

Lenacapavir in HIV prevention care: What the pharmacist should know

KP Selomo,^{ID} NM Moloto,^{ID} MJ Luvhimbi,^{ID} E Bronkhorst^{ID}

Department of Clinical Pharmacy, Sefako Makgatho Health Sciences University, South Africa

Corresponding author, email: elmiien.bronkhorst@smu.ac.za

Abstract

Despite advances in antiretroviral therapy, multidrug-resistant human immunodeficiency virus (HIV) remains a major challenge. Novel agents with unique mechanisms of action and long-acting formulations are needed to improve treatment outcomes, adherence, and patient support. Lenacapavir is the first agent in the class HIV-capsid inhibitors. It disrupts multiple stages of viral replication, including capsid disassembly, nuclear import, and virion maturation. Its administration by long-acting subcutaneous formulation enables dosing every six months, addressing non-compliance associated with daily oral therapy. Lenacapavir shows potent antiviral activity against both treatment-naïve and multidrug-resistant HIV-1 strains. Lenacapavir is a potentially transformative HIV prevention tool, indicated in pre-exposure prophylaxis. Pharmacists play a crucial role in optimising therapy by providing patient education, monitoring adherence, managing drug–drug interactions, and supporting both treatment and preventative strategies, including potential long-acting pre-exposure prophylaxis. Overall, lenacapavir provides a promising and practical alternative that could improve patient outcomes, reduce new infections through effective pre-exposure prophylaxis and strengthen ongoing efforts to control the HIV epidemic.

Keywords: lenacapavir, capsid inhibitor, long-acting ART, HIV, pre-exposure prophylaxis

© Authors

<https://doi.org/10.36303/SAPJ.4587>

Introduction

Human immunodeficiency virus (HIV) remains a significant global health burden despite advances in antiretroviral therapy (ART). The widespread use of potent agents, particularly integrase strand transfer inhibitors, has improved viral suppression rates, reduced HIV-related morbidity and mortality and rendered the disease a manageable chronic condition.^{1,2} While ART has revolutionised HIV care, the requirement for daily, lifelong adherence causes treatment fatigue, leading to missed doses, potential virologic failure, and the development of drug-resistant strains.^{3,4} Even with great successes of ART, the new HIV infection rates recorded in South Africa in 2024 were more than 170 000. This figure reflects the need for improved efforts in prevention of transmission of the virus.⁵

The development of long-acting ART is transforming HIV care by addressing the limitations of older ART regimens, such as a variety of side-effects and the lack of adherence to treatment regimens.⁶ Lenacapavir (GS-6207) is a first-in-class capsid inhibitor that disrupts multiple stages of the HIV replication cycle, offering activity against multidrug-resistant HIV-1.⁷ This is a long-acting formulation administered subcutaneously every six months, presents a promising approach to overcoming adherence barriers associated with daily regimens and high pill-burden.^{8,9}

Beyond its role in HIV treatment, lenacapavir has emerged as a groundbreaking agent for HIV prevention, particularly in the context of pre-exposure prophylaxis (PrEP) where infrequent dosing could improve uptake and adherence.^{9,10} Lenacapavir was registered in October 2025 by the South African Health Products

Regulatory Authority (SAHPRA) and roll-out for the PrEP starts in April 2026.¹¹ This review provides an overview of lenacapavir, focusing on its mechanism of action, safety profile, and the role of a pharmacist in its use.

Mechanism of action

Lenacapavir exerts its antiviral activity by selectively targeting the HIV-1 capsid protein (p24), a structural component essential for multiple stages of the viral replication cycle. It binds to a highly conserved interface between capsid subunits within the hexameric lattice, thereby altering capsid stability and function.^{12,13} In the early stages of infection, lenacapavir interferes with essential capsid-dependent processes such as uncoating and interactions with host nuclear transport proteins, including CPSF6 and nucleoporins. This interference prevents the efficient transport of viral DNA into the nucleus, subsequently inhibiting integration into the host genome.¹⁴

In addition to its early-stage effects, lenacapavir also inhibits the late stage of viral replication by impairing capsid assembly and maturation. It induces abnormal stabilisation of the capsid lattice, a process often described as “hyperstabilisation,” which disrupts the normal balance between capsid hexamer and pentamer formation. This leads to the production of structurally defective and non-infectious virions.¹⁵ Furthermore, lenacapavir does not inhibit proteolytic cleavage of Gag; instead, it alters the structural organisation of the capsid during virion maturation, resulting in impaired infectivity of newly formed viral particles.¹⁶

By targeting a structural protein rather than a viral enzyme, lenacapavir uniquely exerts its effects across multiple stages of the

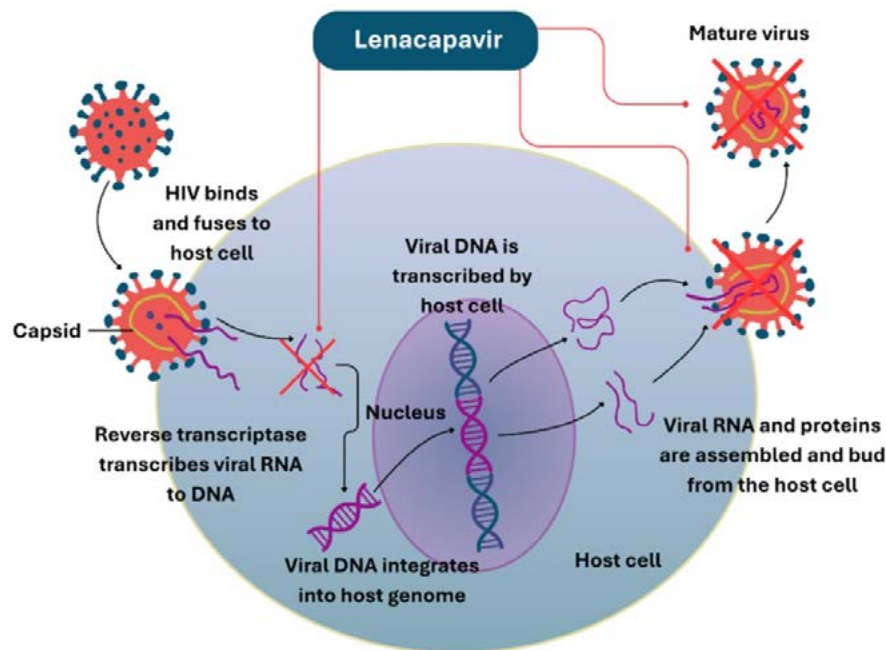


Figure 1: *Multistep inhibition of the HIV life cycle.

*Lenacapavir inhibits HIV by: 1) Target HIV-1 capsid protein, 2) inhibit late-stage replication by impairing capsid assembly, 3) alter structural organisation of capsid during virion maturation
Indication for the use of lenacapavir in South Africa

HIV lifecycle, including nuclear entry, capsid assembly, and virion maturation, preventing viral replication by inhibiting the proper assembly and function of the viral core. This multistage mechanism contributes to its potent antiviral activity and effectiveness against strains of HIV that are resistant to other classes of antiretroviral drugs.^{14,17} Figure 1 shows the mechanism of action of lenacapavir inhibiting multiple stages of the HIV life cycle.

Lenacapavir is indicated for the treatment of multidrug-resistant HIV-1 infection in adults and PrEP in both adults and adolescents.¹⁸

For the treatment of multidrug-resistant HIV-1 infection, it is recommended to be used in combination with other antiretroviral drugs such as emtricitabine and tenofovir. It is specifically indicated for patients with failing ART regimens because of resistance, intolerance or other safety concerns.¹⁹

The significance of lenacapavir registration in South Africa is for PrEP; and approved for reducing the risk of HIV-1 infection in adults and adolescents weighing at least 35 kg. High risk groups of clients who are encouraged to take up PrEP include female sex-workers, men having sex with men, pregnant and breastfeeding women and adolescent girls. For these populations, lenacapavir could reduce the stigma of visible medication use, improve autonomy and unstable access to healthcare, and eliminate barriers related to daily pill burden.⁹ The long-acting sub-cutaneous injection offers a convenient alternative to daily oral PrEP in both high and low-resource settings. Lenacapavir PrEP is highly effective at preventing HIV acquisition, and the long-acting option may increase the uptake of HIV prevention strategies.¹¹

The efficacy of lenacapavir has been shown with the PURPOSE 1 and PURPOSE 2 trials, where lenacapavir was evaluated against

daily oral PrEP and not a placebo. Lenacapavir showed a reduction of new infections in 99%, displaying one of the lowest incidence rates in any HIV trial.⁹

Clinical guidance for using lenacapavir as PrEP

Identifying eligible candidates for PrEP

Clinicians, pharmacists or registered nurses providing PrEP services should first assess the client's HIV acquisition risk and exclude those with acute HIV infection.²⁰

Recommended laboratory testing

Laboratory blood-based HIV antigen/antibody testing is recommended on initial lenacapavir injection to rule out recent HIV infection but may be administered if testing occurred within the previous seven days. At initiation of lenacapavir PrEP, a confirmatory HIV RNA test should be obtained, although the RNA assay should not delay treatment initiation. A repeat antigen/antibody test should be obtained after four weeks to exclude undetected baseline infection. For patients with positive antigen/antibody tests, a full HIV test panel should be performed and first-line ART initiated.²⁰

Hepatitis B viral (HBV) infection should be ruled out if patients are switched from tenofovir-based PrEP to lenacapavir, as tenofovir suppresses HBV. Alternative treatment for HBV should be provided.²⁰

Initiation and dosing regimen

Once a client is deemed eligible for PrEP with lenacapavir, the client can be initiated immediately with a loading dose. Figure 2 provides a visual representation of the dosing regimen, which

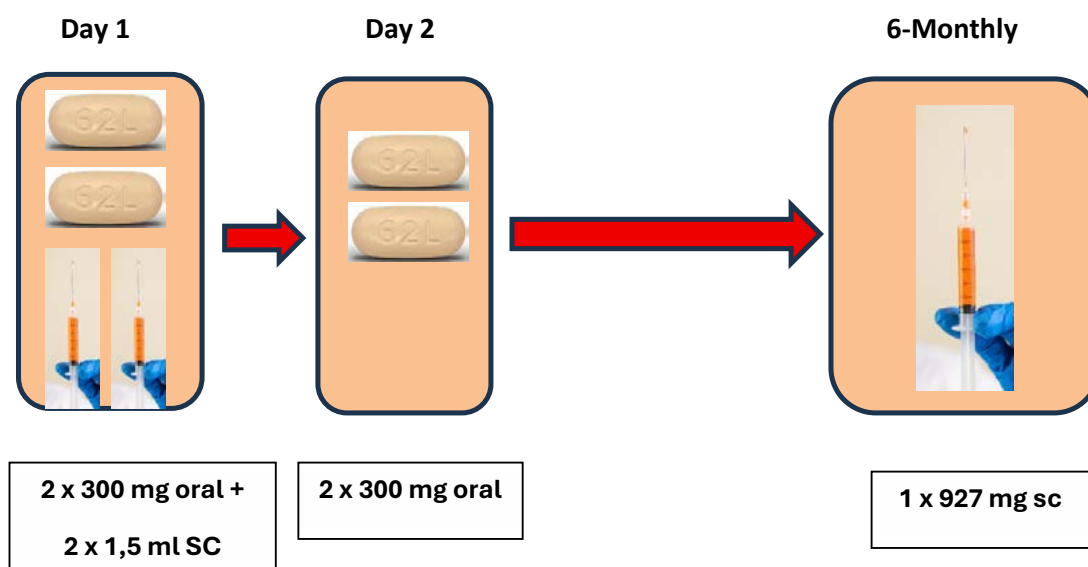


Figure 2: Dosing regimen for lenacapavir PrEP

includes two 300 mg oral tablets and two 1.5 ml subcutaneous injections (927 mg), administered at least 4 inches apart on day one. Injection sites include the abdomen or anterior thigh. Day 2 is followed by two 300 mg tablets, whereafter the subcutaneous injections can be administered 927 mg every six months.^{11,20}

Side effects, adverse events and contraindications

Several studies have assessed the efficacy and safety aspects related to the use of lenacapavir.^{8,17,21-23} In terms of efficacy, long-acting lenacapavir has overall been proven to be highly effective in preventing HIV acquisition and in achieving viral suppression in heavily previously treated people with multidrug-resistant HIV.^{8,23} However, the use of lenacapavir is associated with injection site reactions such as pain, swelling, erythema, induration and nodules.²⁰⁻²³ Nodules are the most reported injection site reaction and are formed because of the drug depot that results in a subcutaneous nodule. It can be several centimetres in size and may last from several months to more than a year.²⁰ Other injection site reactions usually resolve within a couple of days and are mild.²² Other non-injection site side effects include nausea, diarrhoea, cough, headache, pyrexia, urinary tract infections, arthralgia, back pain, constipation, rash and oral candidiasis.^{8,17,22}

Although lenacapavir has no safety concerns and has been shown to be safe to use in pregnancy, it may lead to an increased risk of resistance to capsid inhibitors among those who experience a breakthrough infection.²³ This resistance is due to seven mutations (L56I, M66I, Q67H, K70N, N74D, N74S, and T107N) that have been identified in the HIV-1 capsid protein.²⁴ However, lenacapavir resistance remains a rare occurrence, even in monotherapy, and has only been observed at subtherapeutic levels.²⁴

Lenacapavir has significant interactions with inducers of CYP3A and UGT1A1 enzymes, such as rifampicin, anticonvulsants, carbamazepine, phenytoin, and St. John's wort. This is an aspect that should be considered in TB-co-infection. Some of these

CYP3A4 inducers are antiretrovirals, for example, efavirenz, nevirapine, and etravirine, as well as tipranavir/ritonavir.¹⁸ These drugs reduce the pharmacokinetic exposure of lenacapavir when used simultaneously; therefore, they are contraindicated. Additionally, caution should be practiced when starting lenacapavir after stopping these strong inducers, as their effects can last for weeks, and an interval of four weeks is recommended before initiating lenacapavir.¹⁸

Role of a pharmacist

Pharmacists can play an essential role in promoting the safe, effective, and rational use of lenacapavir in both HIV treatment and prevention settings. These include assessing patient eligibility by reviewing HIV status, patient resistance profiles, and concomitant use of other medications to minimise potential drug-drug interactions, particularly due to lenacapavir's involvement with CYP450 enzymes.^{25,26} Pharmacists are also responsible for monitoring adverse drug reactions, with particular attention to injection site reactions, such as pain, swelling, and erythema associated with the long-acting formulation. In addition, pharmacists provide essential patient education on the importance of maintaining the six-month dosing schedule, as delayed or missed doses may compromise therapeutic effectiveness.

From a stewardship perspective, pharmacists promote the rational use of lenacapavir to minimise the risk of resistance development and ensure alignment with current HIV treatment and prevention guidelines.¹⁰ Furthermore, pharmacists contribute to pharmaco-economic decision-making by evaluating the cost-effectiveness of long-acting therapies compared with conventional daily regimens, which is especially relevant in settings with limited resources. Through these roles, pharmacists support improved clinical outcomes, enhance adherence, and strengthen public health efforts aimed at reducing HIV transmission.

Conclusion

Lenacapavir marks an important advancement in HIV care by addressing some of the key issues and difficulties associated with traditional antiretroviral therapy. Its unique capsid inhibitor mechanism and long-acting formulation offer a more convenient option for HIV prevention and treatment for patients, particularly those with multidrug-resistant HIV-1 or difficulty maintaining daily adherence. However, lenacapavir is not a cure for HIV, but it controls viral replication and reduces the risk of progression to AIDS. For PrEP, lenacapavir should be used in addition to comprehensive HIV prevention strategies, including regular testing and safe sex practices. While lenacapavir is generally well tolerated, with mostly mild injection site reactions, attention must still be paid to possible drug interactions and the risk of resistance if drug levels are not adequately maintained. Pharmacists play a vital role in supporting its safe and effective use through patient counselling, monitoring, and promoting adherence. Overall, lenacapavir provides a promising and practical alternative that could improve patient outcomes and strengthen ongoing efforts to control the HIV epidemic.

ORCID

KP Selomo  <https://orcid.org/0009-0008-7708-9644>

NM Moloto  <https://orcid.org/0009-0003-3984-2387>

MJ Luvhimbi  <https://orcid.org/0009-0009-1244-8068>

E Bronkhorst  <https://orcid.org/0000-0002-6872-5417>

References

- Jacobson K, Ogbuagu O. Integrase inhibitor-based regimens result in more rapid virologic suppression rates among treatment-naïve human immunodeficiency virus-infected patients compared to non-nucleoside and protease inhibitor-based regimens in a real-world clinical setting: A retrospective cohort study. *Medicine*. 2018;97(43):e13016. <https://doi.org/10.1097/MD.00000000000013016>.
- Swinkels HM, Nguyen AD, Samandari T, Gulick PG. HIV and AIDS. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK534860/>. Accessed 19 March 2026.
- Scarsi KK, Swindells S. The promise of improved adherence with long-acting antiretroviral therapy: What are the data? *J Int Assoc Provid AIDS Care*. 2021;20:23259582211009011. <https://doi.org/10.1177/23259582211009011>.
- Fanjul F, Gavalda M, Campins A, et al. HIV therapy: The latest developments in antiviral drugs - a scoping review. *Biomedicine*. 2025;13(11):2629. <https://doi.org/10.3390/biomedicine13112629>.
- Goswami S, Veeramachaneni S, Masurkar PP. Lenacapavir for HIV PrEP: Narrative review of clinical trials and implications for patient access. *Curr Treat Options Infect Dis*. 2025;17:5. <https://doi.org/10.1007/s40506-024-00281-2>.
- Link JO, Rhee MS, Tse WC, et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. *Nature*. 2020;584(7822):614-8. <https://doi.org/10.1038/s41586-020-2443-1>.
- Demirdjian S, Naik V, Margot N, Falkard B, Callebaut C. Phenotypic characterisation of replication-impaired lenacapavir-resistant HIV clinical isolates. *J Med Virol*. 2025;97(4):e70340. <https://doi.org/10.1002/jmv.70340>.
- Ogbuagu O, Molina JM, Chetchotisakd P, et al. Efficacy and safety of long-acting subcutaneous lenacapavir in heavily treatment-experienced people with multidrug-resistant HIV-1: Week 104 results of a phase 2/3 trial. *Clin Infect Dis*. 2025;80(3):566-74. <https://doi.org/10.1093/cid/ciae423>.
- Miteu GD. Lenacapavir and global HIV prevention: A breakthrough at risk of leaving millions behind. *Ann Med Surg*. 2026;88(3):2462-6. <https://doi.org/10.1097/MS9.0000000000004783>.
- World Health Organization. Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis [Internet Who.int.]. World Health Organization; 2025. Available from: <https://www.who.int/publications/i/item/9789240111608>. Accessed 20 March 2026.
- South African Health Products Regulatory Authority. SAHPRA Registers Lenacapavir. In News & Updates, Press Releases; 2025.
- Ma C, Chang J, Yu B. Sunlenca® (lenacapavir): A first-in-class, long-acting HIV-1 capsid inhibitor. *Acta Pharm Sin B*. 2024;14(12):5512-4. <https://doi.org/10.1016/j.apsb.2024.08.009>.
- Canales E, Tse W, Schroeder SD, et al. Discovery of lenacapavir: First-in-class twice-yearly capsid inhibitor for HIV-1 treatment and pre-exposure prophylaxis. *J Med Chem*. 2025;68(20):21072-94. <https://doi.org/10.1021/acs.jmedchem.5c01625>.
- McKellar MS. Lenacapavir: A first-in-class capsid inhibitor for HIV treatment and prevention. *Curr Opin Infect Dis*. 2025;38(3):208-13. <https://doi.org/10.1097/QCO.0000000000001113>.
- Huang S-W, Briganti L, Annamalai AS, et al. The primary mechanism for highly potent inhibition of HIV-1 maturation by lenacapavir. *PLoS Pathogens*. 2025;21(1):e1012862. <https://doi.org/10.1371/journal.ppat.1012862>.
- Hitchcock AM, Kufel WD, Dwyer KAM, Sidman EF. Lenacapavir: A novel injectable HIV-1 capsid inhibitor. *Int J Antimicrob Agents*. 2024;639(1). <https://doi.org/10.1016/j.ijantimicag.2023.107009>.
- De Clercq E, Zhang Y, Li G, et al. Lenacapavir: A capsid inhibitor for HIV-1 treatment and prevention. *Biochem Pharmacol*. 2025;240:117125. <https://doi.org/10.1016/j.bcp.2025.117125>.
- Di Perri G. Pharmacological outlook of lenacapavir: A novel first-in-class long-acting HIV-1 capsid inhibitor. *Infez Med*. 2023;31(4):495. <https://doi.org/10.53854/liim-3104-8>.
- Drugs.com. Lenacapavir: Uses, dosage, side effects, warnings - drugs.com; 2026. Available from: <https://www.drugs.com/lenacapavir.html>.
- Patel RR, Hoover KW, Lale A, et al. Clinical recommendation for the use of injectable lenacapavir as HIV preexposure prophylaxis - United States. *MMWR Morb Mortal Wkly Rep*. 2025;74:541-9. <https://doi.org/10.15585/mmwr.mm7435a1>.
- Segal-Maurer S, DeJesus E, Stellbrink HJ, et al. Capsid inhibition with lenacapavir in multidrug-resistant HIV-1 infection. *N Engl J Med*. 2022;386(19):1793-803. <https://doi.org/10.1056/NEJMoa2115542>.
- Hadia R, Patidar S, Kardani S, et al. A comprehensive review of the safety and efficacy of lenacapavir in the treatment of human immunodeficiency virus. *J Young Pharm*. 2024;16(1). <https://doi.org/10.5530/jyp.2024.16.1>.
- Fonner V, Louis Charles K, Lee MT, et al. Web Annex B: Safety and efficacy of long-acting injectable lenacapavir as pre-exposure prophylaxis to reduce the risk of HIV acquisition: A systematic review. In: Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis (PrEP). Geneva: World Health Organization; 2025. <https://doi.org/10.2471/B09477>.
- Margot N, Vanderveen L, Naik V, et al. Phenotypic resistance to lenacapavir and monotherapy efficacy in a proof-of-concept clinical study. *J Antimicrob Chem*. 2022;77(4):989-95. <https://doi.org/10.1093/jac/dkab503>.
- Koren DE, Chahine EB, Sherman EM. Lenacapavir: A twice-yearly injectable for HIV pre-exposure prophylaxis. *Ann Pharmacother*. 2026;60(3):276-86. <https://doi.org/10.1177/10600280251379877>.
- Marzolini C, Gibbons S, Seddon D, Khoo S. Drug-drug interactions potential with the HIV-1 capsid inhibitor lenacapavir. *Expert Opin Drug Metab Toxicol*. 2025;21(2):161-72. <https://doi.org/10.1080/17425255.2024.2415295>.