Table 19A: Lenacapavir (LEN) Interactions When Used for HIV Treatment [a] (also see prescribing information)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Direct oral anticoagulants (DOACs; apixaban, rivaroxaban, dabigatran, edoxaban, etc.)	DOAC levels potentially increase due to effect on CYP3A4 and P-gP.	• No dose adjustment needed; monitor for increased risk of bleeding. • Refer to DOAC prescribing information for use with moderate CYP3A4 and P-gP inhibitors.
Digoxin	Moderate inhibition of P-gP potentially increases digoxin levels.	Monitor digoxin concentrations when using with LEN.
Anticonvulsants	**Carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone:** CYP3A4 and P-gP induction potentially decreases LEN levels.	• **Carbamazepine, eslicarbazepine, phenytoin:** Do not coadminister. • **Oxcarbazepine, phenobarbital, primidone:** Coadministration is not recommended. • Consider alternative anticonvulsants such as levetiracetam.
Antipsychotics	**Pimozide:** Moderate inhibition of P-gP potentially increases pimozide levels.	**Pimozide:** Do not coadminister.
Cardiac medications	**Amiodarone, disopyramide, quinidine, ivabradine:** Moderate inhibition of P-gP potentially increases cardiac medication levels.	**Amiodarone, disopyramide, quinidine, ivabradine:** Do not coadminister.
• Efavirenz (EFV) • Etravirine (ETR) • Nevirapine (NVP) • Tipranavir (TPV)	CYP3A4 and P-gP induction associated with concomitant HIV treatment potentially deceases LEN levels.	• Do not coadminister. • Drug interactions with rilpivirine and doravirine are unlikely.
COBI- or RTV-boosted atazanavir (ATV)	CYP3A4 and P-gP inhibition potentially increases LEN levels.	• Do not coadminister. • Drug interactions with darunavir boosted with COBI are unlikely. • Other boosted PIs should also be avoided due to late of data.
Rifabutin, rifampin, rifapentine	CYP3A4 and P-gP induction associated with rifamycins potentially decreases LEN levels.	• **Rifampin:** Concomitant use is contraindicated. • **Rifabutin, rifapentine:** Coadministration is not recommended. • Consider alternatives.
Dexamethasone, hydrocortisone (systemic)	• Moderate inhibition of CYP3A4 and P-gP potentially increases corticosteroid concentrations and the related risk of Cushing's syndrome and adrenal suppression. • **Dexamethasone (systemic):** Decreased LEN levels expected with dexamethasone doses >16 mg/day.	• **Dexamethasone, hydrocortisone (systemic):** Initiate at lowest dose and titrate slowly to achieve clinical effect; monitor for adverse effects. • **Dexamethasone (systemic):** Do not coadminister with dexamethasone doses >16 mg/day.
Ergotamine derivatives (dihydroergotamine, ergotamine, methylergonovine, etc.)	Moderate inhibition of CYP3A4 potentially increases ergotamine derivative levels.	Do not coadminister.
St. John's wort	CYP3A4 and P-gP induction potentially decreases LEN levels.	Do not coadminister.

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Class or Drug	**Mechanism of Action**	**Clinical Comments**
Lovastatin, simvastatin, lomitapide	**Lovastatin, simvastatin, lomitapide:** Moderate inhibition of CYP3A4 and P-gP potentially increases levels.	• **Simvastatin, lovastatin:** Initiate at lowest dose and titrate to achieve clinical effect; monitor closely for statin toxicity. • **Lomitapide:** Concomitant use is contraindicated.
Opioids metabolized via CYP3A (i.e., fentanyl, oxycodone, tramadol)	Moderate inhibition of CYP3A4 potentially increases opioid levels.	• Monitor for therapeutic effects and adverse reactions associated with CYP3A-metabolized opioid analgesics, including potentially fatal respiratory depression. • **Tramadol:** Consider tramadol dose reduction with concomitant use.
Methadone, buprenorphine	Moderate inhibition of CYP3A4 and P-gP potentially increases methadone or buprenorphine levels.	• **Patients initiating MAT while already on LEN:** Initiate MAT at lowest initial or maintenance dose. • **Patients initiating LEN while already on MAT:** MAT dose adjustments may be needed. • Monitor for excess sedation and/or respiratory depression.
Naloxegol (opioid antagonist)	Moderate inhibition of CYP3A4 potentially increases naloxegol levels.	Avoid concomitant use. If use is required, decrease naloxegol dose and monitor for adverse effects.
PDE5 inhibitors	Moderate inhibition of CYP3A4 and P-gP potentially increases PDE5 inhibitor levels.	**For pulmonary hypertension:** • **Tadalafil:** Concomitant use is not recommended. • For other medications, refer to dosing guidelines. **For erectile dysfunction**, refer to prescribing information and guidance listed below: • **Avanafil:** Do not coadminister. • **Sildenafil:** Start with 25 mg every 48 hours; monitor for adverse effects. • **Tadalafil:** Start with 5 mg and do not exceed 10 mg every 72 hours; monitor for adverse effects. **Vardenafil:** Administer 2.5 mg every 72 hours; monitor for adverse effects.
Midazolam (oral), triazolam	Moderate inhibition of CYP3A4 and P-gP potentially increases sedative levels.	Use with caution; monitor for excess sedation.
ADHD medications	**Modafinil:** CYP3A4 induction may reduce LEN levels.	**Modafinil:** Consider alternative ADHD medications.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; MAT, medication-assisted therapy; PDE5, phosphodiesterase type 5; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; TDM, therapeutic drug monitoring.

Note:

a. For LEN as HIV treatment, see prescribing information for Sunlenca; for LEN as HIV pre-exposure prophylaxis, see Table 19B: Lenacapavir Interactions When Used for HIV Prevention and prescribing information for Yeztugo.

Table 19A: Lenacapavir (LEN) Interactions When Used for HIV Treatment [a] (also see prescribing information)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
No significant interactions/no dose adjustments necessary (see guideline section Drug-Drug Interactions by Common Medication Class)**:** Common oral antibiotics; antihypertensive medications; antiplatelet medications; antidiabetic medications; acid-reducing agents; polyvalent cations; asthma and allergy medications; long-acting beta agonists; antidepressants; sleep medications; antipsychotics; nonopioid pain medications; hormonal contraceptives; alpha-adrenergic antagonists for benign prostatic hyperplasia; tobacco and smoking cessation products; alcohol, disulfiram, and acamprosate; immunosuppressants; COVID-19 therapeutics; mpox treatments; gender-affirming hormones.		