expresses interest in the long-acting injectable (LAI) regimen cabotegravir/rilpivirine (Cabenuva)
  - Taking pills every day serves as a constant reminder of having HIV infection
- Prior ART (diagnosed in 2014):
  - darunavir/ritonavir + TDF/FTC
  - dolutegravir + TDF/FTC
  - bictegravir/TAF/FTC

TDF=tenofovir disoproxil fumarate, FTC=emtricitabine

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What concerns do you have about using the LAI regimen in Melanie?

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Patient Case

- David is a 52 year old man who is seen to establish care for HIV infection
  - Well-controlled on dolutegravir/lamivudine (Dovato) for the past 2 years
  - HIV VL not detected and CD4 1143 on recent labs
- He is not on any other medications

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Patient Case (continued)

- He expresses interest in the LAI regimen cabotegravir/rilpivirine
- Prior ART (diagnosed in 2009):
  - efavirenz/TDF/FTC (stopped due to declining eGFR)
  - abacavir/lamivudine/dolutegravir (Triumeq)
  - dolutegravir/rilpivirine (Juluca)

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Would you do a proviral DNA genotype prior to starting cabotegravir/rilpivirine?

- Yes
- No

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Stanford University
HIV DRUG RESISTANCE DATABASE
A curated public database to represent, store and analyze HIV drug resistance data.

Drug resistance interpretation: RT — HIVDB 9.5.0 (2023-08-22)

NRTI Mutations:	None
NNRTI Mutations:	E138K
RT Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors		Non-nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Susceptible	**doravirine (DOR)**	Susceptible
zidovudine (AZT)	Susceptible	**efavirenz (EFV)**	Potential Low-Level Resistance
emtricitabine (FTC)	Susceptible	**etravirine (ETR)**	Potential Low-Level Resistance
lamivudine (3TC)	Susceptible	**nevirapine (NVP)**	Potential Low-Level Resistance
tenofovir (TDF)	Susceptible	**rilpivirine (RPV)**	Intermediate Resistance

NNRTI

- **E138K** is a non-polymorphic mutation selected in a high proportion of persons receiving RPV. It reduces RPV susceptibility 2 to 3-fold. In combination with K101E or the NRTI-resistance mutation M184I, it is sufficient to cause VF on a first-line RPV-containing regimen. **E138K** causes low-level cross-resistance to ETR.
- This virus is predicted to have intermediate-level reduced susceptibility to **RPV**. The use of the combination of CAB/**RPV** should be considered to be contraindicated.

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CABOTEGRAVIR/RILPIVIRINE CAB/RPV; CABENUVA

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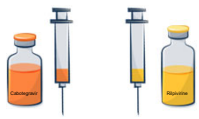
Cabotegravir and Rilpivirine Oral and Injectable Preparations

Optional Lead-In Oral Components

Cabotegravir + Rilpivirine
30 mg 25 mg
INSTI NNRTI

Intramuscular Injection Components



Cabotegravir + Rilpivirine
200 mg/mL 300 mg/mL
INSTI NNRTI

Source: Cabotegravir-Rilpivirine Prescribing Information

National HIV Curriculum

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Cabenuva (CAB/RPV): Key Points

- **Complete long-acting regimen**
  - Residual concentrations may remain for ≥ 12 months
- FDA Indications:
  - Adults and adolescents aged ≥12 and older, weight ≥ 35 kg
  - **Switch therapy**
    - Suppressed HIV viral load (<50 copies/mL) on a stable antiretroviral regimen
    - No history of treatment failure
    - No known or suspected resistance to either component
- **Oral Lead-in is optional**
- Continuation phase injections
  - Approved for every 1-month and every 2-month injections
    - Doses are different for these 2 options

Does not treat Hepatitis B

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Dosing of CAB/RPV

Table 1. Recommended Dosing Schedule with Optional Oral Lead-in or Direct to Injection for Monthly Injection

Drug	Optional Oral Lead-in[a] (at Least 28 Days) Month (at Least 28 Days) Prior to Starting Injections	Intramuscular (Gluteal)Initiation Injections(One-Time Dosing) Initiate Injections at Month 1[b]	Intramuscular (Gluteal)Continuation Injections(Once-Monthly Dosing) One Month after Initiation Injection and Monthly Onwards
Cabotegravir	30 mg once daily with a meal	600 mg (3 mL)	400 mg (2 mL)
Rilpivirine	25 mg once daily with a meal	900 mg (3 mL)	600 mg (2 mL)

Table 2. Recommended Dosing Schedule with Optional Oral Lead-in or Direct to Injection for Every-2-Month Injection

Drug	Optional Oral Lead-in[a] (at Least 28 Days) Month (at Least 28 Days) Prior to Starting Injections	Intramuscular (Gluteal) Injections[b] Initiate Injections[c] at Month 1, Month 2, and then Every 2 Months Onwards(Starting at Month 4)
Cabotegravir	30 mg once daily with a meal	600 mg (3 mL)
Rilpivirine	25 mg once daily with a meal	900 mg (3 mL)

National HIV Curriculum. https://www.hiv.uw.edu/page/treatment/drugs/cabotegravir-rilpivirine-long-acting-injectable. Accessed 9.1.23.

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Missed Injections

- LA CAB/RPV can be given up to 7 days before or after the target date of Options if **planned missed injections:**
  - Oral cabotegravir (Vocabria) + rilpivirine (Edurant) once daily for up to 2 months to replace missed injection visits*
  - Any other fully suppressive oral antiretroviral regimen
- If **unplanned missed injection** and patient didn't take oral therapy in the interim
  - Clinically reassess patient – is resumption of injections appropriate?

*If need oral dosing for more than 2 months, an alternative oral regimen is recommended

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CAB/RPV Contraindications

- Drug –drug interactions(UGR1A1 or CYP3A induction)
  - Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin
  - Antimycobacterials: Rifabutin, rifampin, rifapentine
  - Glucocorticoids (systemic): Dexamethasone (more than single treatment)
  - Herbal product: St John's wort (*Hypericum perforatum*)

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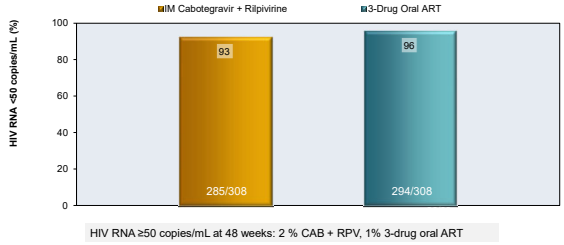
Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance ATLAS Study: Results

Weeks 48: Virologic Response by FDA Snapshot Analysis



HIV RNA ≥50 copies/mL at 48 weeks: 2 % CAB + RPV, 1% 3-drug oral ART

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

National HIV Curriculum

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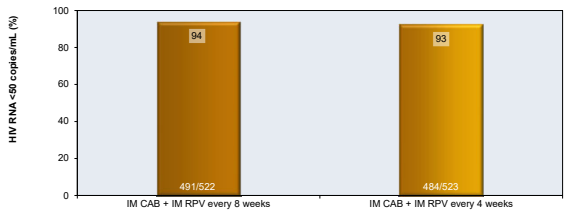
IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance ATLAS-2M Study: Results

Weeks 48: Virologic Response by FDA Snapshot Analysis



HIV RNA ≥50 copies/mL at 48 weeks: 9/522 (2%) in q8-week arm, 5/523 (1%) in q4-week arm

Source: Overton ET, et al. Lancet. 2020:396:1994-2005.

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Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance ATLAS Study: Adverse Events

Injection Site Reactions (ISRs)	
Type of Reactions	**Participants (%) with Reaction**
Participants who received injections, n	303
Any reaction, n (%)	250 (81)
Pain, n (%)	231 (75)
Grade 3 pain, n, (%)	10 (3)
Pain leading to withdrawal	4 (1)
Nodule, n (%)	37 (12)
Induration, n (%)	30 (10)
Swelling, n (%)	23 (7)
Median duration of reaction, days	3

The majority of ISRs (99%) were grade 1-2; 88% resolved within 7 days.

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

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CAB/RPV (Cabenuva) Patient Selection

- Who is at risk factors for virologic failure?
  - 2 or more of the following
    - ✓ Pre-existing rilpivirine resistance mutations
      - Proviral genotypes
    - ✓ HIV subtype A6/A1
      - More common in Eastern Europe, Russia and parts of Africa than US
    - ✓ Obesity
      - BMI ≥ 30 kg/m^2

Orkin C, et al. Clin Infect Dis. 2023 Jun 21. DOI: 10.1093/cid/ciad370

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LAI Potential Advantages

- Lower pill burden
- Less frequents dosing
- Reduced stigma
- Less side effects (e.g., kidney)
- Less drug interactions (e.g., compared to boosted regimens, can use PPI)

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LAI Challenges

- Prior treatment/resistance
- Injection site reaction
- More frequent office visits (6 per year vs. 2 per year)
  - Time away from work
  - Transportation
- Missed doses
  - Coverage of “tail”

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LAI Challenges-Logistics

- Insurance coverage
- Ordering
- Tracking receipt/storage
- Appointments
- Clinic/staff time

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NEW OPTIONS FOR TREATMENT OF HIV IN THE SETTING OF EXTENSIVE DRUG RESISTANCE

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Patient Case

- James is a 55 year old man seen to establish HIV care
- Virologic suppression (VL < 20) for past 5 years on darunavir/cobicistat + doravirine once daily
- James has multimorbidity: morbid obesity, poorly controlled diabetes, hypertension, hyperlipidemia and stage 2 chronic kidney disease.

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Patient Case (continued)

- He returns for his second clinic visit with you and reports he has been twice treated by the local ER for a presumed urinary tract infection with TMP/SMX and ciprofloxacin.
- Labs show new elevation of liver transaminases AST 571 ALT 246 (more than 5 times normal). Hepatitis A and B immune, hepatitis C Ab and RNA negative; Liver ultrasound with cholelithiasis but not cholecystitis, no biliary ductal dilation, no mass.

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Patient Case (continued)

- HIV-1 proviral resistance test indicates there are no antiretrovirals that should be expected to have full susceptibility. Prior trofile testing resulted with X4/R5 dual mixed virus population. No phenotypes are available.
- James lives in a rural area and has significant challenges with transportation and cell phone reception. He reports no alcohol use.

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Which drugs might you consider including in James' regimen at this point?

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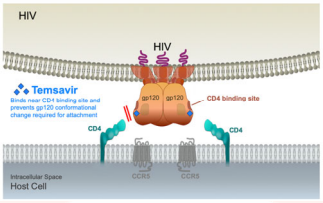
Fostemsavir (FTR; Rukobia)

- Attachment inhibitor
- NOT a complete ART regimen
  - Requires administration with optimal background therapy
- FDA indication
  - HIV-1 infection in heavily treatment-experienced adults failing their current regimen due to resistance, intolerance or safety considerations
- Resistance: gp120 substitutions
  - S375, M426, M434, M475



National HIV Curriculum. https://www.hiv.uw.edu/go/antiretroviral-therapy/general-information/core-concept/all

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Fostemsavir (FTR; Rukobia)

- Dose: **600 mg tablets by mouth twice daily with or without food**
  - No dosage adjustment needed for impaired renal or hepatic function
- Contraindications
  - Allergy to fostemsavir
  - Co-administration with strong P450 (CYP)3A inducers
    - Examples: carbamazepine, phenytoin, rifampin, St John's wort
- Adverse reactions
  - Nausea
  - QTc prolongation
  - Elevations in hepatic transaminases in patients with hepatitis B or C virus co-infection

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Where could fostemsavir fit into clinical care?

- Patients with extensive antiretroviral resistance and
  - Kidney/liver disease (no dose adjustment indicated)
  - Not likely to be adherent to injections/infusions
  - Has less drug-drug interactions than some other agents that might be considered (but always check!)

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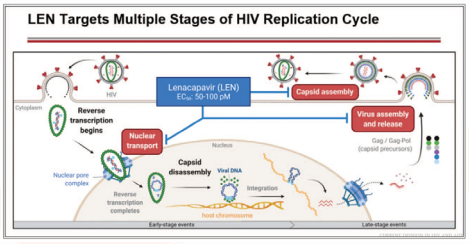
Capsid Inhibitor: Lenacapavir (LEN; Sunlenca)



Dvory-Sobol H, et al. Current Opinion in HIV and AIDS 17(1):15-21, January 2022.

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Lenacapavir

- **Type of Medication**
  - HIV capsid inhibitor
- **Indication**
  - Treatment of HIV-1 in combination with other antiretroviral medications in heavily treatment-experienced adults with multidrug resistant HIV
- **Preparations**
  - Oral: 300 mg tablets
  - Subcutaneous injection: 463.5 mg/1.5 mL vial
- **Adverse Reactions**
  - Most common adverse effects are nausea and injection site reactions
- **Contraindications**
  - Contraindicated to give with strong CYP3A inducers

Source: Lenacapavir Prescribing Information.

National HIV Curriculum

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Lenacapavir

Oral Lenacapavir	Subcutaneous Lenacapavir
 300 mg tablets	 Each 1.5 mL vial = 463.5 mg
Take with or without food	Administer as Subcutaneous Injection

National HIV Curriculum

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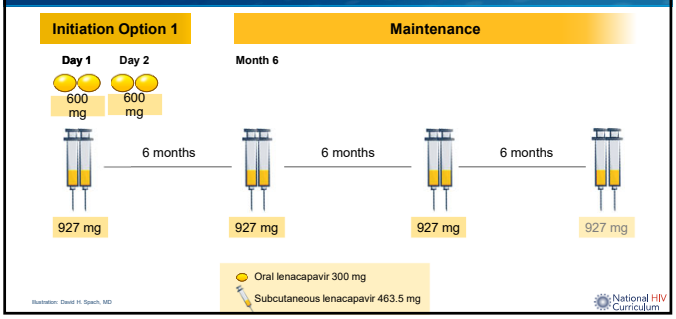
Lenacapavir Dosing: Initiation Option 1



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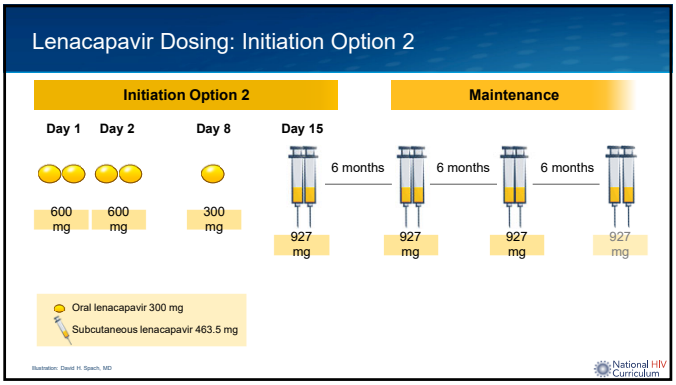
Lenacapavir Dosing: Initiation Option 2



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Lenacapavir

- Dosing in Special Populations
  - Renal impairment
    - No dose adjustment needed; has not been studied in patients with end stage renal disease (CrCl < 15 ml/min)
  - Hepatic impairment
    - No dose adjustment for mild or moderate hepatic impairment' has not been studied in patients with severe hepatic impairment (Child-Pugh Class C)
- Contraindications
  - Hypersensitivity to drug/excipients
  - Co-administration with strong inducers of CYP3A, P-gp, UGT1A1

AETC Southeast

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Where could lenacapavir fit in clinical HIV care?

- Patient with HIV and
  - Extensive antiretroviral resistance mutations
  - Adherent to appointments
  - Amenable to subcutaneous injections
  - Kidney disease
  - Mild or moderate liver disease
- Watch for potential drug-drug interactions

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Case (continued)

- James was transitioned to fostemsavir 600 mg twice daily + dolutegravir 50 mg twice daily + lamivudine 300 mg daily
- Outcome:
  - Liver enzymes normalized and the patient remains virologically suppressed at 4 weeks after change in therapy
  - Liver ultrasound showed fat infiltration and gallstones, but no biliary ductal dilation or gallbladder wall thickening
  - Cause of liver inflammation not defined at this time

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Summary

- Antiretroviral medications have improved over the last 35+ years
  - Fewer serious side effects
  - Fewer drug-drug and drug-food interactions
  - Easier administration – many fixed drug combination regimens
- Ongoing challenges
  - Side effects
  - Multimorbidity and polypharmacy
  - Multi-drug resistant HIV infection

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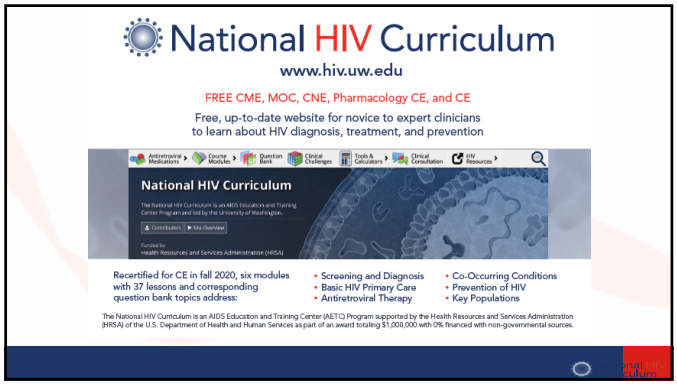

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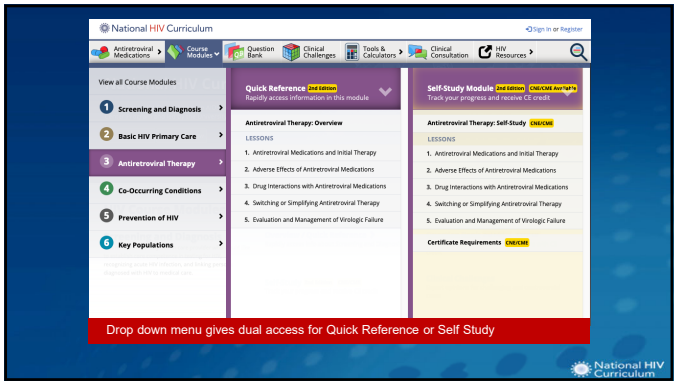

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AETC Program National Centers and HIV Curriculum

- **National Coordinating Resource Center –** serves as the central web –based repository for AETC Program training and capacity building resources; its website includes a free virtual library with training and technical assistance materials, a program directory, and a calendar of trainings and other events. Learn more: https://aidsetc.org/
- **National Clinical Consultation Center –** provides free, peer-to-peer, expert advice for health professionals on HIV prevention, care, and treatment and related topics. Learn more: https://nccc/ucsf.edu

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Thank You!

- *This presentation was supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) under grant number U1OHA30535.. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS, or the U.S. Government. For more information, please visit HRSA.gov.*

- Special thanks to Jennifer Janelle, MD

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