Assessing the potential for drug-drug interaction with long-acting pre-exposure prophylaxis in the OPERA Cohort

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Background

- Pre-exposure prophylaxis (PrEP) is a key component to decreasing the incidence of HIV infection[1,2]
- Recent clinical development has focused on long-acting (LA) PrEP formulations
- Cabotegravir (CAB) LA injections dosed every two months is the only LA PrEP option currently approved in the US
- Lenacapavir (LEN) LA injections dosed every six months are currently under investigation in clinical trials as PrEP
- Given the long-acting nature of newer injectable PrEP formulations, there is a need to understand the potential for drug-drug interactions (DDIs) that people who use PrEP may encounter

Objective

To assess the proportion of people without HIV who may be at risk for a potential DDI when using LA PrEP

Methods

Study population

- OPERA® cohort: prospectively captured, routine clinical data from electronic health records in the US (90 clinics, 23 US states/territories)
- Inclusion criteria (on 30SEP2024):
  - Adults without HIV who were active in care
  - PrEP users: any oral or LA PrEP use between 01OCT2023 and 30SEP2024
  - People who could benefit from PrEP: no PrEP use between 01OCT2023 and 30SEP2024 and met ≥1 of the following criteria, informed by CDC PrEP guidelines[1] and the National HIV AIDS Strategy[2]:
    - Tested for or diagnosed with gonorrhea, syphilis or chlamydia between 01OCT2022 and 30SEP2024
    - Alcohol use disorder (ever)
    - Illicit and/or injection drug use (ever)
    - Black or transgender women
    - 18-24 years old
    - Men who have sex with men
    - Any PrEP use prior to 01OCT2023

Potential for DDI

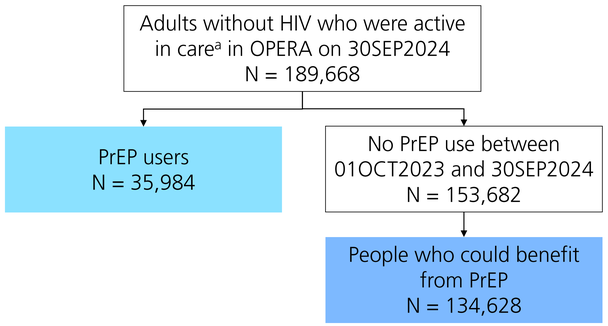
- An individual was considered to have potential for DDI for each of CAB LA and LEN LA if taking medications between 01OCT2023 and 30SEP2024 that were considered as having drug interactions with CAB LA or LEN LA, according to the USPI/SmPC labels and the PURPOSE 1 study protocol

Analyses

- For each group, the number of individuals with potential for DDI with CAB LA and with LEN LA
  - Results were stratified by sex, age group, and level of interaction
- The frequency of select comorbidities that are commonly treated with medications with potential for DDI with either CAB LA or LEN LA were assessed

Results

Figure 1. Identification of the study populations



[a] At least one active healthcare visit between 01OCT2023 and 30SEP2024

Table 1. Baseline characteristics, as of 30SEP2024

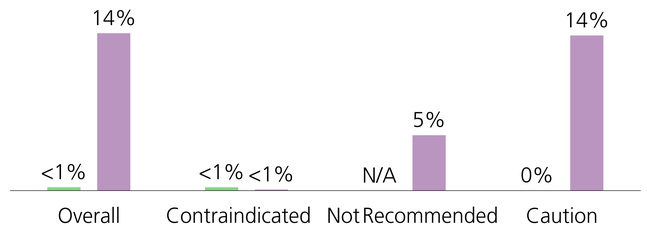
	PrEP users N = 35,984	People who could benefit from PrEP N = 134,628
Age, n (%)		
18-24 years	5,480 (15)	34,189 (25)
25-39 years	20,793 (58)	70,422 (52)
40-49 years	5,271 (15)	14,645 (11)
50-64 years	3,790 (11)	11,592 (9)
≥65 years	650 (2)	3,780 (3)
Female sex, n (%)	2,918 (8)	59,803 (44)[a]
Transgender, n (%)[b]	1,184 (3)	2,214 (2)
Race, n (%)		
Black	8,241 (23)	59,180 (44)
White	17,763 (49)	43,386 (32)
Other	5,295 (15)	17,038 (13)
Unknown	4,685 (13)	15,024 (11)
Hispanic, n (%)	12,297 (34)	32,975 (24)
Any comorbidity commonly treated with medications with potential for DDIs with CAB or LEN LA, n (%)[c]	6,461 (18)	14,504 (11)

[a] Unknown sex: n ≤ 5
[b] Gender identity is not reported by all clinics and physicians; available data may be insufficient to infer cisgender identity
[c] Select comorbidities included: asthma, deep vein thrombosis, COPD, erectile dysfunction, epilepsy, high cholesterol, pulmonary embolism, opioid use disorder, chronic pain disorders, and tuberculosis

Table 2. Medications with potential for drug-drug interaction with CAB LA and LEN LA

Medications with potential for DDI with CAB LA	**Contraindicated:** phenobarbital, oxcarbazepine, carbamazepine, phenytoin, rifampin, rifapentine **Not recommended:** none **Caution (necessitates caution, monitoring, or dose adjustment):** rifabutin
Medications with potential for DDI with LEN LA	**Contraindicated:** carbamazepine, phenytoin, rifampin, St. John's wort **Not recommended:** oxcarbazepine, phenobarbital, atazanavir/cobicistat, atazanavir/ritonavir, efavirenz, nevirapine, tipranavir/ritonavir, rifabutin, rifapentine, dihydroergotamine, ergotamine, methylergonovine, tadalafil **Caution (necessitates caution or monitoring):** digoxin, dexamethasone, hydrocortisone/cortisone, lovastatin, simvastatin, atorvastatin, buprenorphine, methadone, fentanyl, tramadol, oxycodone, naloxegol, midazolam, triazolam, sildenafil, vardenafil, tadalafil, dabigatran, edoxaban, rivaroxaban, apixaban, betrixaban

Figure 2. Proportion of PrEP users with potential for DDI with CAB[a] or LEN[b] LA, overall and by level of interaction (N = 35,984)



[a] Most common medications with potential for DDI with CAB LA: oxcarbazepine (0.1%), rifampin (0.1%), and carbamazepine (<0.1%)
[b] Most common medications with potential for DDI with LEN LA: tadalafil (5%), sildenafil (4%), and atorvastatin (4%)

Figure 3. Proportion of PrEP users with a potential for DDI with CAB or LEN LA, by sex or age group (N = 35,984)

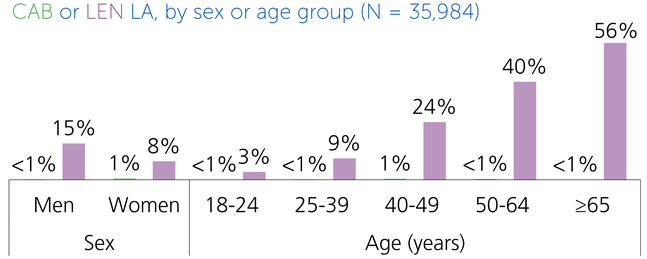
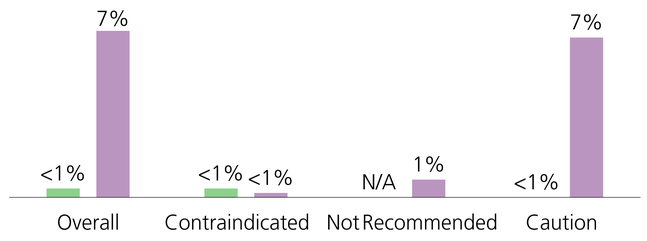
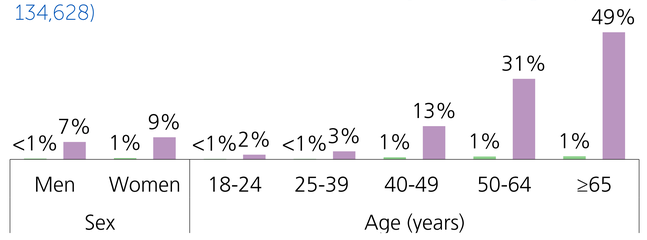


Figure 4. Proportion of people who could benefit from PrEP with a potential for DDI with CAB[a] or LEN[b] LA, overall and by level of interaction (N = 134,628)



[a] Most common medications with potential for DDI with CAB LA: oxcarbazepine (0.2%), rifampin (0.1%), and carbamazepine (0.1%)
[b] Most common medications with potential for DDI with LEN LA: atorvastatin (3%), oxycodone (1%), and tramadol (1%)

Figure 5. Proportion of people who could benefit from PrEP with a potential for DDI with CAB or LEN LA, by sex or age group (N = 134,628)



Discussion

- Compared to people who could benefit from PrEP, PrEP users were predominantly men and were more likely to have a comorbidity commonly treated with medications with potential for DDIs with CAB LA or LEN LA (**Table 1**)
- The proportion of individuals with potential for DDI with CAB LA was lower than with LEN LA among both PrEP users and people who could benefit from PrEP (**Fig 2-5**)
  - Use of contraindicated medications was similarly rare for both CAB LA and LEN LA
  - The proportions of individuals with potential for DDIs with LEN LA that were either not recommended or that necessitate caution, monitoring, or dose adjustment were larger than with CAB LA, especially among PrEP users
- The most common drugs with potential for DDI with LEN LA were treatments for erectile dysfunction and statins
  - Potential for DDIs with LEN LA increased substantially with age in both groups (**Fig 3, 5**)
  - Men were more likely to have potential for DDIs with LEN LA than women among PrEP users only (**Fig 3, 5**)
- Strengths
  - Large study population for both groups
  - Accounts for all medication use recorded in electronic health records
- Limitations
  - Only investigated potential, rather than confirmed, DDIs
  - Analysis did not consider clinical management of DDIs, which may be possible at lower levels of interaction

Key Findings

- In this real-world study of PrEP users and people who could benefit from PrEP in the US, the potential for DDIs was substantially higher with LEN LA than CAB LA, although contraindicated medications were similarly rare
- Providers should exert awareness when prescribing LEN, assessing the risk for potential DDIs with currently or recently taken medications

References

1. Centers for Disease Control and Prevention. Clinical Guidance for PrEP. Centers for Disease Control and Prevention, 2024.
2. National HIV/AIDS Strategy for the United States 2022–2025. The White House, 2021.

Acknowledgements

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