AETC AIDS Education & Training Center Program Southeast

ART Part 2: Modifying Antiretroviral Therapy

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Disclosures

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Learning Objectives

- *By the end of this sessions, participants will be able to:*
  - List potential reasons for modifying antiretroviral therapy (ART)
  - Discuss factors to consider when selecting a regimen in the setting of virologic failure
  - Describe strategies for optimizing therapy in the setting of virologic suppression
  - Select regimen options for individual patient case scenarios

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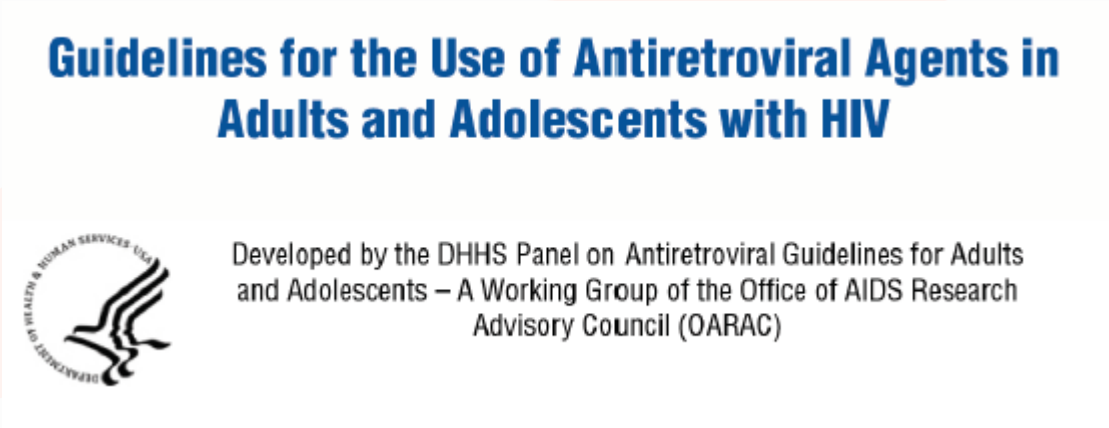
HIV Treatment Guidelines

- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. February 27, 2024.

Unless otherwise noted, information in this presentation is adapted from these guidelines.

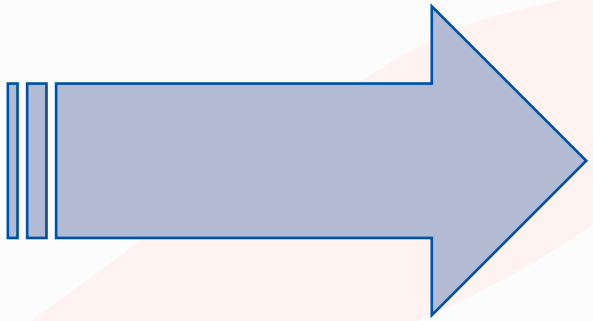


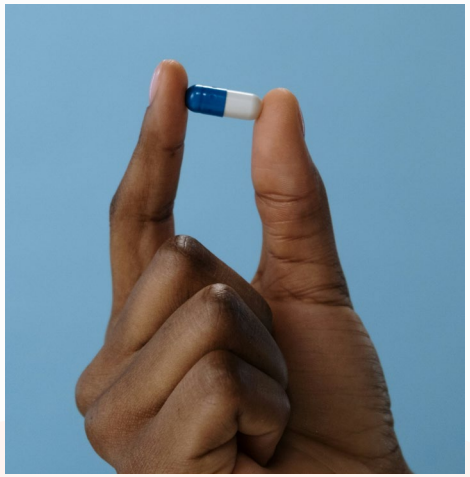
Reasons for Modifying ART

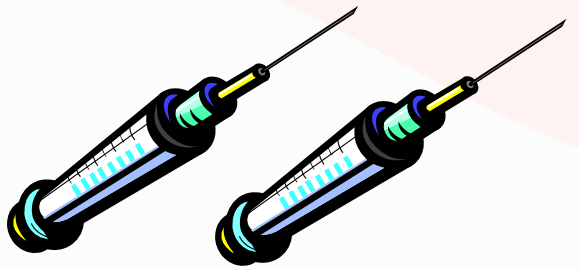
- Virologic failure
- Adverse effects
- Drug-drug or drug-food interactions
- Co-morbid conditions (e.g., hepatitis B, tuberculosis, kidney disease)
- Pregnancy
- Cost/drug availability

Reasons for Modifying Antiretroviral Therapy

- Desire to simplify regimen
  - Pill burden
  - Dosing frequency
  - Food requirements







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Factors Associated with Virologic Failure

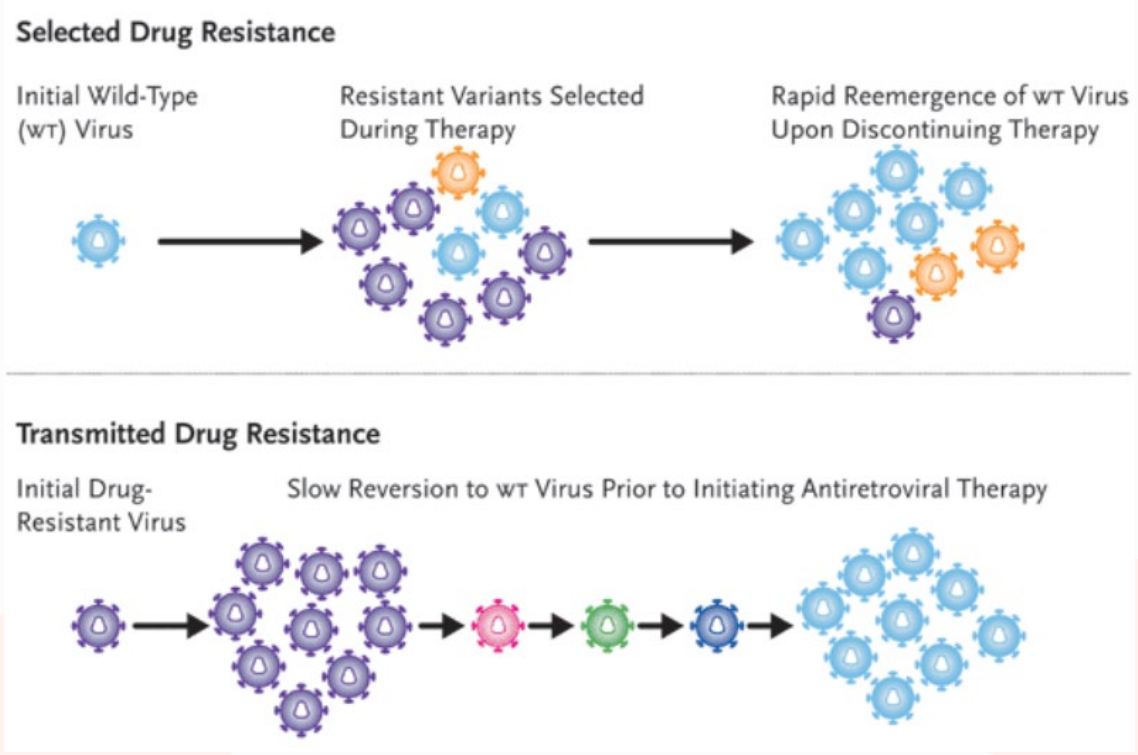
Virologic failure = inability to achieve or maintain HIV-RNA < 200 copies/mL

Patient/Adherence-Related Factors

- Co-morbidities (active substance use, mental health, neurocognitive impairment)
- Unstable housing and other psychosocial factors
- Missed clinic appointments
- Interruption of, or intermittent access to ART
- Adverse effects
- High pill burden and/or dosing frequency

HIV-Related Factors

- Presence of transmitted or acquired resistance
- Prior ART failure
- Innate resistance to prescribed drugs
- Higher pre-treatment HIV RNA levels



https://www.prn.org/index.php/complications/article/hiv_drug_resistance_386

Antiretroviral (ARV) Regimen-Related Factors

- Suboptimal pharmacokinetics or potency
- Low barrier to resistance
- Reduced efficacy due to prior exposure to suboptimal regimens
- Food requirements
- Drug-drug interactions
- Prescription errors (prescribing and dispensing)

General Principles for Designing New Regimen

- Consider factors associated with virologic failure and consider well-tolerated and adherence friendly regimens
- Select new ARV regimen based on treatment history and ***review of current and prior resistance*** test results

https://hivdb.stanford.edu/hivdb

General Principles for Designing New Regimen

- ARVs with high barrier to resistance (emergent resistance not common) include boosted darunavir (DRV), dolutegravir (DTG), and bictegravir (BIC)

General Principles for Designing New Regimen

- Fully active drugs *may include*
  - Newer members of existing drug classes
    - NNRTI: etravirine or doravirine
    - PI: darunavir
    - INSTI: dolutegravir or bictegravir
  - Drugs with novel mechanism of action that patient has not received
    - Post-attachment inhibitor (ibalizumab), gp120 attachment inhibitor (fostemsavir), capsid inhibitor (lenacapavir), fusion inhibitor (T20), CCR5 antagonist (maraviroc)

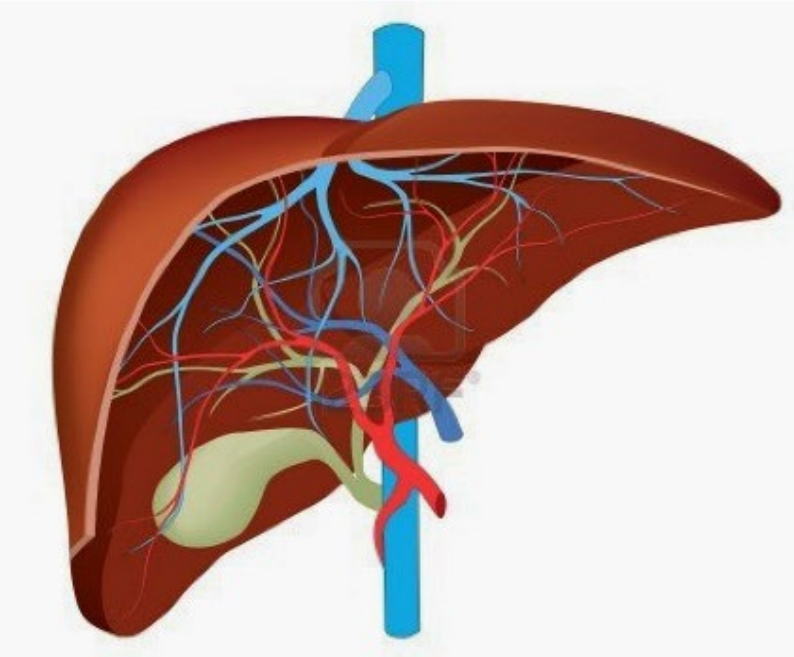
NNRTI=nucleoside reverse transcriptase inhibitor, PI=protease inhibitor, INSTI=integrase strand transfer inhibitor

Strategies for Designing New Regimen

- New regimen can include 2 fully active drugs if at least 1 drug has high barrier to resistance
- New regimen can include INSTI (preferably DTG) plus boosted PI (preferably DRV) if both are fully active
- If no fully active drug with high barrier to resistance is available, regimen should include 3 fully active ARVs if possible

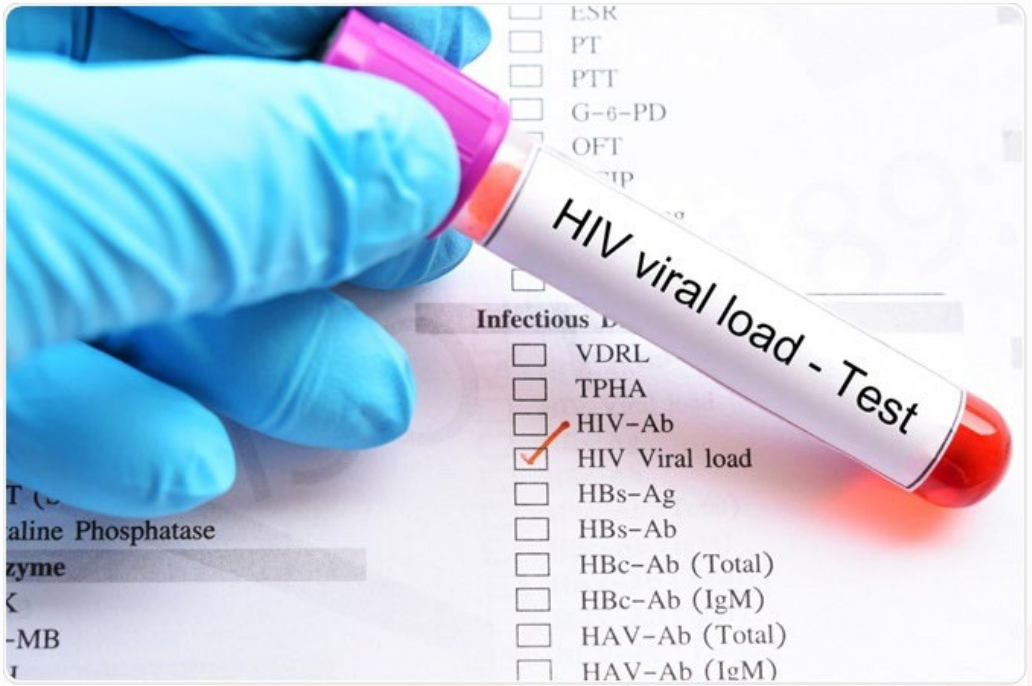
Strategies for Designing New Regimen

- Hepatitis B virus (HBV) coinfection:
  - Include nucleoside reverse transcriptase inhibitors (NRTIs) active against HBV* when possible, if not, entecavir should be started



*tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) ± emtricitabine (FTC) or lamivudine (3TC)

Monitoring Following ART Change



- Check HIV viral load within 4 to 8 weeks following ART change and perform resistance testing if virologic response is not adequate

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Management of the Treatment-Experienced Patient

Updated: May 26, 2023
Reviewed: May 26, 2023

Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/optimizing-antiretroviral-therapy-setting-virologic-suppression?view=full

Optimizing Therapy in Setting of Virologic Suppression

- Adverse events, drug interactions, pill burden, pregnancy, cost, or desire to simplify may prompt a switch
- Review patient's full ARV history, including virologic responses, past ARV-associated toxicities and intolerances, and cumulative resistance test results

Optimizing Therapy in Setting of Virologic Suppression

- Patients with no history of drug resistance or treatment failure can likely can like switch to any regimen known to be effective in ARV-naïve patients
- In the setting of existing NRTI resistance, 2 NRTIs (i.e., TAF or TDF + FTC or 3TC) should be included in the regimen with a fully active, high barrier resistance drug
  - DTG or boosted DRV (BIII)
  - BIC (CIII)

Optimizing Therapy in Setting of Virologic Suppression

- A long-acting injectable (LAI) regimen of cabotegravir (CAB) and rilpivirine (RPV) is an option for patients who are engaged with their health care, virologically suppressed on oral therapy for 3 to 6 months, and who agree to make the frequent clinic visits needed to receive the injectable drugs

Optimizing Therapy in Setting of Virologic Suppression

- Remember to include drugs with HBV activity (e.g., TAF or TDF with FTC or 3TC) in patients with HBV coinfection
  - FTC or 3TC should never be the only active drug against HBV
- Closely monitor patients to assess tolerability, viral suppression, adherence, and safety during the first 3 months after a regimen switch

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Patient Case David

- David is a 52-year-old man who is seen to establish care for HIV infection after relocating to the area
  - Well-controlled on dolutegravir (Tivicay) plus darunavir/cobicistat (Prezcobix) for the past 2 years
  - HIV VL not detected and CD4 585 on recent labs
- He is not on any other medications

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)
- He does not recall regimens being changed due to not working/resistance

Genotype June 2022

Antiretroviral drugs	Resistance Predicted	Mutations Detected
NRTIs		
ZDV (zidovudine or Retrovir)	NO	
ABC (abacavir or Ziagen)	NO	
ddI (didanosine or Videx)	NO	
3TC (lamivudine or Epivir)	NO	
FTC (emtricitabine or Emtriva)	NO	
d4T (stavudine or Zerit)	NO	
TDF (tenofovir or Viread)	NO	
NNRTIs		
ETR (etravirine or Intelence)	NO	
EFV (efavirenz or Sustiva)	NO	
NVP (nevirapine or Viramune)	NO	
RPV (rilpivirine or Edurant)	NO	
DOR (doravirine or Pifeltro)	NO	
PIs		
FPV (fos-amprenavir or Lexiva)	NO	
IDV (indinavir or Crixivan)	NO	
NFV (nelfinavir or Viracept)	NO	
SQV (saquinavir or Invirase)	NO	
LPV (lopinavir or Kaletra)	NO	
ATV (atazanavir or Reyataz)	NO	
TPV (tipranavir or Aptivus)	NO	
DRV (darunavir or Prezista)	NO	

Would you start David on cabotegravir/rilpivirine (Cabenuva) long-acting injection?

Genotype July 2014

Drug Class	Drug		Evidence of Resistance
NRTI	EPIVIR®	(lamivudine, 3TC)	Resistance
	EMTRIVA®	(emtricitabine, FTC)	Resistance
	RETROVIR®	(zidovudine, AZT)	None
	VIDEX®	(didanosine, ddI)	Possible Resistance
	ZERIT®	(stavudine, d4T)	None
	ZIAGEN®	(abacavir, ABC)	Resistance
	VIREAD®	(tenofovir, TDF)	Possible Resistance
NNRTI	RESCRIPTOR®	(delavirdine, DLV)	Resistance***
	SUSTIVA®	(efavirenz, EFV)	Resistance***
	VIRAMUNE®	(nevirapine, NVP)	Resistance***
	INTELENCE™	(etravirine, ETR)	Possible Resistance***
PI +	AGENERASE®	(amprenavir, APV)	None
	LEXIVA®	(fosamprenavir, FOS)	None
	CRIXIVAN®	(indinavir, IDV)	None
	FORTOVASE® / INVIRASE®	(saquinavir, SQV)	None
	KALETRA®	(lopinavir + ritonavir, LPV)	None
	PREZISTA®	(darunavir, DRV)	None
	VIRACEPT®	(nelfinavir, NFV)	None
	REYATAZ®	(atazanavir, ATV)	None
	APTIVUS®	(tipranavir, TPV)	None

Drug Class	Drug Resistance Mutations Identified
NRTI	K65R, M184V
NNRTI	A98G, K101Q, Y181C, G190E
PI	

NRTI Mutations: **K65R** • **M184V**
NNRTI Mutations: **A98G** • **Y181C** • **G190E**
RT Other Mutations: K101Q

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	High-Level Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Intermediate Resistance

Non-nucleoside Reverse Transcriptase Inhibitors

doravirine (DOR)	High-Level Resistance
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	High-Level Resistance
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	High-Level Resistance

Patient Case Rhonda

- Rhonda is a 58-year-old woman with HIV infection since 2015 who recently relocated from South Florida.
- Her HIV VL has been well-controlled on a regimen of BIC/TAF/FTC (Biktarvy) since 2018

- PMH: HIV, diabetes, hypertension, hyperlipidemia, reflux
- Medications: lisinopril 20 mg daily, metformin ER 1000 mg daily, omeprazole 20 mg daily, simvastatin 40 mg daily

Patient Case Rhonda

- Most recent labs
  - HIV VL < 20, CD4 354
  - eGFR 48 (down from 87 one year prior)
- The provider would like to modify the regimen to one that does not contain tenofovir due to declining renal function.

- Additional information:
  - Hepatitis B surf Ag negative, surface Ab 53 mIU/mL (immune)
  - Prior ART:
    - Boosted DRV + TAF/FTC 2015-2018 (always suppressed on this regimen)

What regimen would you consider for Rhonda?

A. Dolutegravir + doravirine (Tivicay + Pifeltro)
B. Dolutegravir/lamivudine (Dovato)
C. Dolutegravir + darunavir/cobicistat (Tivicay + Prezcobix)
D. Dolutegravir/rilpivirine (Juluca)
E. Cabotegravir/rilpivirine (Cabenuva)

Are there any drug-drug interactions of concern with Rhonda's medications?

www.hiv-druginteractions.org

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Interaction Report

Antiretroviral Treatment	Co-medications
Cabotegravir/rilpivirine [long acting] (CAB/RPV LA)	Lisinopril
Darunavir/cobicistat (DRV/c)	Metformin
Dolutegravir (DTG)	Omeprazole
Doravirine (DOR)	Simvastatin
Lamivudine (3TC)	
Rilpivirine (RPV)	

Drugs that should not be coadministered (RED)

Rilpivirine (RPV) + Omeprazole

Coadministration is contraindicated as significant decreases in rilpivirine plasma concentrations may occur. When rilpivirine (150 mg once daily) and omeprazole (20 mg once daily) were coadministered, rilpivirine exposure decreased by ~40% and omeprazole exposure decreased by ~14%. [Note: this interaction study has been performed with a dose higher than the licensed dose for rilpivirine assessing the maximal effect on the co-administered drug. The recommendation is applicable to the licensed dose of rilpivirine 25 mg once daily.]

Darunavir/cobicistat (DRV/c) + Simvastatin

Coadministration is contraindicated as it is expected to markedly increase simvastatin concentrations which may cause myopathy, including rhabdomyolysis.

www.hiv-druginteractions.org

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Doravirine (DOR)	Simvastatin
Lamivudine (3TC)	
Rilpivirine (RPV)	

Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

Dolutegravir (DTG) + Metformin

Coadministration of metformin (500 mg twice daily) was studied with dolutegravir (50 mg once or twice daily) in 15 subjects. Coadministration with once daily dolutegravir increased metformin Cmax and AUC by 66% and 79%, whereas coadministration with twice daily dolutegravir increased metformin Cmax and AUC by 111% and 145%. A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin in order to maintain glycaemic control. The US Prescribing Information suggests limiting the total daily dose of metformin to 1000 mg when starting metformin or dolutegravir. Monitoring renal function during coadministration and monitoring blood glucose when starting and stopping coadministration is recommended. As metformin is eliminated renally, patients with moderate renal impairment may be at increased risk for lactic acidosis due to increased metformin concentrations.

Darunavir/cobicistat (DRV/c) + Metformin

Coadministration has not been studied. Metformin is mainly eliminated unchanged in the urine (via OCT2) and cobicistat is unlikely to inhibit OCTs at clinically relevant concentrations. However, cobicistat reversibly inhibits MATE1, and concentrations of metformin may be increased when coadministered with darunavir/cobicistat. Careful patient monitoring and dosage adjustment of metformin is recommended.

What regimen would you consider for Rhonda?

A. Dolutegravir + doravirine (Tivicay + Pifeltro)
B. Dolutegravir/lamivudine (Dovato)
C. Dolutegravir + darunavir/cobicistat (Tivicay + Prezcobix)
D. Dolutegravir/rilpivirine (Juluca)
E. Cabotegravir/rilpivirine (Cabenuva)

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

Dosing of CAB/RPV

Table 1. Recommended Dosing Schedule with Optional Oral Lead-in or Direct to Injection for Monthly Injection			
	Optional Oral Lead-in[a] (at Least 28 Days)	**Intramuscular (Gluteal)Initiation Injections(One-Time Dosing)**	**Intramuscular (Gluteal)Continuation Injections(Once-Monthly Dosing)**
Drug	**Month (at Least 28 Days) Prior to Starting Injections**	**Initiate Injections at Month 1[b]**	**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		
	Optional Oral Lead-in[a] (at Least 28 Days)	**Intramuscular (Gluteal) Injections[b]**
Drug	**Month (at Least 28 Days) Prior to Starting Injections**	**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.

Oral Cabotegravir/Rilpivirine Interactions with ARAs

ARA	Oral Rilpivirine Dosing Recommendation
Antacids (e.g., Al, Mg, Ca)	Take antacids ≥ 2 hours before or ≥ 4 hours after RPV
H2-Receptor Antagonists	Take H2-Receptor antagonists ≥ 12 hours before or ≥ 4 hours after RPV
Proton Pump Inhibitors	Do not combine-contraindicated

- No interaction between cabotegravir and H2-RAs or PPIs
- Take antacids ≥ 2 hours before or ≥ 4 hours after cabotegravir

LAI Potential Advantages

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

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”

LAI Challenges-Logistics

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

Summary

- Reason for changing ART:

- Virologic failure
- Adverse effects
- Drug-drug or drug-food interactions
- Co-morbid conditions (e.g., hepatitis B, tuberculosis, kidney disease)
- Pregnancy
- Cost/drug availability

Summary

- Regimen Simplification:

PILL BURDEN

FOOD REQUIREMENTS

DOSING FREQUENCY

Remember…

- Review patient's full ARV history, including virologic responses, past ARV-associated toxicities and intolerances, and cumulative resistance test results

Remember

Check HIV RNA 4 to 8 weeks following regimen change

Closely monitor patients to assess tolerability, viral suppression, adherence, and safety during the first 3 months after a regimen switch