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Lenacapavir – a strong weapon to accelerate HIV prevention

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Abstract

Globally, the 2025 prevention target, that is, 95% of people at risk of HIV infection having access to and using effective combination prevention options, is not within reach. Rapid, wider access to pre-exposure prophylaxis (PrEP) could quickly reduce the number of new infections, ultimately among people from key populations. In 2015, the World Health Organization recommended daily oral PrEP using tenofovir-based drugs; however, expanded access to PrEP is still limited. Key barriers to HIV PrEP uptake and persistence are daily adherence, fear of stigma and discrimination, and limited awareness of the acceptability of and access to PrEP services. Long-acting options could address these barriers. New prevention products such as long-acting injectable cabotegravir and, most recently, lenacapavir provide very high levels of protection against HIV when compared with daily oral PrEP.

Keywords: *HIV. Prevention. Daily oral pre-exposure prophylaxis. Long-acting. Injectable drugs. Cabotegravir. Lenacapavir.*

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Received: 18-07-2025
Accepted: 09-09-2025
DOI: 10.24875/AIDSRev.25000016

Available online: 16-10-2025
AIDS Rev. 2025;27(2):63-67
www.aidsreviews.com

Introduction

Due to the lack of progress on prevention, the global number of new infections is not declining fast enough. In three regions of the world, the numbers of new HIV infections are rising[1]. Globally, the 2025 prevention target, that is, 95% of people at risk of HIV infection having access to and using effective prevention options (condoms, harm reduction services for people who inject drugs, voluntary medical male circumcision in eastern and southern Africa, and pre-exposure prophylaxis [PrEP]), is not within reach.

Condom use remains the most effective low-cost HIV prevention method. The only current technology that offers triple protection for HIV, sexually transmitted infections, and unintended pregnancy, but condom programs have been defunded and social marketing schemes cut back in many countries[2-4]. Access to harm reduction services for people who inject drugs is low in all but a few countries. Voluntary medical male circumcision programs enabled 35 million circumcisions between 2008 and 2022 in countries in Eastern and Southern Africa, preventing hundreds of thousands of HIV infections[5]. This preventive option reduces the risk of acquiring HIV during heterosexual intercourse in men by up to 60% and provides lifelong benefit without subsequent intervention[6-8].

On the other hand, providing antiretroviral therapy (ART) played a special role, along with primary prevention programs, in the decline in the number of new HIV infections globally. The interim results of the HPTN052 clinical trial showed a 96% reduction in HIV transmission risk among heterosexual HIV-discordant couples, when the partner with HIV had a suppressed viral load[9,10]. This is sometimes called treatment as prevention. However, in 2023, a quarter of people living with HIV (9.3 million) are not receiving ART[1].

Persistent stigma and discrimination related to HIV status, gender, sexuality, or behavior are the main reasons, together with hostile legal and institutional environments, for the slow declines in new infections globally.

Daily oral PrEP is highly effective, with studies reporting 90% efficacy when taken consistently. However, some people have trouble remembering to take a pill every day, feel stigma around using drugs that are also used on ART, or have pill bottles that could be lost or stolen[11]. Rapid, wider access to PrEP could reduce the number of new HIV infections, but in 2023, the total number of people using oral PrEP is far short of the global 2025 target, and to meet the 2030 goal of ending AIDS as a public health threat[1].

In 2015, the World Health Organization recommended daily oral PrEP using tenofovir-based drugs as a prevention choice for people at substantial risk of HIV[12].

Expanded access to PrEP is still limited to a small number of countries and is not reaching regions where the need for PrEP is predominantly among people from key populations. Limited awareness of the acceptability of and access to PrEP services are the main hurdles, along with affordability issues and debilitating legal and social environments. High uptake of oral PrEP alone does not guarantee high levels of HIV prevention, and appropriate use of PrEP during periods of HIV risk is needed[13]. Some demonstration projects have reported strong adherence to PrEP, including among young women, but adherence in real-world situations may be much lower[14].

Females who use PrEP have cited many reasons for discontinuing oral PrEP, including side effects, stockouts, and social anxieties (e.g., fear of stigma, judgment, and violence)[13].

Not all discontinuation of PrEP use is inappropriate, taking into account that some people who stopped using PrEP have reasonable reasons: (a) HIV risks have changed, for example, partners have achieved viral suppression or separated from partner; (b) using other prevention options, according to the circumstances or needs. This is a reminder that PrEP is best offered as one of several prevention options, with people able to switch, including the dapivirine vaginal ring, which protects against HIV for up to a month, and may reduce the risk of acquiring HIV by more than 50%[15,16]. The convenience and discretion offered by the ring make it an attractive option for many women. The options of long-acting injectable PrEP may address several of these concerns. Long-acting injectable PrEP is a powerful prevention technology, and is raising expectations due to its combination of convenience and high efficacy. Despite the availability of several HIV PrEP options, only 17% (3.5 million) of the 21.2 million people who would benefit from PrEP globally were receiving it in 2023[1].

Key barriers to HIV PrEP uptake and persistence include the requirement for daily adherence, stigma associated with PrEP use, concerns regarding disclosure and discrimination or other potential social harms, challenges with frequent healthcare access, and the need for frequent clinic visits beyond the standard of care for PrEP[17-19].

Long-acting options could address these barriers.

Long-acting injectable PrEP

New prevention products such as long-acting injectable cabotegravir (CAB-LA) and, most recently, lenacapavir (LEN) provide high levels of protection against HIV. Cabotegravir is an integrase strand transfer inhibitor, which was first approved as an injectable form of HIV prevention and treatment, in combination with rilpivirine. Cabotegravir administered intramuscularly every 2 months was shown to be superior to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in two phase 3 studies[20,21].

When delivered as a suspension via a gluteal 600 mg intramuscular injection, it provides protection for at least 8 weeks across populations, among cisgender men and women, and transgender women, and across geographies[20-22]. This necessitates injections every 8 weeks, with an initial two injections 4 weeks apart. Long-acting injectable CAB-LA has few safety concerns[23].

A modeling study suggested that CAB-LA has the potential to be an option to reduce new HIV infections in pregnant and breastfeeding women and vertical transmission of HIV to infants in settings with a high burden of HIV[24]. In most medium- and low-income countries, CAB-LA remains inaccessible, unless a well-funded national health system that provides PrEP free of cost to all key populations, longstanding investment in demonstration projects to guide policy and PrEP roll-out receiving minimal external funds to support HIV prevention, access to CAB-LA at a discounted price, and logistical support to meet long-term PrEP goals[25].

PrEP care delivery with CAB-LA is further complicated by the requirement of clinic-administered bimonthly injection needing trained healthcare professionals to administer the product, which requires PrEP users to visit health facilities every 2 months – a high clinic frequency compared to oral PrEP, which can give a 3-month supply, highlighting the need for longer-acting injectable PrEP products to facilitate roll-out[13,26]. Alternative injectable formulations may offer a better solution, as it is LEN for PrEP, currently available in a subcutaneous administration every 6 months, and also with the advantage of possible self-administration[27,28]. The results of phase 1 of LEN for PrEP administered intramuscularly once-yearly were recently published[29].

LEN – accelerating in curbing the HIV epidemic

LEN, the first in class long-acting capsid inhibitor, works by targeting a different stage of the HIV life cycle compared to other antiretroviral (ARV) drugs, with near 100% efficacy in preventing HIV. It became commercially available in the United States and has submitted a marketing authorization application to the European Medicines Agency for a twice-yearly injectable for HIV prevention as PrEP. However, LEN (brand name Sunlence) was approved in the European Union in August 2022. It was approved for use in combination with other ARV drugs to treat adults with multidrug-resistant HIV-1 infection, for whom other treatments are not sufficient to suppress the virus. LEN is characterized by high potency, low metabolic clearance, and low aqueous solubility, which facilitates drug depot-mediated, long-acting pharmacokinetics following an injection[30,31]. The depot then dissolves over time, resulting in slow drug absorption and allowing an extended dosing interval[32].

In 2024, two landmark efficacy clinical trials, PURPOSE 1 and PURPOSE 2, showed LEN's high efficacy and safety for PrEP, when administered subcutaneously every 6 months (927 mg, administered as two 1.5 mL injections of 309 mg/mL, with oral loading doses of 600 mg on days 1 and 2)[27,28]. In PURPOSE 1, LEN among cisgender women in Uganda and South Africa was 100% efficacious in preventing HIV, when compared to the background local incidence, and was superior to daily oral TDF/FTC, the only oral option for PrEP for cisgender women[27]. In PURPOSE 2, LEN among men who have sex with men, transgender, and gender non-binary individuals in the United States, Brazil, Peru, Mexico, South Africa, and Thailand was 96% lower for PrEP when compared to the background HIV incidence. It was 89% lower than with daily oral TDF/FTC[28]. Twice-yearly subcutaneous LEN was well tolerated, with the most common adverse events being injection-site reactions. In both studies, daily oral PrEP adherence was suboptimal and decreased over time. Due to the LEN efficacy and easier schedule of administration, this is the opportunity to revolutionize HIV prevention, contributing to prompt access to LEN, particularly in lower and middle-income countries. This requires an efficient regulatory process to accelerate drug approval, and to prepare for an equitable roll-out of LEN, governments need to start integrating LEN into their existing HIV prevention programs[27]. This process includes involving the communities mostly vulnerable to HIV, who face sociostructural barriers to accessing PrEP.

The current LEN cost for HIV treatment in the United States is $40,000/person year[33]. Significant price reductions will be needed to ensure that LEN reaches a real

public health effect of decreasing HIV incidence worldwide. In October 2024, Gilead signed royalty-free licensing agreements to supply generic LEN in 120 high-incidence, resource-limited countries — primarily low- and lower-middle-income — and committed to providing it at no profit until generics are available[25]. A recent cost-effectiveness analysis in South Africa showed that scale-up of LEN, at a maximum of $100/injection, could be more cost-effective than scaling up daily oral PrEP or CAB-LA in reducing HIV incidence[34].

LEN, with two injections a year providing nearly 100% HIV prevention efficacy, has the potential to achieve the end of the HIV epidemic globally. Once-yearly intramuscular LEN could build on this advantage by further decreasing the dosing frequency and need for clinic visits, reducing the potential for PrEP-related stigma, and avoiding the need for daily oral tablet adherence, thereby increasing the uptake of persistence on, and, therefore, scalability and public health effect of PrEP in populations who would benefit most[29].

The pharmacokinetics and safety of two different once-yearly intramuscular LEN formulations were evaluated, with the aim of maintaining a similar concentration to twice-yearly subcutaneous LEN[29].

Twenty participants received LEN formulation 1 (LEN 500 mg/mL with 5% w/w ethanol) and 20 participants received formulation 2 (LEN 500 mg/mL with 10% w/w ethanol) as a single 5000 mg dose administered by intramuscular injection[29]. In this study of two LEN formulations administered intramuscularly, plasma LEN concentrations remained above those associated with twice-yearly subcutaneous LEN efficacy for more than 1 year after administration. Injections were generally well tolerated, with injection-site pain being the most common adverse event[29]. These findings suggest that once-yearly intramuscular LEN should confer similar HIV prevention efficacy as twice-yearly subcutaneous LEN and could be a well-tolerated PrEP.

Evaluation of oral loading regimen for a once-yearly intramuscular LEN to achieve similar pharmacokinetics to twice-yearly subcutaneous LEN will be established, and to understand the potential for HIV acquisition during the pharmacokinetic tail period. Additional data from a larger number and more diverse participant population with an indication for PrEP is planned by Gilead Sciences.

Conclusions

As one of the prevention options, greater access to long-acting PrEP has the potential to accelerate the end of the HIV epidemic. Cabotegravir and, most recently, LEN, a 6-month-long-acting antiretroviral medicine, have shown extremely high efficacy in preventing HIV among people from key populations. LEN once-yearly is under evaluation, and should offer similar HIV prevention efficacy as twice-yearly LEN.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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