Lenacapavir: a first-in-class capsid inhibitor for HIV treatment and prevention

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Purpose of review
This review summarizes available data for lenacapavir (LEN), a first-in-class agent that targets several functions of the HIV capsid in the viral cycle, including nuclear entry, viral assembly, and capsid formation.

Recent findings
LEN has been approved in the United States as both oral tablets and injectable solution for treatment in heavily treatment-experienced adults with multidrug-resistant HIV-1. The subcutaneous injections are administered every 26 weeks (6 months). In 2024, LEN was named the biggest science breakthrough for HIV prevention, and is currently under review at the FDA.

Summary
LEN is a novel agent that can be administered subcutaneously every 6 months. Approved for treatment-experienced adults with multidrug-resistant HIV, lenacapavir may have additional uses including for HIV prevention.

Keywords
capsid inhibitor, lenacapavir, long acting antiretroviral, multidrug-resistant HIV, preexposure prophylaxis

INTRODUCTION

Antiretroviral agents provide life-saving treatments for millions of people living with HIV and can prevent new infections via preexposure prophylaxis (PrEP). However, some people living with HIV who are heavily treatment-experienced have limited or no treatment options, due to multidrug resistance. Additionally, suboptimal adherence to oral daily regimens can lead to virologic failure, resistance and viral transmission to others. Long-acting antiretroviral agents from novel drug classes offer promising alternatives, enhancing adherence and expanding treatment and prevention options.

Lenacapavir (LEN), a first-in-class capsid inhibitor, was approved in December 2022 in the United States for multidrug-resistant HIV treatment. Recently completed studies also support its use in PrEP and its approval for prevention is currently under review by the U.S. Food and Drug Administration (FDA).

MECHANISM OF ACTION

LEN is a potent, long-acting HIV-1 capsid inhibitor with a prolonged half-life, allowing for twice-yearly subcutaneous injection (two 1.5 ml subcutaneous injections in the abdomen) every 26 weeks ± 2 weeks from the date of last injection. The oral form (300 mg tablet) is approved for loading during treatment initiation and as a bridging option for missed injections. Unlike other antiretroviral therapies which interfere with viral enzymes, LEN targets the HIV-1 capsid protein, disrupting key viral replication processes, including nuclear import of preintegration complexes, virion production, and capsid core formation (Fig. 1). As a result, virus produced in the presence of LEN displays deformed capsids that can enter new target cells but cannot replicate [1▪,2]. Many other viruses have their own capsid proteins, which raises the possibility that similar capsid inhibitors could fight other viral diseases [3▪▪]. Additionally, LEN's interference at multiple viral life cycle stages may inherently limit the development of resistance [4▪].

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Curr Opin Infect Dis 2025, 38:208–213

DOI:10.1097/QCO.0000000000001113

KEY POINTS

- Lenacapavir (LEN), as the first-in-class capsid inhibitor, targets multiple stages of HIV replication, offering a potent, long-acting option for both HIV treatment and prevention.
- Clinical trials have demonstrated LEN's efficacy in suppressing multidrug-resistant HIV and shown unprecedented success in PrEP trials, with near total prevention of HIV in vulnerable populations.
- Despite its promise, LEN's widespread adoption faces hurdles including high costs and the need for long-acting combination partners for treatment.
- While LEN has the potential to truly impact the HIV epidemic, particularly through PrEP, its success depends on expanded access through strategic pricing, patient assistance programs, and global financing mechanisms.

LONG-ACTING ANTIRETROVIRALS

The high potency of LEN with low in-vivo systemic clearance and slow kinetics from the subcutaneous injection site make it well suited for long-acting therapy [5]. Despite the widespread use of single tablet regimens, adherence to daily oral regimens remains a challenge, with large retrospective studies reporting that over 60% of people with HIV had adherence rates below 90%, and more than 40% below 80% [6]. Long-acting agents can mitigate barriers such as pill fatigue, stigma, or privacy concerns [7]. Subcutaneous LEN, administered by healthcare providers every 6 months, aligns with routine clinical visits, reducing additional burden. While cabotegravir and rilpivirine injections have been available since 2021, further studies on long acting injectables are needed to assess their long-term efficacy, cost-effectiveness, and suitability among patients at risk of nonadherence and other diverse populations.

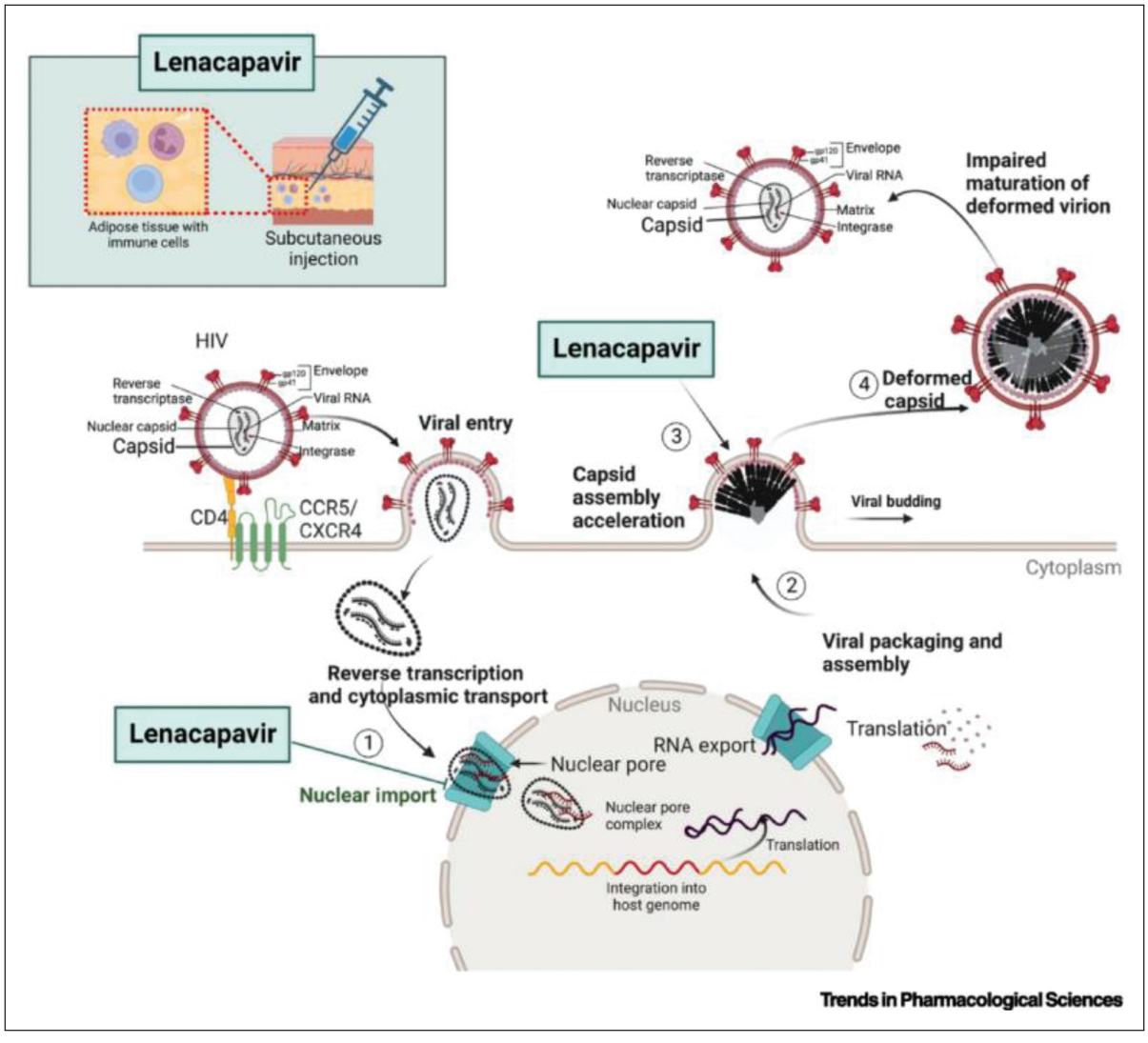

FIGURE 1. LEN in the HIV lifecycle [1▪].

LENACAPAVIR IN HIV TREATMENT STUDIES

LEN has demonstrated efficacy in treating multidrug-resistant HIV and is being investigated for broader use in first-line therapy. Key clinical trials include the following.

CAPELLA study (multidrug resistance)

CAPELLA, a Phase 2/3 study, evaluated LEN in individuals with multidrug-resistant HIV-1 [8▪,9]. Among 72 participants with documented resistance to at least three major antiretroviral classes, 17% had no fully active agents in their optimized baseline regimen (OBR). In cohort 1, 36 participants were randomized to receive oral LEN or matching placebo alongside their failing treatment for 14 days, followed by subcutaneous LEN every 6 months plus an OBR. In the nonrandomized cohort 2, 36 participants started an OBR concurrent with LEN. The primary endpoint – $\geq$0.5 log10 copies/ml reduction in viral load by day 15 – was achieved in 88% of LEN recipients versus 17% of placebo recipients. At week 52, 78% of participants had an HIV viral load less than 50 copies/ml. The most common adverse events were mild injection site reactions, nausea, constipation, and diarrhea. ClinicalTrials.gov NCT04150068.

CALIBRATE study (treatment-naive individuals)

CALIBRATE, a Phase 2 study, assessed LEN in treatment-naive adults randomized to one of four open label daily groups which included subcutaneous and oral LEN, compared to a control group of bictegravir/emtricitabine/tenofovir alafenamide [10▪]. At week 54, virological suppression rates ranged from 85 to 92%, comparable to standard-of care regimens. The most frequent adverse events were mild-to-moderate injection site reactions, headache, and nausea. ClinicalTrials.gov NCT04143594.

FUTURE TREATMENT REGIMENS

Research is ongoing to develop long-acting partner agents to combine with LEN for a complete injectable regimen. LEN is also being studied in combination with islatravir, a nucleoside reverse transcriptase translocation inhibitor (NRTTI), as part of a weekly oral regimen in virologically suppressed people with HIV. (ClinicalTrials.gov NCT05052996, Clinicaltrials.gov NCT06630286, Clinicaltrials.gov NCT06630299.) An injectable regimen of LEN and islatravir with a longer dosing interval is also being developed.

LENACAPAVIR IN HIV PREVENTION STUDIES

Two pivotal Phase 3 trials, PURPOSE 1 and PURPOSE 2, evaluated LEN for PrEP.

PURPOSE 1: Conducted in South Africa and Uganda, this study enrolled over 5300 cisgender women and adolescent girls aged 16–25 years [11▪▪]. Participants received either twice-yearly subcutaneous LEN, daily oral emtricitabine/tenofovir alafenamide (F/TAF), or daily oral emtricitabine/tenofovir disoproxil fumarate (F/TDF). LEN demonstrated 100% efficacy (Fig. 2), with zero infections compared to background HIV incidence rates of 2.41 per 100 person-years, and incidence rates of 2.02 and 1.69 per 100-person years in the F/TAF and F/TDF groups, respectively. Due to its overwhelming efficacy, the trial was stopped early. Notably, results in F/TAF and F/TDF arms were not meaningfully different, and medication adherence in the oral PrEP arms was felt to be a factor. LEN was generally well tolerated. ClinicalTrials.gov NCT04994509.

PURPOSE 2: This study enrolled 3,273 cisgender men, transgender women, transgender men, and gender nonbinary individuals who have sex with male partners [12▪▪]. The LEN group demonstrated a 95% reduction in HIV incidence compared to oral PrEP (F/TDF), with only two new infections in the LEN group (2180 participants) versus nine in the oral PrEP group (1087 participants). ClinicalTrials.gov NCT04925752.

Ongoing studies include PURPOSE 3 (focusing on U.S. cisgender women of color) and PURPOSE 4 (evaluating LEN among people who inject drugs). Given the successful earlier findings, regulatory approval for PrEP is anticipated in June, 2025.

SIDE EFFECTS

Due to the long-acting nature of LEN, the safety data are important to evaluate, including among women who are not well represented in HIV treatment studies [4▪]. Hypersensitivity reactions were not reported in the studies [9]. The oral loading period may help rule out acute adverse drug reactions, although a 2-day initiation period which is now available may not be long enough. Common adverse events include mild-to-moderate injection site reactions with swelling, induration, redness and pain. To some extent, injection-site reactions are expected after subcutaneous administration of LEN owing to depot formation. Nausea and increases in liver enzymes and direct bilirubin have also been reported. Weight gain was not reported in the CAPELLA or PURPOSE studies; the weight gain seen

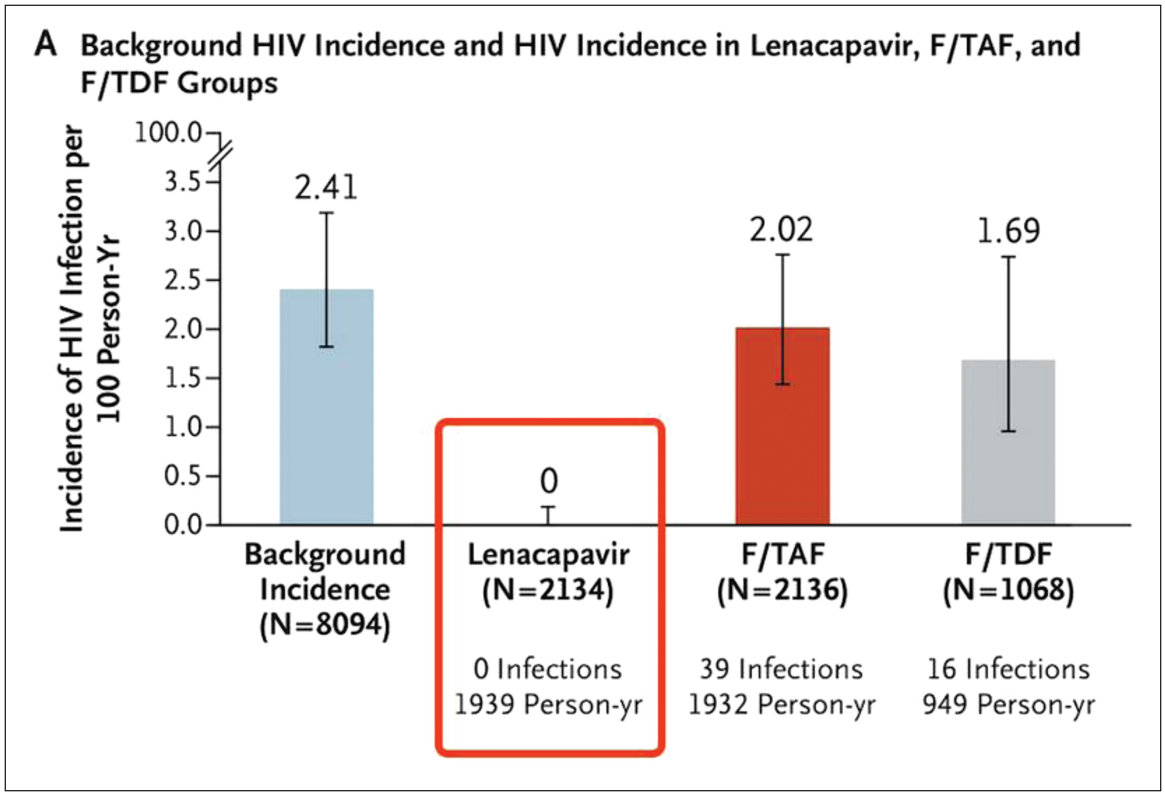

FIGURE 2. PURPOSE 1 study; LEN for PrEP in cisgender women [11▪▪].

in the CALIBRATE (treatment naive) study appears consistent with the expected 'return to health' phenomenon, without any clinically relevant lipid elevations [13].

DRUG INTERACTIONS

Inhibitors of CYP3A and CYP3A/P-gp can increase LEN exposure, but not to a clinically relevant extent, allowing for coadministration with agents such as cobicistat (https://www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi). However, strong inducers of CYP3A/P-gp/UGT1A (e.g. rifampin) significantly reduce LEN exposure and are contraindicated. LEN is a moderate CYP3A inhibitor, necessitating caution with sensitive CYP3A substrates with narrow therapeutic windows. Most of the commonly used antiretroviral agents have no clinically relevant drug–drug interactions with LEN. However, some are not recommended due to their strong inhibition potential (e.g. atazanavir, which inhibits all three of CYP3A/P-gp/UGT1a10) or moderate induction potential (e.g. efavirenz, nevirapine, or tipranavir/ritonavir) [1▪]. No meaningful interactions are expected with sex-affirming hormones or oral contraceptives.

RESISTANCE

LEN is expected to be fully active regardless of prior treatment history because of its first-in-class nature. *In vitro*, LEN retains antiviral activity against HIV-1 mutations that confer to other antiretroviral classes [5,14]. Resistance selection assays have identified Q67H and N74D as the major resistance-associated capsid mutations [15]. Additional variants included L56I, M66I, K70N, Q67H/N74S, and Q67H/T107N. These mutations, alone or in combination, confer reduced susceptibility to LEN by six to more than 3200-fold resistance relative to wild type [1▪]. However, all but the low-level resistant variant Q67H display reduced replication capacity *in vitro*. While the clinical relevance of these findings has yet to be established, this reduction in replication capacity suggests that such variants may have a reduced ability to establish or maintain infection [5].

Furthermore, these in-vitro capsid mutations are not common in the community yet. Plasma samples from ART-naive or ART-experienced people living with HIV, including those with protease inhibitor exposure, were sequenced and analyzed for the presence of resistance-associated capsid variants (L56I, M66I, Q67H, K70N, N74D, N74S, and T107N). Among the 1500 patient samples, none of

these mutations were detected, regardless of HIV subtype or treatment history [16].

FUTURE CHALLENGES AND DIRECTIONS

LEN was named *Science*'s 2024 Breakthrough of the Year for its novel mechanism and transformative potential in HIV treatment and prevention [3▪▪]. The favorable long-term results from CAPELLA suggest that LEN could be a valuable treatment option for people with multidrug resistant HIV, a population which is fortunately small. However, its full impact depends on the development of a viable long-acting partner to create a complete injectable treatment regimen administered every 6 months. LEN's current annual cost (~$43 000 in the U.S) has posed a major barrier to accessibility and expanded roll-out. Similar challenges of high costs and insurance barriers have hindered the uptake of injectable cabotegravir with rilpivirine, approved for treatment in 2021.

For PrEP, the potential rewards and looming challenges seem even greater. The remarkable results from the PURPOSE 1 and 2 trials demonstrate that LEN could be a game changer, particularly for young women and adolescent girls facing adherence barriers driven by sigma and relationship dynamics [17]. Regulatory approval for LEN for PrEP is anticipated in mid-2025 at the earliest, but again, its pricing will dictate affordability and uptake. A pharmaceutical-sponsored patient assistance program has yet to be published. While Gilead has partnered with generic manufacturers to supply low-cost versions in 120 developing countries, middle-income countries such as Brazil, which has the largest number of people living with HIV in South America, remain excluded from these agreements [3▪▪]. Even discounted products may remain unaffordable for resource-limited governments.

Ensuring continued access to HIV care and prevention in resource-limited settings is critical, particularly through PEPFAR-funded programs which now face uncertainty under the new U.S. administration. Expanded antiretroviral access has resulted in a global decline in new HIV infections, from 2.1 million in 2011 to 1.3 million in 2023 [18]. Rolling back such programs would reverse this progress, jeopardizing the UNAIDS targets for HIV elimination.

Looking ahead, Gilead is developing a reformulated yearly LEN and plans to launch trials to evaluate whether a single dose could provide year-long protection. This effort complements research into other long-acting PrEP options, including weekly and monthly oral LEN regimens. While these innovations are exciting, future strategies must focus on financing mechanisms to ensure equitable access [19].

CONCLUSION

Lenacapavir, as a first-in-class capsid inhibitor, offers a novel approach to HIV treatment and prevention through its unique mechanism of action and long-acting properties. While its current use in treatment is limited by the lack of a co-administered long-acting agent, its potential in HIV prevention is substantial. The widespread adoption of LEN and its impact on ending the HIV epidemic will depend on access, delivery infrastructure, and demand. Future research and policy efforts should prioritize optimizing clinical applications and ensuring global accessibility to support HIV elimination goals.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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