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REVIEW

Emerging concepts in HIV pre-exposure prophylaxis: focus on twice-yearly lenacapavir

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Abstract

The persistent global burden of HIV and the need for more flexible, durable prevention strategies have accelerated the development of long-acting pre-exposure prophylaxis (PrEP) options. Lenacapavir (LEN), a first-in-class capsid inhibitor, is approved as a twice-yearly subcutaneous injection for HIV prevention and represents a major advance beyond oral injectable PrEP regimens administered daily or every 2 months. Data from phase III trials demonstrate high efficacy, sustained drug levels and strong adherence potential, positioning LEN as a transformative option for individuals seeking long-acting protection. Its unique mechanism of action and extended dosing interval can address key barriers to PrEP uptake and persistence, particularly amongst populations disproportionately at risk for HIV. LEN may play a central role in expanding choice and improving the real-world effectiveness of PrEP. Ongoing considerations include implementation logistics, equitable access, potential drug resistance and integration into existing prevention frameworks. Twice-yearly LEN is a critical addition to the evolution of HIV prevention strategies.

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Introduction

More than four decades after the discovery of HIV, the virus remains a major global health challenge. In 2023, approximately 1.3 million people worldwide acquired HIV, underscoring persistent transmission despite widespread testing, treatment and prevention initiatives.[1] Biomedical prevention strategies have been central to reducing new infections, with pre-exposure prophylaxis (PrEP) emerging as one of the most effective tools to date. Daily oral PrEP with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or emtricitabine/tenofovir alafenamide (FTC/TAF) demonstrated high efficacy when taken consistently.[2] However, real-world uptake and adherence have been constrained by social, structural and behavioural barriers, particularly amongst key populations, including young women in sub-Saharan Africa, men who have sex with men, and transgender individuals.[3]

The need for more durable, user-friendly HIV prevention options has driven the development of long-acting PrEP formulations. Injectable cabotegravir (CAB), administered every 2 months, was the first long-acting agent to demonstrate superior efficacy to daily oral PrEP and represented a major step forward in overcoming adherence limitations.[4] Its approval marked a turning point in PrEP delivery, offering sustained protection with infrequent dosing. Yet, logistical challenges, such as injection frequency and clinical infrastructure, continue to limit accessibility in many settings.[5] These factors have spurred interest in next-generation long-acting modalities capable of maintaining therapeutic levels for even longer intervals whilst simplifying administration.

Lenacapavir (LEN), a first-in-class HIV1 capsid inhibitor, represents the most recent advance in this evolving prevention landscape. Administered subcutaneously every 6 months, LEN provides potent, sustained antiviral activity

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through a novel mechanism distinct from existing PrEP agents.[6] Its twice-yearly dosing schedule has the potential to transform HIV prevention by minimizing adherence barriers, improving user acceptability and extending protection to populations not well served by current options. As research and implementation efforts advance, LEN stands at the forefront of a paradigm shift towards ultra-long-acting HIV prevention—bringing the field closer to the durability and simplicity long envisioned for an HIV vaccine.

Whilst recent publications have reported the primary efficacy outcomes of PURPOSE 1 and PURPOSE 2 and summarized regulatory decisions, this narrative review integrates pharmacological rationale, early-phase clinical development, implementation considerations, safety nuances and real-world delivery challenges to contextualize twice-yearly LEN within the evolving PrEP landscape. Particular emphasis is placed on clinical decision-making, adherence implications and health system integration relevant to practitioners. An English-language MEDLINE search was conducted through 31 October 2025 using the search terms "lenacapavir", "HIV", "pre-exposure prophylaxis", "PrEP", "long-acting" and "capsid inhibitor". A manual search of the references cited within the research manuscripts and review articles was conducted to identify additional relevant sources.

Pharmacology

Mechanism of action

LEN is a first-in-class HIV1 capsid inhibitor that distinguishes itself from existing antiretrovirals by targeting the viral capsid protein rather than a viral enzyme.[7,8] By binding to a hydrophobic pocket located at the interface between adjacent capsid hexamers, LEN disrupts essential interactions needed for capsid stability and proper assembly.[7,8] This binding interferes with multiple stages of the HIV1 life cycle: it impairs capsid-mediated nuclear import of the pre-integration complex, disrupts proper capsid core formation during virion maturation, and hinders virus assembly and release.[7,8] The result is production of malformed, non-infectious virions and markedly reduced viral infectivity, with activity demonstrated at picomolar concentrations in vitro.[7,8] Because the mechanism of action is novel and does not overlap with the targets of other antiretroviral classes, LEN exhibits minimal cross-resistance with existing drug classes, an attribute that holds promise for both treatment and prevention settings.

Pharmacodynamics

LEN is characterized by exceptionally strong antiviral activity at picomolar concentrations and a prolonged systemic exposure profile that supports infrequent dosing. In in vitro assays, LEN achieved a half-maximum effective concentration (EC_{50}) of approximately 105 pM in MT-4 cells, with similarly low values (e.g. ~32–56 pM) observed in primary $CD4^+$ T cells and macrophages, underscoring its high potency.[7,9] The injectable formulation creates a subcutaneous depot allowing sustained release and stable plasma concentrations above the target inhibitory threshold for 6 months or more, thereby enabling a twice-yearly dosing interval that offers the potential to circumvent adherence challenges associated with daily oral regimens.[10]

Pharmacokinetics

The pharmacokinetic profile of LEN underpins its 6-monthly dosing regimen for HIV pre-exposure prophylaxis. Following subcutaneous administration, the drug's low aqueous solubility leads to the formation of a slow-dissolving injection depot, resulting in a 'flip-flop' absorption pattern in which the input rate from the depot is slower than the systemic elimination rate.[9,11,12] This sustained release supports long-term plasma concentrations that remain above the protein-adjusted 95% effective concentration for at least 24 weeks in humans.[9,11,12] Oral administration of LEN exhibits a median terminal half-life of approximately 10–12 days, which translates into a much longer apparent half-life (8–12 weeks) when delivered subcutaneously due to the depot effect.[9,11,12] LEN is administered with an oral loading dose to achieve steady state more rapidly and provide immediate protection whilst the depot forms.[13] Unlike injectable CAB, where oral lead-in dosing is optional, LEN requires an oral loading phase to achieve rapid therapeutic plasma concentrations before the subcutaneous depot forms.[13,14]

High protein binding, limited systemic clearance and minimal renal excretion further contribute to the extended exposure.[9,11,12] As a moderate inhibitor of cytochrome P450 3A (CYP3A) and a weak inhibitor of breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp), LEN may increase exposure to co-administered substrates of these pathways, which is clinically relevant given its prolonged terminal phase and extended post-discontinuation exposure. LEN is not significantly affected by hepatic impairment.[12] Because of its long half-life, long-acting LEN may remain in the body for up to 9 months after receiving the last injection, which may have drug–drug interaction implications, as noted previously.[13]

Lenacapavir in early-phase trials

LEN was studied in a phase I clinical trial as an HIV prevention agent to establish pharmacokinetics, safety and potential for extended dosing intervals in people at risk for HIV exposure, supporting subsequent pivotal phase III studies.

A phase I trial evaluated two once-yearly intramuscular formulations of LEN in 40 adults without HIV (5000 mg, formulation 1 with 5% w/w ethanol and formulation 2 with 10% w/w ethanol). Key findings included that the median time to maximum concentration was 84.1 days (formulation 1) and 69.9 days (formulation 2). Median trough concentrations at 52 weeks exceeded those of twice-yearly subcutaneous LEN at 26 weeks. Injection-site pain occurred in approximately 80% of participants but was generally mild and resolved within 7 days. This study demonstrated that LEN achieves sustained plasma concentrations well above the threshold for HIV1 inhibition, with a favourable safety profile.[11] These results confirmed the feasibility of long-acting PrEP and informed the dosing strategies for later trials.

Phase II trials of LEN were conducted in people with HIV; no new trials were conducted in people at risk for HIV acquisition. The phase II trials of LEN in people with HIV characterized the pharmacokinetics, safety and acceptability of a long-acting injectable agent. These studies reinforced the phase I findings: the depot effect after LEN injection allows for slow, sustained drug release, supporting infrequent dosing. Safety data continued to show mostly mild to moderate injection-site reactions (ISRs), with no significant laboratory or systemic adverse events.[12] These early-phase trial data provided the basis for the design and dosing regimen of the pivotal phase III PURPOSE 1 and PURPOSE 2 trials in people at risk for HIV acquisition.

In summary, early-phase trials established that long-acting LEN is safe, well tolerated and maintains protective drug levels for at least 6 months, supporting its use as a twice-yearly PrEP agent and paving the way for phase III efficacy trials in people who could benefit from HIV prevention.

Lenacapavir phase III trials

Phase III efficacy trials of LEN for PrEP — PURPOSE 1 and PURPOSE 2 — demonstrate that twice-yearly subcutaneous LEN is highly effective in preventing HIV infection across diverse populations, with efficacy superior to daily oral PrEP and no significant safety concerns (Table 1).[15,16]

PURPOSE 1

PURPOSE 1 was a large, multicentre, randomized, double-blind, controlled trial conducted amongst cisgender adolescent girls and young women (ages 16–25 years old) in South Africa and Uganda, in regions characterized by high HIV incidence. Participants were randomly assigned in a 2:2:1 ratio to receive twice-yearly subcutaneous LEN, once-daily oral FTC/TDF, or once-daily oral FTC/TAF.[15]

In the LEN arm (n=2134), there were zero incident HIV infections over the 52-week primary analysis interval, corresponding to an incidence of 0.00 per 100 person-years. This contrasted with a calculated background incidence of 2.41 per 100 person-years in the population and demonstrated statistical superiority *versus* the background rate (p<0.0001). A secondary endpoint was HIV infection incidence with LEN (zero) compared to FTC/TDF (1.69 per 100 person-years), and again, LEN was statistically superior (p<0.001). All participants who acquired HIV in the FTC/TDF group had low adherence or adherence decreased over time. The incidence rate ratio of HIV infection with FTC/TAF (2.02 per 100 person-years) was not statistically different from either the background incidence or FTC/TDF.[15]

An important subpopulation to note is that the PURPOSE 1 trial included 56 adolescents (aged 16 and 17 years old). In this subpopulation, there were zero HIV infections in any study arm (LEN, FTC/TDF, FTC/TAF).[15]

The safety profile in the LEN group was favourable. The most common adverse events were ISRs (e.g. mild pain, nodules and erythema). Nodule development occurred in 63.8% of participants receiving LEN *versus* in 16.6% of those receiving placebo injections. Fortunately, the frequency and severity of ISRs, including nodules, diminished with subsequent injections. Discontinuations due to ISRs were low and occurred in fewer than 0.3% of participants; however, given the frequency of the injections and the length of the study, there were not many opportunities or touchpoints where participants could discontinue treatment.[15]

Importantly, data from PURPOSE 1 included known outcomes in 208 pregnancies with exposure to LEN. The rate of major birth defects in LEN-exposed pregnancies did not exceed background prevalence rates, though risk estimates are imprecise due to the small numbers of exposed pregnancies. The most common major birth defects observed were ventricular septal defects, and the overall rate was consistent with the general population. Adverse pregnancy outcomes, such as spontaneous abortion, stillbirth, preterm birth and small for gestational age, were similar across both LEN and oral PrEP groups.[15] This adds to the growing body of safety evidence for LEN use during periconception, antepartum and postpartum periods. There is an antiretroviral pregnancy registry to monitor fetal outcomes in pregnant individuals exposed to LEN.[13]

These results provided compelling evidence of high efficacy and good tolerability in a young cisgender female population at high risk, paving the way for further LEN studies in other populations.

Table 1. PURPOSE 1 and PURPOSE 2 trials of lenacapavir for PrEP.

Trial	Design	Participants	Duration	Intervention	Primary outcome	Secondary outcomes
PURPOSE 1[15]	Phase III, randomized, double-blind, controlled	Adolescent girls and young women (ages 16–25 years old) in South Africa and Uganda; *n*=4278	52 weeks	Subcutaneous LEN every 26 weeks; daily oral FTC/TAF; daily oral FTC/TDF	HIV incidence over 52 weeks: 0/2134 in LEN arm (0.00 per 100 PY) *versus* background incidence 2.41 per 100 PY	LEN superior to FTC/TDF (IRR 0, 0–0.04; $p<0.001$) No difference in HIV incidence between FTC/TDF and TDF/TAF Safety: injection-site reactions most common (mild/moderate); discontinuation due to injection-site events 0.2%
PURPOSE 2[16]	Phase III, randomized, double-blind, controlled	Cisgender men who have sex with men, transgender women, transgender men, and gender-nonbinary persons; *n*=4366	52 weeks	Subcutaneous LEN every 26 weeks; daily oral FTC/TDF	HIV incidence over 52 weeks: 2/2183 in LEN arm (0.10 per 100 PY) *versus* background 2.37 per 100 PY	LEN superior to FTC/TDF (IRR 0.11, 0.02–0.51; $p=0.0025$) Safety: injection-site reactions most common (mild/moderate); discontinuation due to injection-site events 1.2%

FTC, emtricitabine; IRR, incidence rate ratio; LEN, lenacapavir; OLE, open-label extension; PrEP, pre-exposure prophylaxis; PY, person-years; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

PURPOSE 2

PURPOSE 2 extended the evaluation of twice-yearly LEN to a broader and more diverse cohort, including cisgender men who have sex with men, transgender women, transgender men and gender-nonbinary individuals who have sex with male-assigned-at-birth partners, across the USA, South Africa, Peru, Brazil, Argentina, Mexico and Thailand.[16]

In this trial, participants were randomized to receive LEN or daily oral FTC/TDF. In the LEN arm (*n*=2183), there were two incident HIV infections, yielding an incidence of approximately 0.10 per 100 person-years. This represented a 96% reduction compared with the background incidence rate of 2.37 per 100 person-years, and an 89% reduction compared with the FTC/TDF group (incidence 0.93 per 100 person-years; incidence rate ratio 0.11; $p=0.002$).[16]

The safety findings mirrored those of PURPOSE 1 with predominantly mild-to-moderate ISRs. Nodule development occurred in 63.4% of participants receiving LEN *versus* 39.2% of those receiving placebo injections. The median duration of nodules was 183 days (interquartile range [IQR], 89–274 days) in the LEN group, which was substantially longer than the 64-day median duration (IQR, 19–98 days) in those who developed nodules whilst receiving placebo injections. The median diameter of the largest nodule per participant was 3.0 cm (IQR 2.0–4.0 cm) in the LEN group *versus* 2.0 cm (IQR 1.0–2.5 cm) in the placebo group. Fortunately, as in PURPOSE 1, the frequency and severity of nodules decreased with subsequent injections. As in PURPOSE 1, the discontinuation rate due to these reactions was low (approximately 1.2%), but there were not many opportunities to discontinue therapy based on the length of the trial and the number of injections received.[16]

These results confirmed that the high efficacy and acceptable safety seen in young people in the PURPOSE 1 trial are reproducible in other key populations who could benefit from PrEP and support the use of LEN as a broadly applicable long-acting PrEP option.

Injection-site nodules observed in both PURPOSE 1 and PURPOSE 2 represent an important area for clinician and patient education in real-world use. These nodules are

thought to reflect a localized granulomatous or foreign-body reaction to the subcutaneous drug depot formed at the injection site, a pattern supported by biopsy findings from both animal and human studies. As LEN gradually elutes from the depot over the 6-month dosing interval, the depot decreases in size, and nodules typically resolve or substantially diminish before the subsequent scheduled injection.[15] This pharmacological explanation helps contextualize why injection-site nodules, despite a prolonged median duration of 183 days reported in PURPOSE 2, generally do not lead to treatment discontinuation.[16] Individuals considering LEN for PrEP should be counselled regarding the potential for nodule development and reassured that this reaction does not preclude continued use of the medication.

Drug resistance data

Although no LEN-associated resistance mutations have been reported amongst seroconversions to date,[15,16] ongoing surveillance is warranted given the potential for capsid-target resistance. There is the potential for development of LEN resistance if an individual acquires HIV before, during or after discontinuation of LEN, which highlights the importance of routine HIV testing in individuals at risk for HIV exposure.[13]

Approved indication for PrEP and dosing

LEN is approved by the FDA and EMA for PrEP to reduce the risk of sexually acquired HIV1 infection in adults and adolescents who weigh at least 35 kg and are confirmed to be HIV1 negative.[13,17] The approved initiation regimen consists of subcutaneous injections every 6 months (927 mg) combined with oral tablets on days 1 (600 mg) and 2 (600 mg), which is required for achieving initial protective plasma concentrations; the efficacy of LEN has only been established with this complete dosing schedule that includes the oral tablets. Once the initiation regimen is completed, maintenance dosing continues every 6 months via subcutaneous injection only. This long-acting dosing schedule provides sustained systemic drug levels that maintain HIV1 suppression over the 6-month interval, addressing adherence challenges associated with daily oral PrEP.[13,17]

Clinical efficacy data for HIV2 prevention are not available, and current approval and efficacy data are specific to HIV1.

LEN is also approved by the FDA and EMA for people with HIV who have multidrug-resistant HIV. Like LEN for PrEP, it is initiated by starting with oral tablets in conjunction with a subcutaneous injection dose before the injection-only maintenance regimen is continued. LEN for HIV treatment is given in combination with other antiretrovirals.[18,19]

Current guideline recommendations

Recent updates to national and international guidelines now strongly recommend long-acting LEN as a first-line PrEP option for individuals at risk of HIV exposure, regardless of sex, gender identity or route of sexual exposure.

In July 2025, the WHO issued its guideline Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis, recommending LEN as an additional choice for PrEP for people at risk of sexual acquisition of HIV.[20] The guidance positions twice-yearly injectable LEN alongside other available PrEP options to broaden choice, underlining that increasing the number of modalities available may enhance uptake and persistence in populations at high risk. Implementation considerations, such as HIV rapid diagnostic testing, community acceptability and service delivery, are highlighted as essential to ensure access and safe use.

The CDC PrEP Guidelines Work Group, using high-certainty evidence from the PURPOSE 1 and PURPOSE 2 trials, endorses long-acting LEN every 6 months for persons weighing ≥35 kg who would benefit from PrEP, emphasizing its potential to improve adherence and persistence compared to daily oral regimens.[6]

The International Antiviral Society-USA Panel also recommends long-acting LEN for all routes of sexual exposure, with an evidence rating of AIa, reflecting robust efficacy and safety data. The guidelines specify that the initial subcutaneous injection should be overlapped with two daily oral doses of LEN (600 mg each) to rapidly achieve protective drug levels.[21] LEN is positioned alongside other PrEP agents, such as daily oral tenofovir-based regimens and injectable CAB, offering a tailored approach for patients who prefer less frequent dosing or have difficulty with daily adherence.

Clinical practice implications

The availability of long-acting LEN for PrEP represents a major advance in HIV prevention and a meaningful shift in clinical practice. Since the advent of PrEP, effective PrEP has relied on daily oral regimens such as FTC/TDF and FTC/TAF, which have demonstrated high efficacy but are limited

by adherence challenges, stigma and structural barriers that disproportionately affect populations at greatest risk. The introduction of twice-yearly subcutaneous LEN offers a new approach — one that decouples adherence from daily pill-taking and provides sustained protection for 6 months following a single clinic-administered injection. This extended dosing interval has the potential to improve adherence, persistence and overall effectiveness of PrEP programmes, especially amongst individuals who face barriers to consistent medication use.[6]

From a clinical and programmatic perspective, the pharmacological and logistical profile of LEN may help bridge critical gaps in PrEP delivery. Because LEN is administered only twice per year and has minimal drug–drug interactions, it can be integrated into a range of healthcare settings, including community clinics and mobile health units. The reduced dosing frequency also aligns with existing models for biannual care visits, potentially lowering the burden on healthcare systems and patients alike. Importantly, its injectable formulation may help overcome PrEP discontinuation due to pill fatigue, forgetfulness or stigma associated with daily oral medication (including privacy issues related to having the medication at home) — issues that remain persistent barriers to PrEP uptake amongst key populations who are at risk for HIV exposure.[22]

However, the integration of LEN into PrEP prescribing will require careful attention to implementation and equity considerations. The need for oral lead-in dosing at initiation, the requirement for healthcare-administered injections, and the potential for delayed discontinuation of protection (due to the long terminal phase) introduce new clinical management considerations.[13] Additionally, ensuring equitable access, particularly in low-income and middle-income countries, will depend on cost, supply and inclusion in national PrEP guidelines. Early incorporation into global and regional policies, as reflected in the 2025 WHO update on long-acting injectable PrEP, is an encouraging step towards expanding prevention options worldwide.[20] The Global Fund to Fight AIDS, Tuberculosis and Malaria signed an access agreement with the manufacturer of LEN in July 2025 to procure LEN for low-income and middle-income countries.[23] Collectively, the introduction of long-acting LEN for PrEP has the potential to redefine HIV prevention by addressing adherence barriers, diversifying PrEP modalities, and advancing progress towards global HIV elimination goals.

Conclusions

LEN represents a landmark advance in HIV prevention, offering the first twice-yearly injectable option for PrEP with potent, multistage antiviral activity, a favourable safety profile, and robust efficacy across diverse populations. The results of the PURPOSE 1 and PURPOSE 2 trials demonstrate that LEN can achieve near-complete protection against HIV acquisition whilst addressing the adherence and persistence challenges inherent to daily oral regimens. Its long-acting pharmacokinetics, minimal drug–drug interactions and subcutaneous administration route create new opportunities for broader and more equitable PrEP delivery, particularly amongst populations facing barriers to conventional daily dosing. As regulatory approvals expand and implementation strategies evolve, LEN is poised to transform clinical practice, diversify the HIV prevention toolkit, and accelerate global efforts towards ending HIV transmission. Continued post-marketing surveillance, real-world effectiveness studies, and integration into comprehensive prevention programmes will be critical to maximizing the public health impact of this breakthrough therapy.

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