Welcome to the DDI Considerations with Long-Acting PrEP Innovations webinar

We will begin shortly...

Your audio has been muted upon entry.

Please utilize the Q&A Function to submit any questions you may have

For technical difficulties, please contact Keegan Girouard at 814-404-5205

Tuesday, September 23, 2025
Virtual Webinar

These slides are being provided in response to your request for information and not for further distribution.

Some information contained in these slides may be outside the approved US Prescribing Information. This information is not intended to offer recommendations for administration of this product in a manner inconsistent with the US Prescribing Information.

In order for ViiV Healthcare to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 1-888-825-5249.

Please consult the accompanying US Prescribing Information.

DDI Considerations with Long-Acting PrEP Innovations Webinar

Marisa Brizzi, PharmD, BCPS, AAHIVP
HIV/Pain Stewardship Clinical Pharmacist
UC Health

Josh Havens, PharmD
Associate Clinical Professor, University of Nebraska Medical Center
HIV Clinical Pharmacist, Specialty Care Center

Caitlin Prather, PharmD, BCACP, AAHIVP
Clinical Pharmacy Specialist
Inova Health System

Tuesday, September 23, 2025

Agenda

September 23 • 7:00 - 8:15 PM ET

1 **Relevance of DDIs**

2 **DDIs & LAI PrEP**

3 **DDIs & Special Populations**

- Please use the Q&A function to submit comments and questions throughout the Webinar

Relevance of DDIs: Back to the Basics

Caitlin Prather, PharmD, BCACP, AAHIVP
Clinical Pharmacy Specialist
Inova Health System

What is a drug-drug interaction (DDI)?

A drug-drug interaction occurs when the effect of one drug is altered by the presence of another, potentially leading to reduced efficacy or increased toxicity

DDIs: Why do we care?

1

Enhance Patient Safety

- DDIs can lead to adverse drug reactions (ADRs), reduced therapeutic efficacy or toxic effects
- Monitoring DDIs is crucial to prevent medication-related harm, especially in patients with polypharmacy or chronic conditions[1]

2

Improve Clinical Outcomes

- Proactively identifying DDIs supports optimal treatment regimens and prevents complications such as hospitalizations due to medication-related admissions
- Tailored drug selection and dosing minimize unintended consequences[2]

3

Reduce Healthcare Costs

- ADRs associated with DDIs are significant contributors to avoidable healthcare expenses
- DDIs contribute to 20% of adverse drug-related hospitalizations annually in the U.S with costs >$35 billion[3]

4

Leverage Technology for Prevention

- EHR and clinical decision support systems are vital tools for identifying high-risk DDIs
- Integration of DDI alerts in prescribing workflows ensures real-time risk mitigation[4]

EHR, electronic health record; ADR, adverse drug reaction

1. US FDA Drug Interactions, What you should know; 2. Hansten, PD et al Drug Interactions: Analysis and Management 2020; 3. Reilly, T et al JMCP 2023, 29(4): 243-440; 4. Wright A et al J Am Med Inform Assoc 2018, 25(5): 496-506. .

Pharmacokinetics determine dosing, efficacy, and safety of a given drug

Absorption

- The process of a drug entering the bloodstream
- Influenced by factors like bioavailability, route of administration, and P-gp activity

Distribution

- The movement of a drug throughout the body
- Affected by protein binding (e.g. albumin), tissue permeability, and blood flow

Metabolism

- The chemical modifications of drugs to aid elimination
- Phase 1 (CYP enzymes) and Phase 2 (UGT and others) pathways play key roles

Excretion

- The removal of drugs and their metabolites from the body
- Primarily via the kidneys (urine) and live (bile/feces)

Grogan, S et al. Pharmacokinetics, 2023 Pharmacokinetics - StatPearls - NCBI Bookshelf

Metabolic pathways: Overview of drug metabolism

Phase 1 Metabolism
(Functionalization Reactions)

- Involves enzymes called CYP P450 which add or expose functional groups to make drugs more polar.
- About 75% of drugs are metabolized this way, with CYP3A4 being responsible for around 50% of these reactions.

Phase 2 Metabolism
(Conjugation Reactions)

- Involves enzymes called UGT which conjugate drugs with molecules like glucuronic acid to increase solubility for excretion.
- About 35% of drugs undergo this type of metabolism.

Transport Proteins

- P-gp is a key transporter that pumps drugs out of cells, affecting their absorption and bioavailability.
- Many drugs are substrates for both CYP enzymes and P-gp, leading to complex drug-drug interactions

CYP, cytochrome; *P-glycoprotein*

Dakshanamurthy, S. et al 2023 J Med and Org Chem: 6(6)139-149.

Substrates, inhibitors, and inducers relative to DDIs

Substrates

- Drugs that are metabolized by specific enzymes or transporters (e.g., CYP450, P-gp).
- *Example*: Simvastatin is a substrate of CYP3A4.

Inhibitors

- Drugs that block the activity of enzymes or transporters.
- Can increase the concentration of a substrate, leading to toxicity.
- *Example:* Ketoconazole inhibits CYP3A4, increasing levels of co-administered substrates.

Inducers

- Drugs that enhance the activity or expression of enzymes or transporters.
- Can decrease the concentration of a substrate, reducing efficacy.
- *Example:* Rifampin induces CYP3A4, lowering levels of co-administered substrates.

Understanding these roles is critical for predicting and managing drug-drug interactions to optimize therapeutic outcomes.

US FDA. 2025 CYP Enzyme- and Transporter System-Based Clinical Substrates, Inhibitors, or Inducers from https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems

Risk factors for polypharmacy

Patient-related

- Advanced age
- Cognitive impairment
- Developmental disability
- Frailty
- Lack of a primary care physician
- Mental health issues
- Severe chronic medical conditions
- Receiving care from several doctors
- Residency in a long-term care facility

System-related

- Inadequate transition of care
- Poor medical recordkeeping
- Prescription of medications in order to meet disease-specific quality metrics
- Use of automated refill systems

Haili-Tierney AD et al. Am Fam Physician 2019;100:32-8.

The “AVOID Me Mistakes” mnemonic for obtaining a medical history

“AVOID ME”		
A	**Allergies**	Identification of medication that should not be prescribed for any reason
V	**Vitamins**	Including natural products and/or herbs
O	**Old and new medications**	Including prescriptions and OTC medications
I	**Interactions**	Initial assessment of potential interactions
D	**Dependence**	Consider the need for a behavioral contract in the case of either drug dependence or adherence to a therapeutic regimen
ME	**MEndel**	Family history of beneficial or negative outcomes with medications

Information from FDA. Preventable Adverse Drug Reactions: A Focus on Drug Interactions

Clinical decision support (CDS) systems and DDIs

Key questions	Recommendations
What process should be used to develop and maintain a standard set of DDIs?	• Establish a national expert panel to create and update a clinically relevant DDI set using systematic evidence, risk grading, and community feedback • Ensure regular updates and oversight by a recognized organization
What information should be included in a knowledgebase of standard DDIs?	Each DDI should include: • Severity, clinical impact, frequency, and modifying factors • Mechanism, recommended actions (with strength), and evidence (quality-rated)
Can/should a list of contraindicated drug pairs be established?	• Classifying an interaction as “contraindicated” should occur infrequently and should be reserved for drug pairs where coadministration should not be permitted under any circumstances
How can DDI alerts be more intelligently filtered?	• Convene a committee to review overrides, suppress low-value alerts, and refine presentation formats • Implement user feedback and carefully evaluate modifications to ensure patient safety • Incorporate active monitoring for harm in CDS systems

CDS, clinical decision support

Tilson H et al Am J Health Syst Pharm 2016, 73: 576-85.

Limitations of EHRs and monitoring DDIs

- **Incomplete or inaccurate patient data**
  - EHRs rely on accurate input from healthcare providers and patients. Missing or outdated information about medications, allergies, or health conditions may lead to ineffective DDI alerts[1]
- **Alert fatigue among healthcare providers**
  - Excessive or non-specific alerts within EHR systems can be overwhelm providers, leading to the dismissal of critical warnings. This reduces the effectiveness of DDI monitoring[2]
- **Lack of contextual clinical information**
  - EHRs often fail to incorporate nuanced clinical factors, such as renal function, hepatic impairment, or patient-specific pharmacogenomics, which are crucial for assessing DDI risks[3]
- **Inconsistent drug interaction databases**
  - EHR systems may use varying drug interaction databases, leading to discrepancies in the identification of potential interactions. This inconsistency can undermine clinical decision-making[4]
- **Limited integration with real-time data sources**
  - Many EHR systems lack real-time integration with external data (e.g. lab results or pharmacy records), which can delay identification of interactions or changes in patient health status

1. Classen, DC et al J Am Med Inform Assoc 2011; 2. van der Sijs, H et ak J Am Med Inform Assoc 2006; 3. Bates DW et al Am J Health Syst Pharm 2003; 4. Wright A et al J Am Med Inform Assoc 2012; 5. Payne TH et al J Biomed Inform 2015

DDIs and LAIs

Josh Havens, PharmD

Associate Clinical Professor, University of Nebraska Medical Center

HIV Clinical Pharmacist, Specialty Care Center

LAI PrEP dosing overview: Cabotegravir and lenacapavir

	CABOTEGRAVIR[1]	LENACAPAVIR2
Product dosing	*Optional oral lead in* **Day 1:** 1 x 3mL IM injection (600mg) **Month 2**: 1 x 3mL IM injection (600mg) **Month 4 and every 2 months after:** 1 x 3mL IM injection (600mg)	**Day 1:** 2 x 1.5mL SQ injections (927mg) + 2 x 300mg tablets (600mg) **Day 2:** 2 x 300 tablets (600mg) **Month 6 and every 6 months after:** 2 x 1.5mL SQ injections (927mg)
Administration site	By healthcare provider, ventrogluteal injection **(IM)** preferred, dorsogluteal **(IM)** acceptable	By healthcare provider, abdominal injection **(SC)** or thigh injection **(SC)**

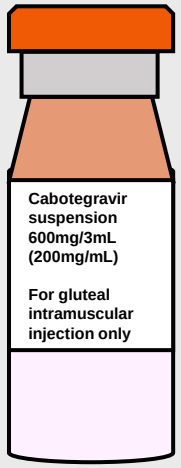
Administration tips	• **Injection should be given on the same date every 2 months; there is a +/- 7-day dosing window surrounding the target injection date**
	• Missed injections:
	  • If <1 month has elapsed since the last injection, continue with injections every 2 months
	  • If ≥1 month has elapsed since the last injection, re-initiate injections: 2 injections one month apart, then every 2 months thereafter
	• Planned missed injection:
	  • If missed injection is anticipated, oral bridging is available for up to 2 months
		• **Injections should be given every 26 weeks, +/- 2 weeks from the date of last injection**
		• Missed injections:
		  • If more than 28 weeks have elapsed since last injections, restart the initiation dosage regimen from Day 1
		• Planned missed injection:
		  • If missed doses are anticipated, oral bridging is available for up to 6 months

** optional oral lead in available to assess tolerability, not required per USPI

1. **APREUTDE USPI,** ViiV Healthcare, April 2025; 2. **YEZTUGO USPI**, Gilead Sciences, June 2025

Cabotegravir LA for PrEP product overview

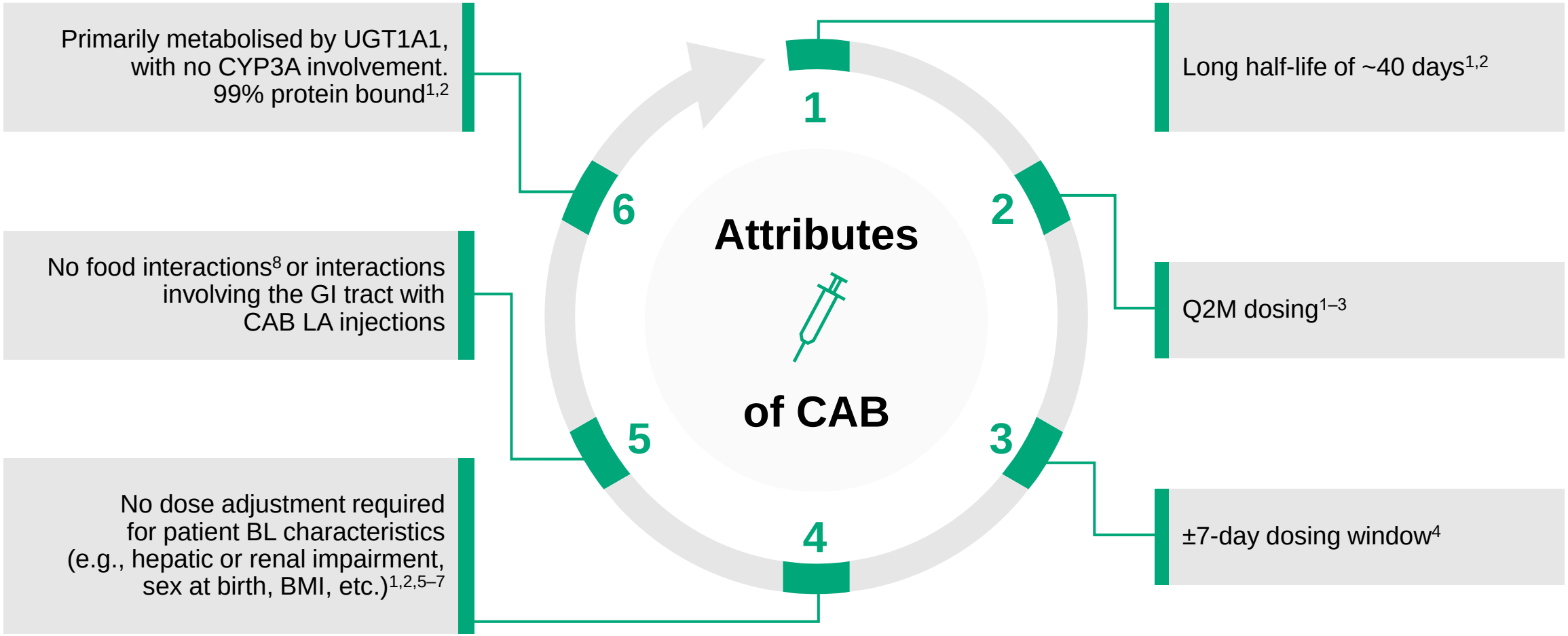
	CABOTEGRAVIR
Metabolic pathway	
Drug Class	2nd generation integrase strand transfer inhibitor
Half-life	41 hours (Oral, Optional) – 5.6-11.5 weeks (Long-acting)
Long-acting properties	• Residual concentrations of cabotegravir may remain in systemic circulation for up to **12 months or longer**.
Drug metabolism	• Cabotegravir is primarily metabolized by UGT1A1 with some contribution from UGT1A9[1] • Strong inducers of UGT1A1 or UGT1A9 are expected to decrease cabotegravir plasma concentrations[1-3]



INSTI, integrase strand inhibitors; **LA,** long-acting; P-pg, P-glycoprotein
**Dosing recommendations are not available for lenacapavir LA use in individuals already receiving moderate or strong CYP3A4 inducers OR receiving the oral formulation of lenacapavir

1. **APREUTDE USPI,** ViiV Healthcare, March 2025; **2.** Hodge D, Back DJ, et. al. *Clin Pharmacokinet*. 2021;60(7):835-853. **3.** Di Perri G. *Infez Med*. 2023;31(4):495-499. Published 2023 Dec

Pharmacological attributes of CAB LA



BL, baseline; **BMI,** body mass index; **CYP3A,** cytochrome P450 3A; **GI,** gastrointestinal; **UGT,** UDP-glucuronosyltransferase

1. Trezza C, et al. Curr Opin HIV AIDS 2015;10:239–45; **2.** Vocabria EU SmPC. Jan 2023
3. Overton ET, et al. Lancet 2021;396:1994–2005; **4.** Teichner P, et al. IDWeek 2019. Oral 884
5. Shaik JSB, et al. Clin Pharmacol Drug Dev 2019;8:664–73; **6.** Parasrampuria R, et al. Clin Pharmacol Drug Dev 2019;8:674–81
7. Elliot E, et al. EACS 2021. Oral BPD1/8; **8.** Patel P, et al. Clin Pharmacol Drug Dev 2019;8:443–8

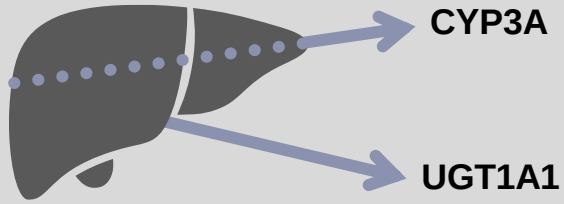
Cabotegravir LA DDIs are Unidirectional

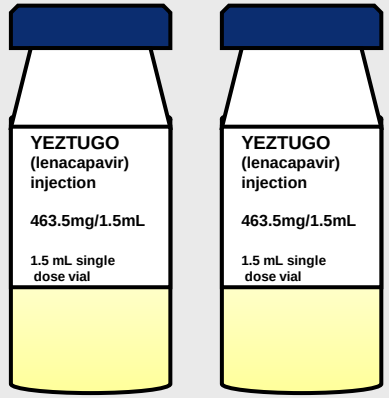
Other medications ------→ Cabotegravir

Metabolism	Drugs		IMPACT on CAB LA
Strong UGT1A1 and UGT1A9 inducers	Carbamazepine	Oxcarbazepine	↓ **CONTRAINDICATED** Decreases plasma concentrations of cabotegravir
	Phenobarbital	Phenytoin	
	Rifapentine		
	Rifabutin		↓ Decreases plasma concentrations of cabotegravir
			Dose adjustment doses required when coadministering cabotegravir LA and rifabutin. See USPI for details.

APREUTDE USPI, ViiV Healthcare, March 2025;

Lenacapavir for PrEP product overview

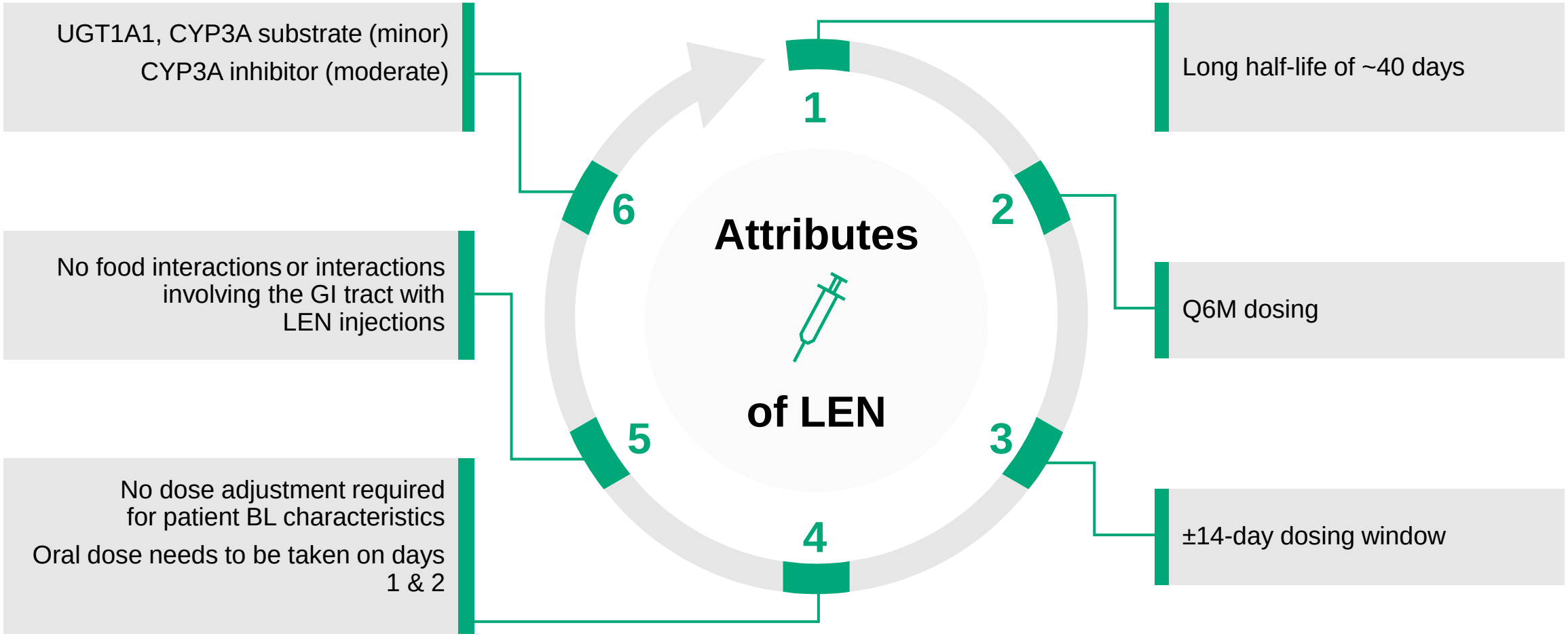
	LENACAPAVIR
Metabolic pathway	
Drug Class	First-in-class, multistage HIV-1 capsid inhibitor
Half-life	10-12 days (Oral, Required) – 8-12 weeks (Long-acting)
Long-acting properties	• Residual concentrations of lenacapavir may remain in systemic circulation for up to **12 months or longer**.
Drug metabolism	**Lenacapavir is a <u>substrate of CYP3A, UGT1A1 and P-gp</u>[2]** • Strong or moderate CYP3A4 inducers may significantly decrease plasma lenacapavir concentrations **Lenacapavir is a <u>moderate inhibitor of CYP3A and a P-gp</u>[2]** • Lenacapavir used with P-gp UGT1A1 and strong CYP3A4 inhibitors may significantly increase plasma lenacapavir concentrations • Co-administration with sensitive substrates of CYP3A or P-gp may increase substrate concentrations and risk of adverse events



INSTI, integrase strand inhibitors; **LA,** long-acting; P-pg, P-glycoprotein
**Dosing recommendations are not available for lenacapavir LA use in individuals already receiving moderate or strong CYP3A4 inducers OR receiving the oral formulation of lenacapavir

1.. **YEZTUGO USPI**, Gilead Sciences, June 2025

Pharmacological attributes of LEN



BL, baseline; **BMI,** body mass index; **CYP3A,** cytochrome P450 3A; **GI,** gastrointestinal; **UGT,** UDP-glucuronosyltransferase

YEZTUGO USPI, Gilead Sciences, June 2025

Lenacapavir DDIs are Bidirectional

Other medications ------→ Lenacapavir

Metabolism[1]	Drugs*[2]			IMPACT on LEN
Strong or moderate CYP3A inducers	Dexamethasone	Carbamazepine	Phenytoin	↓ Decreases plasma concentrations of lenacapavir
	Rifampin			

Dose adjustment required when coadministering with a new strong or moderate CYP3A inducer. See USPI for details*

Lenacapavir -------→ Other medications

Metabolism[1]	Medications*[2]			IMPACT on other medications
CYP3A substrates	Alprazolam	Amlodipine	Apixiban	↑ Increases plasma concentrations of other medications
	Budenoside	Clonazepam	Fludrocortisone	
	Buspirone	Diazepam	Quetiapine	
	Fentanyl	Felodipine	Rivaroxaban	
	Fluticasone	Oxycodone	Sildenafil	
	Salmeterol	Saxagliptin	Simvastatin	
	Tadalafil	Warfarin		
P-gp substrates	Apixaban	Digoxin	Dabigatran	
	Edoxaban	Fexofenadine		

*Medications listed are examples from the FDA and are not a comprehensive list

**Dosing recommendations are not available for lenacapavir LA use in individuals already receiving moderate or strong CYP3A4 inducers OR receiving the oral formulation of lenacapavir

1. YEZTUGO USPI, Gilead Sciences, June 2025; 2.U.S. Food and Drug Administration. Examples of drugs that interact with CYP Enzymes and Transporter Systems: www.fda.gov

Cabotegravir and Lenacapavir: Additional DDIs described

Yeztugo
(lenacapavir)

Lenacapavir (for PrEP) Prescribing Information[1]

Apretude
(cabotegravir LA)

Cabotegravir LA (for PrEP) Prescribing Information[2]

HIV Drug Interactions

University of Liverpool HIV Interaction Checker[3]

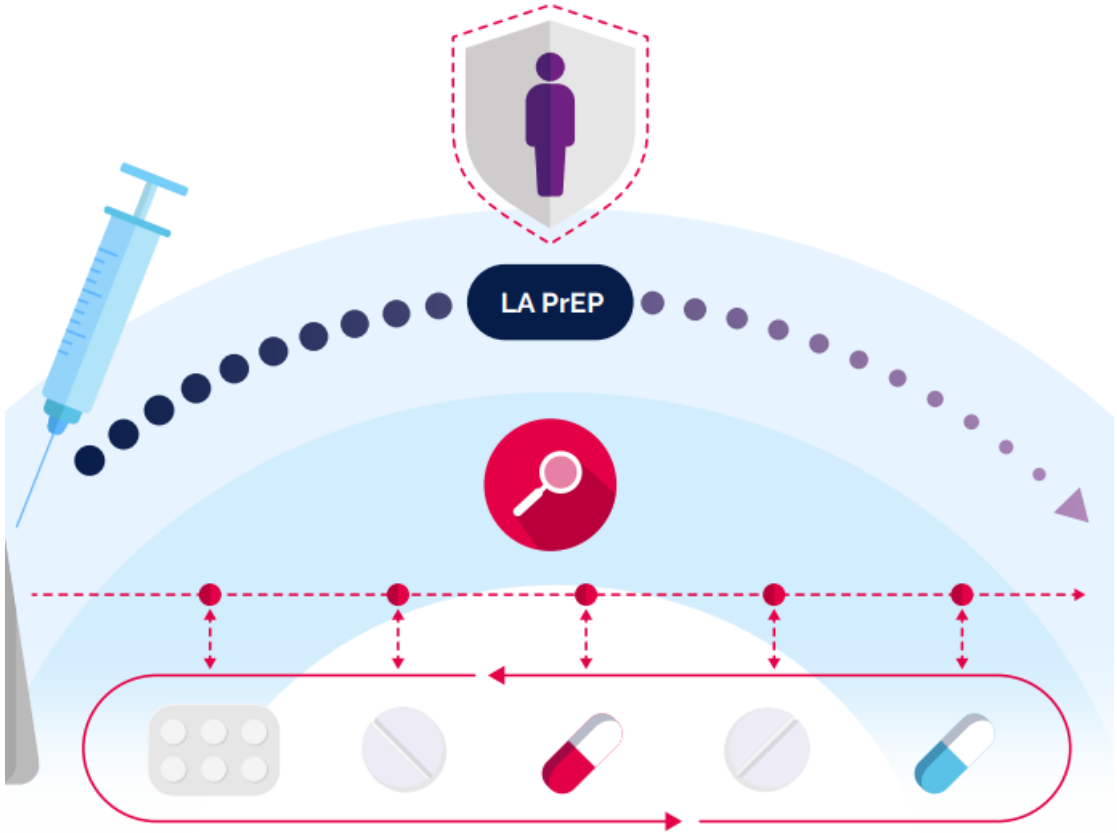
CLINICAL INFO HIV.gov

DHHS Guidelines Drug-Drug Interactions[4]

1. **YEZTUGO USPI**, Gilead Sciences, June 2025; 2. **APREUTDE USPI,** ViiV Healthcare, March 2025; **3**. University of Liverpool HIV Interaction Checker, October 2024. From: https://liverpool-hiv-hep.s3.amazonaws.com/prescribing_resources/pdfs/000/000/276/original/Lenacapavir_2024_Oct.pdf?1730389168; **4**. DHHS Guidelines, September 2024.. From: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/drug-interactions-capsid-inhibitor

LAI PrEP Takeaways

- DDIs with LAIs are manageable
- DDIs with CAB LA are unidirectional
- Impact of other medications on CAB LA
- (UGT1A1 substrate)
- DDIs with LEN are bidirectional
- Impact of other medications on LEN (3A substrate)
- Impact of LEN on other medications (3A inhibition)
- DDI impacts with LAIs can be challenging due to long half-life and can last for a long time (up to 9 to 12 months after last dose)



DDIs and Special Considerations

Population and Practice Setting

Marisa Brizzi, PharmD, BCPS, AAHIVP

HIV/Pain Stewardship Clinical Pharmacist

UC Health

John Smith (he/him)

34 y/o African American cisgender male

Medical & Social History

- Social History: Cocaine use; works out 7 days/week
- Sexual History: Sexually active with >10 male partners in the past 30 days
- Current Medications: sildenafil prn (telehealth); TDF/FTC daily (d/c'd due to vomiting)
- Medical history:
  - Past Medical History: Tested positive for syphilis 3 years ago
  - Current Health Condition: No current STI symptoms

John presents for routine STI screening and to discuss LAI PrEP

Patient case studies are not real cases and are illustrative only
Image generated by AI

Liverpool DDI Database: Interaction Potential of Chemsex Drugs with ART (treatment and prevention)

Drug	Metabolism	Drug class	Signs of toxicity
Benzodiazepines: Midazolam, triazolam	CYP3A4	**Boosted PI, capsid inhibitor, INSTI, NNRTI, NRTI**	Drowsiness, disorientation
Benzodiazepines, other	CYP3A4	**Boosted PI, capsid inhibitor, INSTI, NNRTI, NRTI**	Drowsiness, disorientation
Cocaine	CYP3A4	**Boosted PI, capsid inhibitor, INSTI*, NNRTI, NRTI**	Tremors, paranoia, seizures, headache, hyperthermia
Ecstasy (MDMA)	CYP2D6	**Boosted PI†, capsid inhibitor, INSTI, NNRTI, NRTI**	Hypertension, seizures, hyperthermia, arrythmia, tachycardia, teeth grinding
GHB	GHB dehydrogenase CYP ?	**Boosted PI‡, capsid inhibitor‡, INSTI, NNRTI, NRTI**	Seizures, bradycardia, respiratory depression
Ketamine	CYP3A4	**Boosted PI, capsid inhibitor, INSTI, NNRTI, NRTI**	Respiratory depression, hallucinations
Mephedrone	CYP2D6	**Boosted PI§, capsid inhibitor, INSTI, NNRTI, NRTI**	Tachycardia, agitation
Methamphetamine	CYP2D6	**Boosted PI¶, capsid inhibitor, INSTI, NNRTI, NRTI**	Hypertension, seizures, hyperthermia, arrythmia, tachycardia, teeth grinding
Poppers (nitrates)	Non-CYP mediated	**Boosted PI, capsid inhibitor, INSTI, NNRTI, NRTI**	Dizziness, hypotension
Sildenafil, tadenafil, vardenafil	CYP3A4	**Boosted PI, capsid inhibitor, INSTI, NNRTI, NRTI**	Chest pain, nausea, arrythmia

PI, protease inhibitor; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reuptake inhibitor; NRTI, nucleoside reuptake inhibitor;

*Note caution with drugs with known risk of QT prolongation; Always refer to the prescribing information for list of DDIs with licensed medications; † Limited CYP2D6 inhibition by small PK changes could be significant due to non-linear PK; ‡Unknown – caution due to GHB narrow therapeutic index; § Limited CYP2D6 inhibitor; ¶ Limited CYP2D5 inhibition by small PK changes could be significant due to non-linear PK CYP3A, cytochrome P450 3A

Interaction potential **Black**=Limited **Orange=**Intermediate **Green=**Low **Red=**High

"Interaction Potential of Chemsex Drugs, Liverpool Drug Interactions Group, University of Liverpool. Available at: www.hiv-druginteractions.org

Lenacapavir DDIs are Bidirectional

Other medications ------→ Lenacapavir

Metabolism[1]	Drugs*[2]			IMPACT on LEN
Strong or moderate CYP3A inducers	Dexamethasone	Carbamazepine	Phenytoin	↓ Decreases plasma concentrations of lenacapavir
	Rifampin			

Dose adjustment required when coadministering with a new strong or moderate CYP3A inducer. See USPI for details*

Lenacapavir -------→ Other medications

Metabolism[1]	Medications*[2]			IMPACT on other medications
CYP3A substrates	Alprazolam	Amlodipine	Apixiban	↑ Increases plasma concentrations of other medications
	Budenoside	Clonazepam	Fludrocortisone	
	Buspirone	Diazepam	Quetiapine	
	Fentanyl	Felodipine	Rivaroxaban	
	Fluticasone	Oxycodone	Sildenafil	
	Salmeterol	Saxagliptin	Simvastatin	
	Tadalafil	Warfarin		
P-gp substrates	Apixaban	Digoxin	Dabigatran	
	Edoxaban	Fexofenadine		

*Medications listed are examples from the FDA and are not a comprehensive list

**Dosing recommendations are not available for lenacapavir LA use in individuals already receiving moderate or strong CYP3A4 inducers OR receiving the oral formulation of lenacapavir

1. YEZTUGO USPI, Gilead Sciences, June 2025; 2.U.S. Food and Drug Administration. Examples of drugs that interact with CYP Enzymes and Transporter Systems: www.fda.gov

DDIs and telehealth: Challenges

- **Limited access to complete patient medication history**
  - Telehealth providers face challenges such as fragmented records, reliance on patient self-reporting, and lack of coordination, which can result in incomplete medication histories and increased risk of drug-drug interactions.[1,2]
- **Absence of automated DDI alerts**
  - Many telehealth platforms lack built-in clinical decision support systems (CDSS) that flag potential DDIs during the prescribing process.[3,4]
- **Challenges with polypharmacy**
  - Lack of communication between telehealth providers and primary care physicians can result in overlapping or conflicting prescriptions.[2,7,9]
- **Limited physical assessments for DDI symptoms**
  - DDIs can cause physical symptoms that telehealth providers cannot observe directly during virtual consultations.[2,10]
- **Lack of EHR integration**
  - Non-integrated telehealth platforms limit access to full patient histories, complicating drug interaction identification.[3,5,9]
- **Limited collaboration between providers**
  - Telehealth providers may not communicate with pharmacists involved in the patient's care, reducing opportunities for identifying DDIs.[6,7]

1. Kruse CS et al BMJ Open 2017; 2. Totten AM et al AHRQ 2016; 3. Wright E et al Int J Pharm Pract 2016; 4. Bates DW et al NEJM 2003; 5. Adler-Milstein J et al Am J of Managed Care 2013; 6. Downing NJ et al Health Services Research 2018; 7. Maher RL et al Expert Opinion on Drug Safety 2014; 8. Riedl MA et al J Am Geriatrics Society; 9. Bashshur RL et al Telemedicine and e-Health 2016; 10; Lopez AM et al JAMA 2021.

Discussion

Alexi Johnson (she/her)

28 y/o African-American cisgender female

Medical & Social History

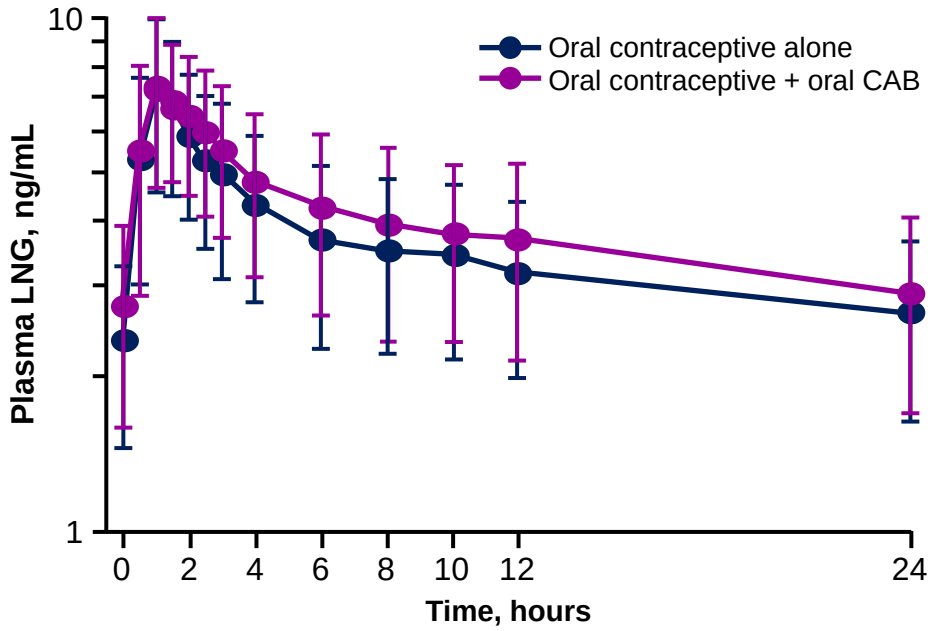
- Social History: Denies any recreational drug use
- Sexual History: Heterosexual in an open relationship with one male partner; reports inconsistent condom use
- Current Medications: lenacapavir for PrEP, planning to start treatment for tuberculosis (TB): rifampin, isoniazid, pyrazinamide, ethambutol
- Medical History:
  - Tested positive for chlamydia 1 year prior
  - Current Health Condition: Reports no symptoms of STIs.
- Medical Notes: Open to planning a family within the next year

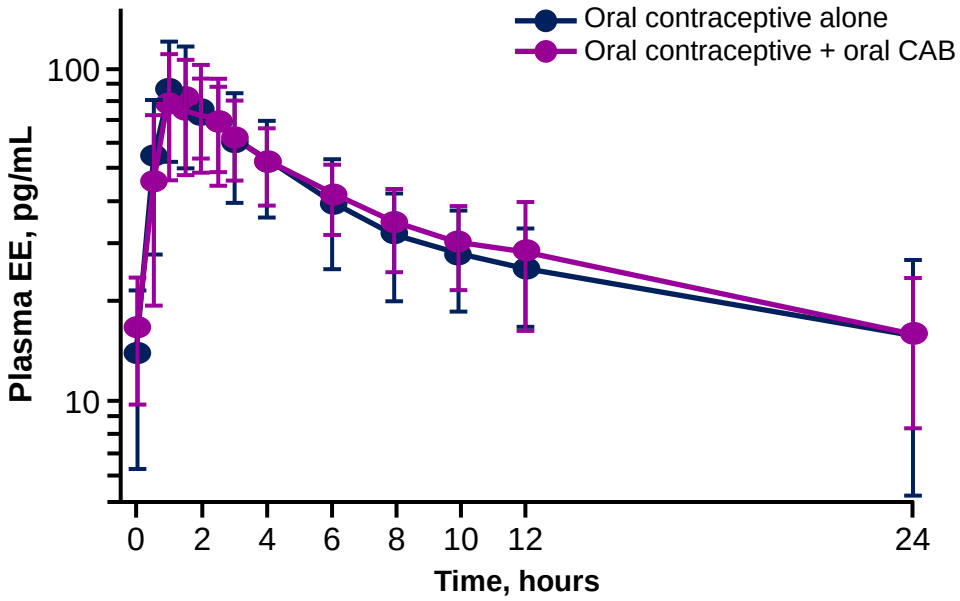
Alexi presents for annual Well-Woman exam and STI screening

Patient case studies are not real cases and are illustrative only
Image generated by AI

CAB LA does not interact with oral contraceptives

- CAB can be administered with hormonal contraceptives without dose adjustment





GLS ratio (90% CI)	C_{max}*	$AUC_{(0–\tau)}$†	C_{τ}*
LNG + CAB versus LNG	1.05 (0.96, 1.15)	1.12 (1.07, 1.18)	1.07 (1.01, 1.15)
EE + CAB versus EE	0.92 (0.83, 1.03)	1.02 (0.97, 1.08)	1.00 (0.92, 1.10)

*C_{max} and $C\tau$ values were measured in ng/mL for LNG and in pg/mL for EE
†$AUC_{(0–\tau)}$ values were calculated in ng*h/mL for LNG and in pg*h/mL for EE

Trezza C, et al. Br J Clin Pharmacol 2017;83:1499–505

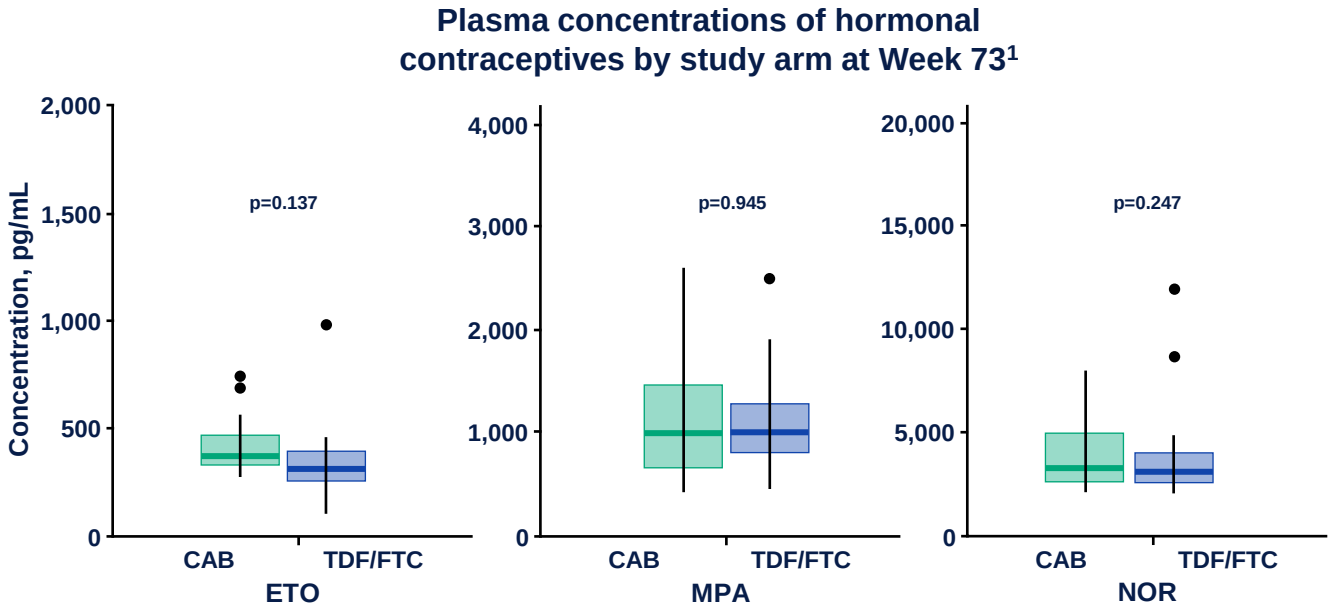
HPTN 084 sub-study: No impact of CAB on hormonal contraceptives

Analysis Details

The registrational HPTN 084 trial provided an opportunity to assess pharmacologic interactions between CAB, TDF/FTC, and commonly used hormonal contraceptives[1]

- 170 consenting participants provided samples whilst on treatment (CAB LA: 80; TDF/FTC: 90)*

- In CAB LA users, **contraceptive concentrations were comparable to participants receiving TDF/FTC for all three contraceptives[1]**
- Percentage of participants with contraceptive concentrations exceeding threshold for ovulation suppression was high[1]
- CAB concentrations were comparable across contraceptive types[1]
- Associations between TDF/FTC and hormone concentrations could not be effectively evaluated due to low adherence to TDF/FTC[1]



Data confirm CAB's low potential for significant clinically relevant interactions with hormonal contraception[1,2]

*Based on the reported contraceptive regimen at BL and subsequent study visits, plasma concentrations of ETO, MPA, and NOR were evaluated at enrollment and Weeks 25, 49, and 73; plasma tenofovir and CAB concentrations were determined at contemporaneous visits. Participants were allowed to switch contraceptive and pharmacokinetic assessments were adjusted accordingly. Changes in contraceptive regimens were common across study arms (CAB LA: 24%; TDF/FTC: 24%)
ETO, etonogestrel; **MPA,** medroxyprogesterone acetate; **NOR,** norethindrone

1. Marzinke M, et al. HIVR4P 2024. Oral OA2306
2. Trezza C, et al. Br J Clin Pharmacol 2017;83:1499–505

LEN for PrEP and Oral Contraceptives

- At present, there are no subgroup analyses evaluating the efficacy and safety outcomes of LEN in participants receiving hormones in PURPOSE1

Bekker LG et al. N Engl J Med. 2024;39(13):1179-92.

Cabotegravir LA Drug-Drug interactions (per Apretude USPI)

DRUG CLASS	EFFECT ON CONCENTRATION	SEVERITY
Anticonvulsants: Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	↓ cabotegravir	CONTRAINDICATED
Antimycobacterials: Rifampin, rifapentine	↓ cabotegravir	CONTRAINDICATED
rifabutin[b]	↓ cabotegravir	DOSING ALTERATION RECOMMENDED*

UGT1A1 inducers

UGT1A1 inducers and CYP3A inducers

When prescribing LA PrEP, consider DDIs that might occur now and in the future with polypharmacy, including Rx / OTC / recreational drugs and supplements

USPI, US prescribing information
*For patients concomitantly receiving rifabutin, please see the full Prescribing Information for the adjusted recommended dosing schedule for APRETUDE.
↑ = Increase, ↓ = Decrease. b. Drug-drug interaction study was conducted

APRETUDE. PI. ViiV Healthcare, 2024

Recommendation for dosing adjustments for those on lenacapavir initiating therapy with strong CYP3A4 inducers (per Yeztugo USPI[1])

Maintain Scheduled Continuation Injection Dosing	Schedule for Supplemental Doses of Lenacapavir	
	Time	Dosage
Continue to administer once every 6-months scheduled continuation dosing of lenacapavir 927 mg SC (2 x 1.5 mL injections), plus administer supplemental doses of lenacapavir as shown in this table	• On the day strong CYP3A4 inducer is initiated (which should be at least 2 days after lenacapavir is first initiated	**Supplemental dosage: Step 1** 927 mg SC lenacapavir (2 x 1.5 ml) and 600 mg orally (2 x 300 mg tablets)
	• On day after strong CYP3A inducer is initiated	**Supplemental dosage: Step 2** 600 mg orally (2 x 300 mg tablets)
	• If strong CYP3A inducer is co-administered for longer than 6 months	**Subsequent supplemental dosage** Every 6-months[a] from initiation of strong CYP3A inducer, continue to administer supplemental doses of YEZTUGO as described above in Steps 1 and 2.
	After stopping the strong CYP3A inducer, continue the once every 6-months scheduled continuation injection dosing of lenacapavir	

a. 26 weeks +/- 2 weeks

Dosing recommendations are not available for lenacapavir use in individuals already receiving moderate or strong CYP3A4 inducers OR receiving the oral formulation of lenacapavir

Examples of STRONG CYP 3A4 inducers[2]:

- Carbamazepine
- Apalutamide
- Enzalutamide
- Ivosidenib
- Lumacaftor
- Mitotane
- Phenytoin
- Rifampin
- St. John's Wort

1. YEZTUGO USPI, Gilead Sciences, June 2025; 2. https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems; date accessed June 23, 2025

Discussion

Maria Fernandez (she/her)

27 y/o Hispanic transgender woman

Medical & Social History

- Social History: Denies any recreational drug use
- Sexual History: Sexually active with multiple men
- Current Medications: spironolactone and estradiol (Feminizing Gender-Affirming Hormone Therapy)
- Medical History:
  - Previous STI: Tested positive for gonorrhea 6 months ago, treated successfully with antibiotics
  - Current Health Condition: Reports no current symptoms of STIs

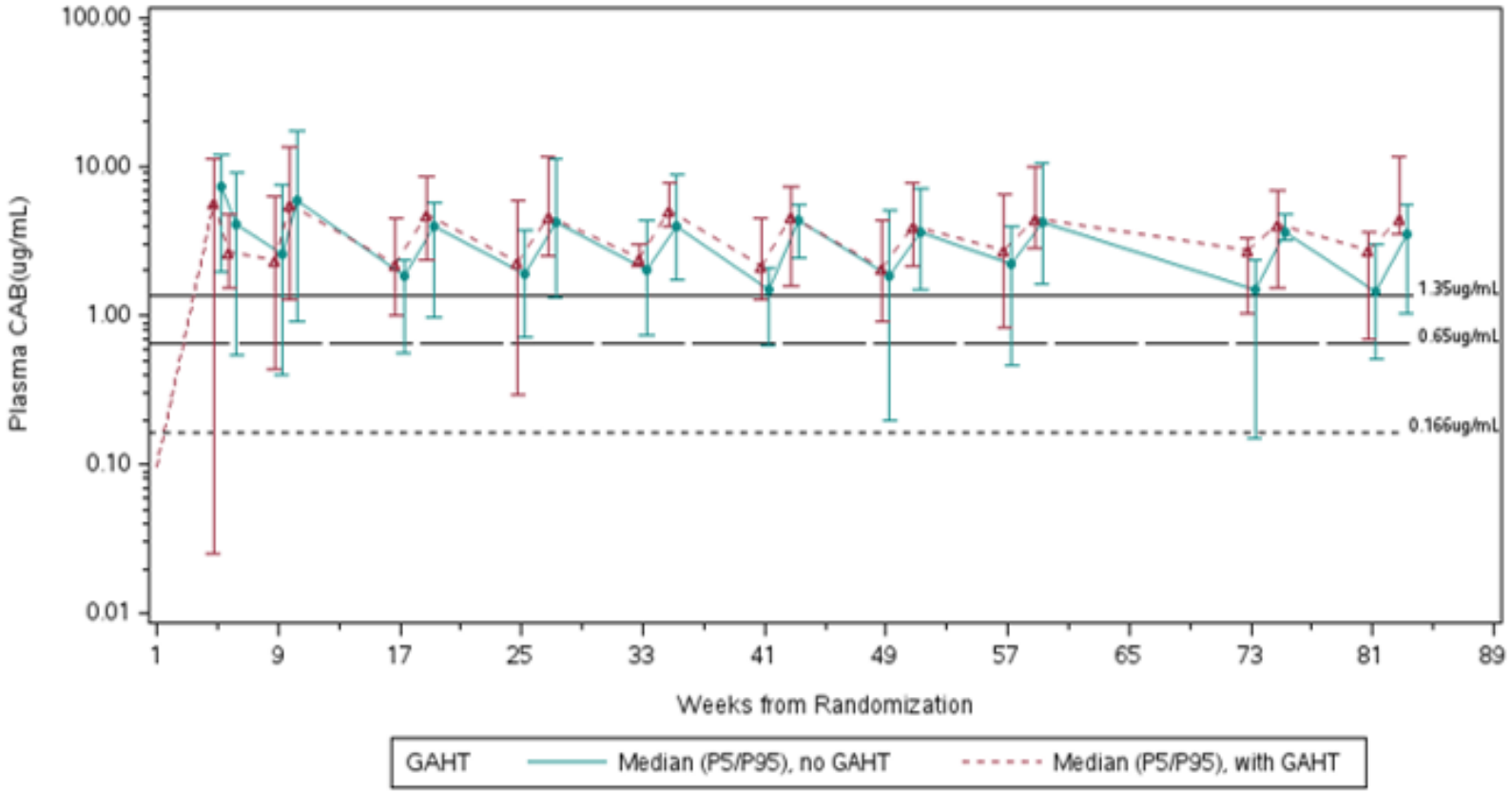
Maria presents for routine STI screening

Patient case studies are not real cases and are illustrative only
Image generated by AI

TGW in HPTN 083: CAB LA PK not impacted by GAHT

- CAB PK was compared in a subset of TGW in the presence or absence of GAHT; in this analysis, 30 participants accessed GAHT, while 23 participants were not using GAHT
- CAB drug concentrations were comparable between the 2 groups, suggesting the lack of a GAHT effect on CAB PK

Concentration-time profiles of CAB in TGW in the absence (solid blue line) or presence (dotted red line) of GAHT



Grinsztejn et al. AIDS 2022; Virtual and Montreal, Canada. Poster EPLBC04.

LEN for PrEP and GAHT

- Gender-affirming hormone therapy was reported in 253 participants (11.6%) in the LEN group (n=2,183) and 131 participants (12%) in the FTC/TDF group (n=1,088).
- Currently, there are no subgroup analyses available that assess the efficacy and safety outcomes of LEN specifically in participants receiving gender-affirming hormone therapy.
- In total, 534 participants in the PURPOSE 2 study were evaluated for their use of gender-affirming hormone therapy. Pharmacokinetic (PK) analysis indicated that gender-affirming hormone therapy did not affect LEN exposure levels.

Imperial M, Hughes E, Panchia R, et al. Population Pharmacokinetic Analysis of Lenacapavir in People Who Want or Need Pre-Exposure Prophylaxisfor HIV [Poster I-109]. 2025:

Discussion

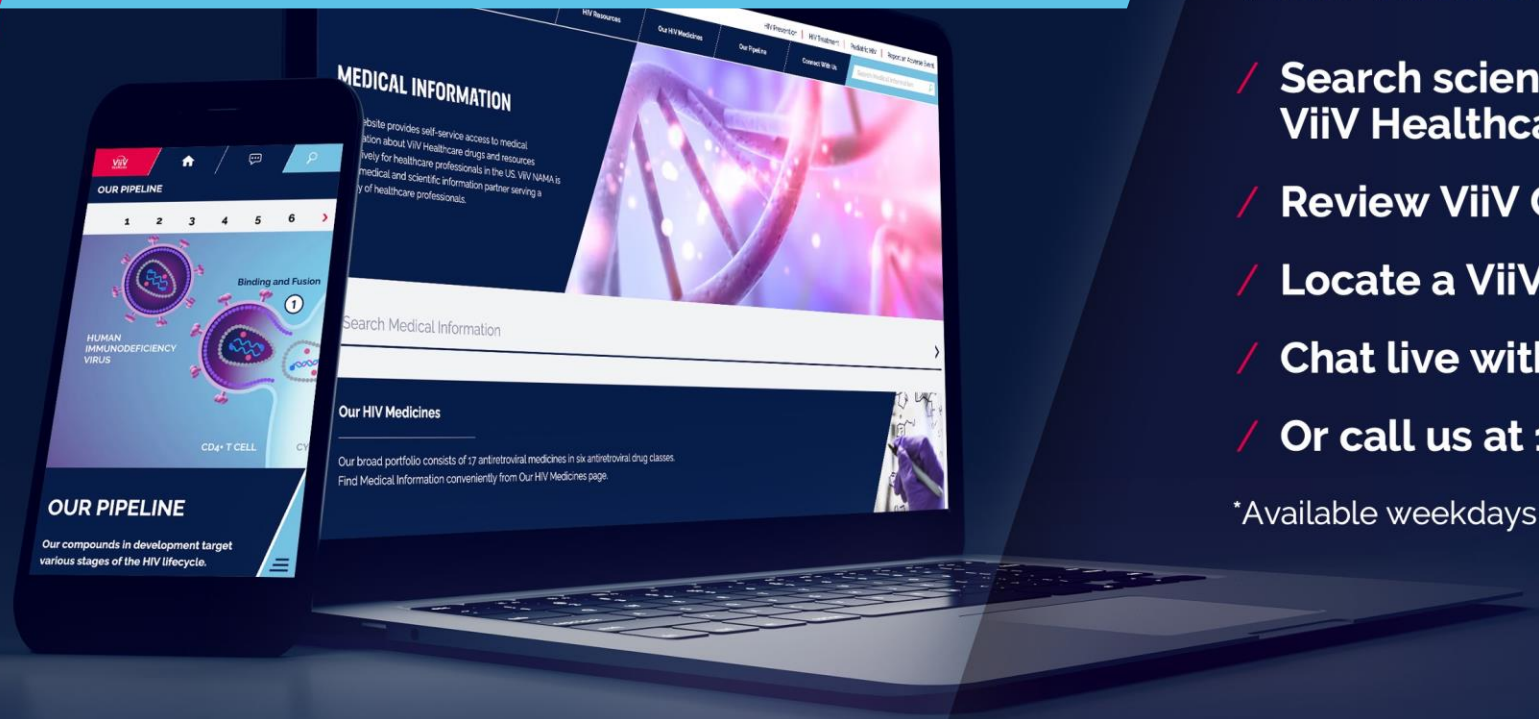
Q & A

- Please use the Q&A function to submit comments and questions
- If we are unable to get to your question, we will ensure to follow up with you!

FEEDBACK

Tell us what you think of today's program

Thank You!



Visit viivhcmedinfo.com to:

- Search scientific and medical information for ViiV Healthcare medicines
- Review ViiV Congress presentations and posters
- Locate a ViiV Medical Science Liaison
- Chat live with ViiV Healthcare Professionals*
- Or call us at 1-888-226-8434*

*Available weekdays from 8am—6pm EST

MEDICAL INFORMATION WEBSITE

viivhcmedinfo.com

SCAN TO VISIT
OUR WEBSITE

Back up slides

CAB clinical pharmacology attributes

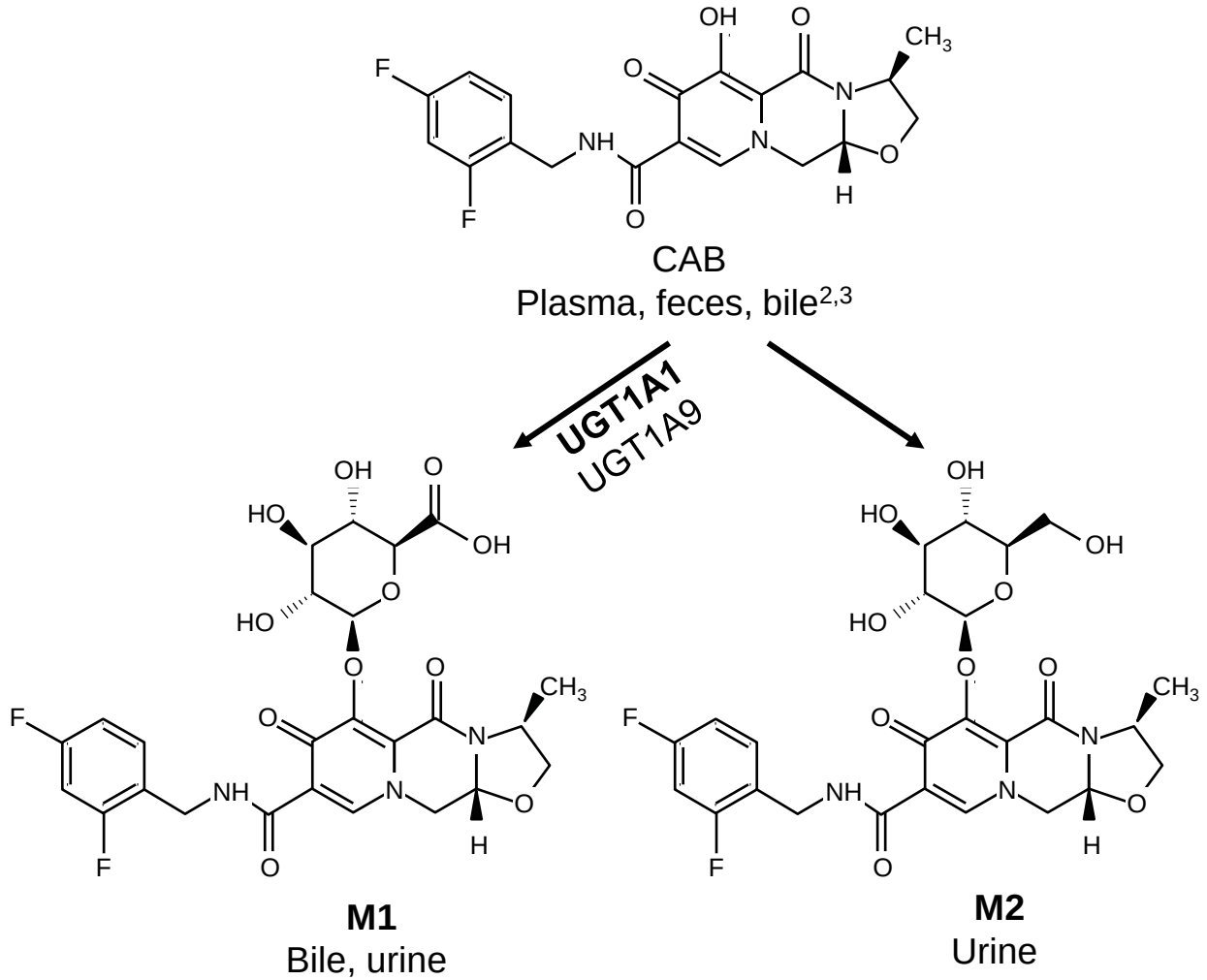
Attribute	Oral CAB QD	CAB LA	
		Q1M	Q2M
Dose (Phase III)	30 mg[1]	600 mg (3 mL) initiation dose 400 mg (2 mL) continuation dose[2,3]	600 mg (3 mL) initiation and continuation doses[3]
Absorption	Rapidly absorbed; T_{max} 3 hours[1]	Slowly absorbed; T_{max} 1 week[2,3]	
Impact of food	None[1]	NA	
Inter-subject PK variability	Low to moderate[4]	Moderate to high, consistent with IM dosing[3]	
Impact of covariates on PK	No age, race, or gender impact[1]	Slower initial absorption rates were observed in females and subjects with high BMI. No clinically significant differences were observed based on age, sex, race/ethnicity or *UGT1A1* polymorphisms[2,3] In analyses of BL factors, a small association between BMI (which is correlated with CAB PK) and CVF was seen, mostly in the presence of ≥1 other BL factor[5]	
Elimination $t_{1/2}$	41 hours[1]	5.6–11.5 weeks (absorption-limited rate)[2,3]	
Metabolism	Primarily metabolised by UGT1A1, with minor UGT1A9 component[1–3]		
Protein binding	99.8% protein bound[1–3]		
Drug interaction liability	Low potential to cause or be a victim of DDI[2,3]		

CVF, confirmed virologic failure; **NA,** not applicable; **QD,** once daily; **T_{max}**, time to peak plasma concentration

1. Vocabria US PI. Feb 2023; **2.** Cabenuva US PI. Feb 2023
3. Vocabria EU SmPC. Jan 2023; **4.** Min S, et al. Antimicrob Agents Chemother 2010;54:254–8
5. Orkin C, et al. HIV Glasgow 2022. Oral O44

CAB: Human metabolism and excretion

- CAB is primarily metabolised by UGT1A1 with a minor UGT1A9 component; there is no CYP3A4 involvement[1]
- Renal elimination of unchanged CAB is negligible (0% of dose)[2]
- CAB is the predominant circulating compound in plasma[2]



1. Reese M, et al. IWCP 2014. Abstract PP_20
2. Culp A, et al. ICAAC 2014. Abstract H-1010
3. Trezza C, et al. Curr Opin HIV AIDS 2015;10:239–45

Table 4. Recommendations for the Selection of DDIs for CDS Systems

Key Questions	Recommendations
What process should be used to develop and maintain a standard set of DDIs?	• Form a national consensus expert panel to develop and maintain a standard set of clinically relevant DDIs for CDS systems, with oversight by a national organization • Use a systematic process for assembling DDI evidence • Grade recommendations for risk management • Develop a web-based tool to solicit community feedback on recommendations • Ensure periodic and timely updates of the standard DDI set
What information should be included in a knowledgebase of standard DDIs?	• Each DDI should include: ◦ Severity classification ◦ Clinical consequences ◦ Frequency of harm and exposure ◦ Modifying factors ◦ Mechanism of the interaction ◦ Recommended actions, with strength of recommendation ◦ Evidence, with quality ratings
Can/should a list of contraindicated drug pairs be established?	• Classifying an interaction as "contraindicated" should occur infrequently and should be reserved for drug pairs where coadministration should not be permitted under any circumstances
How can DDI alerts be more intelligently filtered?	• Health care institutions should convene an interdisciplinary committee to periodically review commonly overridden alerts and suggest ways to either suppress alerts of minimal value or change their presentation format • Allow users to provide feedback on alerts as part of continuous quality improvement • Do not indiscriminately "turn off" alerts • Modifications to DDI alerts should be done cautiously, with careful evaluation to ensure that patient safety is not compromised • Strategies to actively monitor for signs of harm for patients receiving concurrent medications that may result in a DDI should be incorporated into CDS systems

CDS = clinical decision support.

Information from: Tilson H, Hines LE, McEvoy G, et al. Recommendations for selecting drug-drug interactions for clinical decision support. Am J Health Syst Pharm 2016;73:576-85.