Act Farma Terap. 2022; 20(1): 32-36

Lenacapavir, a long-acting capsid inhibitor for HIV-1 infection with potential as HIV preexposure prophylaxis (PrEP) medication

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Resumen

El lenacapavir, desarrollado por Gilead Sciences, es el primer inhibidor de la cápside de acción prolongada de su clase diseñado para el tratamiento de la infección por VIH-1. Se dirige a la proteína de la cápside del VIH-1, un componente crítico de la estructura vírica. Se dirige a la proteína de la cápside del VIH-1, un componente crítico de la estructura vírica, interrumpiendo múltiples etapas del ciclo vital vírico, como el ensamblaje de la cápside, la importación nuclear y la replicación vírica. Este mecanismo de acción único hace que el lenacapavir sea eficaz tanto contra las cepas de VIH-1 de tipo salvaje como contra las multirresistentes.

El lenacapavir está disponible en formulaciones subcutánea y oral, con un esquema de dosificación cada seis meses para la forma inyectable. Este régimen de acción prolongada aborda los retos de adherencia a los que se enfrentan los pacientes que siguen una terapia antirretrovírica diaria (TAR), en particular aquellos con VIH-1 multirresistente que tienen opciones de tratamiento limitadas. Los ensayos clínicos, como el estudio CAPELLA, han demostrado su potente eficacia antivírica, con reducciones significativas de la carga vírica observadas en pacientes muy experimentados en el tratamiento.

Aprobado por organismos reguladores como la FDA y la EMA estadounidenses, el lenacapavir está indicado para su uso en combinación con otros agentes antirretrovirales para el tratamiento de la infección por VIH-1 multirresistente. Su perfil de seguridad es generalmente favorable, con efectos secundarios frecuentes como reacciones en el lugar de inyección y síntomas gastrointestinales.

En resumen, el lenacapavir representa un avance revolucionario en el tratamiento del VIH, ya que ofrece una opción terapéutica potente y de acción prolongada que mejora la adherencia y los resultados en pacientes con necesidades terapéuticas complejas. Su mecanismo innovador y su pauta de dosificación poco frecuente lo posicionan como una herramienta transformadora en la lucha contra el VIH-1.

Palabras clave

Lenacapavir; VIH; SIDA.

Conflicto de intereses

Este artículo no presenta conflicto de interés.

Summary

Lenacapavir, developed by Gilead Sciences, is a first-in-class, long-acting capsid inhibitor designed for the treatment of HIV-1 infection. It targets the HIV-1 capsid protein, a critical component of the viral structure, disrupting multiple stages of the viral life cycle, including capsid assembly, nuclear import, and viral replication. This unique mechanism of action makes lenacapavir effective against both wild-type and multidrug-resistant HIV-1 strains. Lenacapavir is available in both subcutaneous and oral formulations, with a dosing schedule of every six months for the injectable form. This long-acting regimen addresses adherence challenges faced by patients on daily antiretroviral therapy (ART), particularly those with multidrug-resistant HIV-1 who have limited treatment options. Clinical trials, such as the CAPELLA study, have demonstrated its potent antiviral efficacy, with significant reductions in viral load observed in heavily treatment-experienced patients.

Approved by regulatory agencies like the U.S. FDA and EMA, lenacapavir is indicated for use in combination with other antiretroviral agents for the treatment of multidrug-resistant HIV-1 infection. Its safety profile is generally favorable, with common side effects including injection site reactions and gastrointestinal symptoms.

In summary, lenacapavir represents a groundbreaking advancement in HIV therapy, offering a potent, long-acting treatment option that improves adherence and outcomes for patients with complex treatment needs. Its innovative mechanism and infrequent dosing schedule position it as a transformative tool in the fight against HIV-1.

Key words

Lenacapavir; HIV; AIDS.

Conflict of interests

This article does not present a conflict of interest.

INTRODUCTION

Lenacapavir, developed by Gilead Sciences (brand name Sunlenca®), has been recognized as a significant breakthrough in the treatment of HIV. It is a long-acting capsid inhibitor that offers a novel mechanism of action, targeting the HIV capsid protein, which is essential for viral replication (Link et al, 2020). This innovative approach provides a new option for individuals with multi-drug resistant HIV, addressing a critical need in the management of the virus (Segal-Maurer et al., 2022).

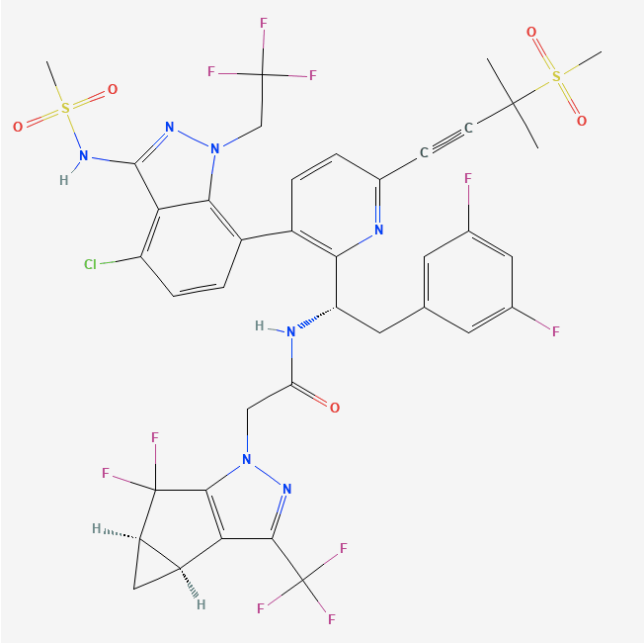

Figure 1. Lenacapavir structural formula (source: https://pubchem.ncbi.nlm.nih.gov). IUPAC nomenclature: N-[(1S)-1-(3-{4-Chloro-3-[(methylsulfonyl)amino]-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl}-6-[3-methyl-3-(methylsulfonyl)-1-butyn-1-yl]-2-pyridinyl)-2-(3,5-difluorophenyl) ethyl]-2-[(3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl]acetamide.

In 2022, Lenacapavir received approval from the U.S. Food and Drug Administration (FDA) for the treatment of HIV in heavily treatment-experienced adults with multi-drug resistant HIV. Its long-acting formulation allows for dosing every six months, which is a substantial improvement over daily oral medications, potentially improving adherence and quality of life for patients.

PHARMACOLOGICAL CHARACTERISTICS

The recognition of Lenacapavir as a breakthrough highlights its potential to transform HIV treatment paradigms, particularly for those who have limited therapeutic options. Its development underscores the ongoing advancements in antiretroviral therapy and the commitment to addressing the challenges faced by individuals living with HIV. Lenacapavir is considered a scientific breakthrough of the 2024 year (Cohen, 2024) due to its innovative mechanism of action, long-acting formulation, and potential to address unmet needs in HIV treatment. Here are some key reasons why it stands out:

Mechanism of Action

Lenacapavir targets the HIV capsid protein, a critical component of the virus's structure and replication process. The proposed mechanism includes capsid-mediated nuclear uptake of preintegration complexes, virion production and proper capsid core formation.. By disrupting the capsid, Lenacapavir interferes with multiple stages of the HIV life cycle, including viral replication and assembly, offering a new way to combat the virus.

Long-Acting Formulation

One of the most groundbreaking aspects of Lenacapavir is its long-acting dosing regimen. It can be administered subcutaneously every six months, significantly reducing the burden of daily oral medications. This innovation is particularly beneficial for individuals who struggle with adherence to daily regimens, improving treatment outcomes and quality of life.

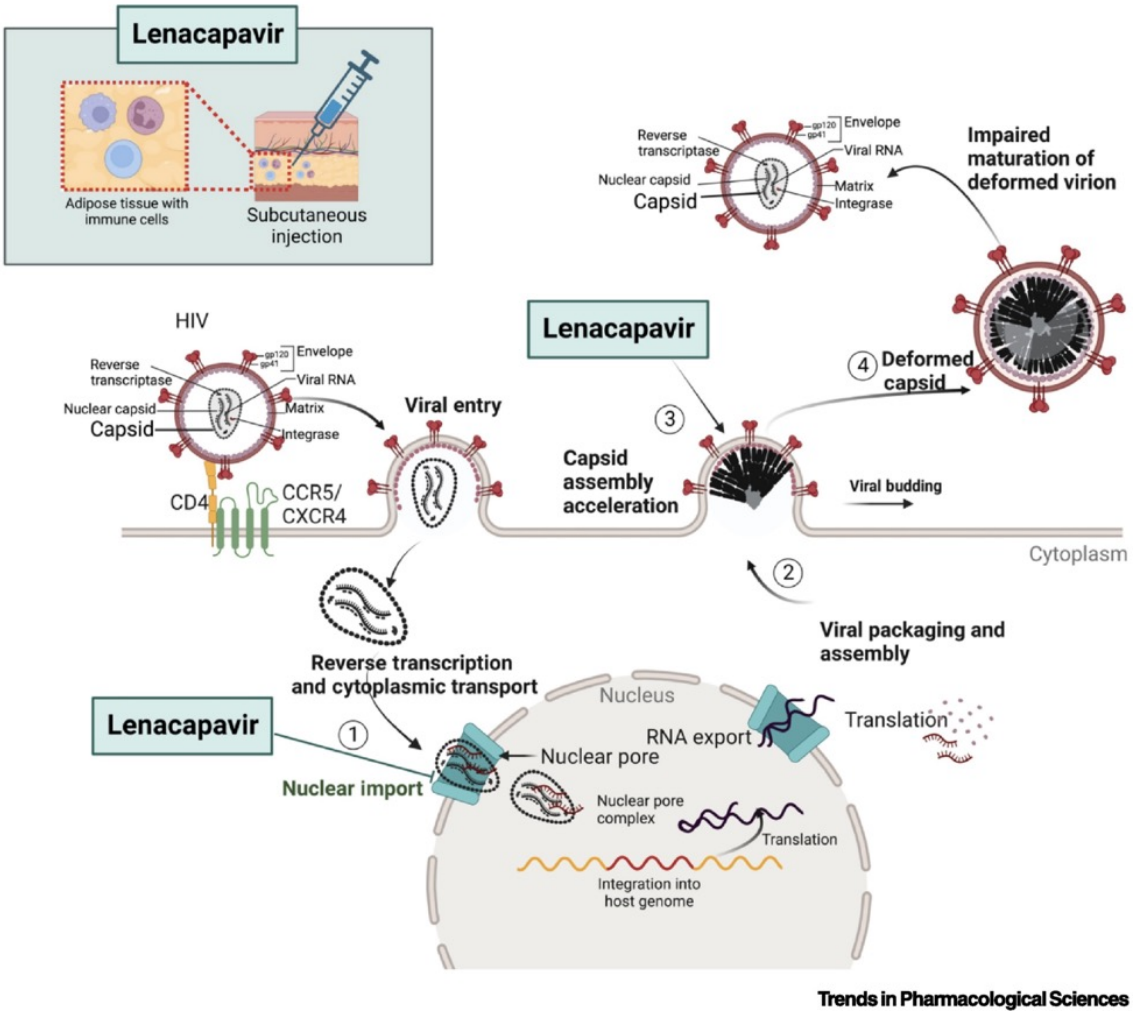

Figure 2. Lenacapavir mechanism of action. Extracted from Patel et, 2023, DOI: 10.1016/j.tips.2023.05.002

Addressing Multi-Drug Resistant HIV

Lenacapavir has shown efficacy in treating heavily treatment-experienced patients with multi-drug resistant HIV, a population with limited therapeutic options. Its approval by the FDA in 2022 for this specific group marked a critical advancement in managing complex HIV cases.

Potential to Transform HIV Treatment

The long-acting nature of Lenacapavir could revolutionize HIV care by shifting from daily pills to bi-annual injections, making treatment more convenient and accessible. It also opens the door for its use in HIV prevention (PrEP), potentially offering a long-acting alternative to daily oral PrEP medications.

Clinical Trials Success

Clinical trials demonstrated Lenacapavir's ability to significantly reduce viral load in patients with multi-drug resistant HIV, even when used in combination with other antiretrovirals. Its safety and efficacy profile has been robust, further solidifying its role as a transformative therapy. For instance, the PURPOSE 1 study in the use of preexposure prophylaxis for human immunodeficiency virus prevention (Funded by Gilead Sciences; ClinicalTrials.gov number NCT04994509) has highlighted a large efficacy trial in African adolescent girls and young women that reduced HIV infections to zero—an astonishing 100% efficacy. It was a blinded study in more than 5000 cisgender women and adolescent girls in South

Africa and Uganda, and not a single person who received the injections became infected. The clinical trial has assigned the participants in a 2:2:1 ratio to receive subcutaneous Lenacapavir every 26 weeks, daily oral Emtricitabine–Tenofovir alafenamide (F/TAF), or daily oral Emtricitabine–Tenofovir disoproxil fumarate (F/TDF; active control); all participants also received the alternate subcutaneous or oral placebo. The efficacy of Lenacapavir and F/TAF was assessed by comparing the incidence of HIV infection with the estimated background incidence in the screened population and evaluated relative efficacy as compared with F/TDF. The results of the study were published in "The New England Journal of Medicine" (L.-G. Bekker et al, 2024), and Authors have pointed out that:

"Among 5338 participants who were initially HIV-negative, 55 incident HIV infections were observed: 0 infections among 2134 participants in the lenacapavir group (0 per 100 person-years; 95% confidence interval [CI], 0.00 to 0.19), 39 infections among 2136 participants in the F/TAF group (2.02 per 100 person-years; 95% CI, 1.44 to 2.76), and 16 infections among 1068 participants in the F/TDF group (1.69 per 100 person-years; 95% CI, 0.96 to 2.74). Background HIV incidence in the screened population (8094 participants) was 2.41 per 100 person-years (95% CI, 1.82 to 3.19). HIV incidence with lenacapavir was significantly lower than background HIV incidence (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.04; P<0.001) and than HIV incidence with F/TDF (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.10; P<0.001). HIV incidence with F/TAF did not differ significantly from background HIV incidence (incidence rate ratio, 0.84; 95% CI, 0.55 to 1.28; P = 0.21), and no evidence of a meaningful difference in HIV incidence was observed between F/TAF and F/TDF (incidence rate ratio, 1.20; 95% CI, 0.67 to 2.14). Adherence to F/TAF and F/TDF was low. No safety concerns were found. Injection-site reactions were more common in the lenacapavir group (68.8%) than in the placebo injection group (F/TAF and F/TDF combined) (34.9%); 4 participants in the lenacapavir group (0.2%) discontinued the trial regimen owing to injection-site reactions."

Considering the results above, hopeful the drug Lenacapavir will powerfully drive down global infection rates when used as pre-exposure prophylaxis (PrEP).

Adverse effects

Lenacapavir's adverse effect profile is generally manageable, and its benefits in treating multidrug-resistant HIV-1 often outweigh the risks. Lenacapavir, like all medications, may cause adverse effects. While it is generally well-tolerated, some patients may experience side effects during treatment, as for instance: Injection site reactions, gastrointestinal disturbs, fatigue, headache (Hitchcock et al., 2024).

CONCLUSION

HIV infection remains a global health challenge, with millions of people living with the virus. Lenacapavir's introduction provides hope for better management of the epidemic, particularly in resource-limited settings where adherence to daily regimens can be challenging. Lenacapavir may represent a paradigm shift in HIV treatment, combining scientific innovation with practical benefits for patients. Its recognition as a breakthrough underscores its potential to improve outcomes for individuals with HIV, particularly those with limited treatment options, and highlights the ongoing progress in the fight against the virus. Nevertheless some caution may be need in the interpretation of the results in the real world, especially concerned to pharmacological resistance, since the clinical trials on it are still ongoing.

Referencias

1. Link JO, Rhee MS, Tse WC, et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. Nature 2020;584:614-8. DOI: 10.1038/s41586-020-2443-1
2. Segal-Maurer S, De Jesus E, Stellbrink H-J, et al. Capsid inhibition with lenacapavir in multidrug-resistant HIV-1 infection. N Engl J Med 2022;386:1793-803. DOI: 10.1056/NEJMoa2115542.
3. Patel, Pratish C. et al. Lenacapavir (Sunlenca®) for the treatment of HIV-1 Trends in Pharmacological Sciences 2023 Volume 44, Issue 8, 553 – 554. DOI: 10.1016/j.tips.2023.05.002
4. Cohen, 2024. 2024 BREAKTHROUGH OF THE YEAR. https://www.science.org/content/article/breakthrough-2024#section_breakthrough. Accessed in March 6th, 2025.
5. L.-G. Bekker et al. Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women. N Engl J Med 2024; 391:1179-92. DOI: 10.1056/NEJMoa2407001
6. Hitchcock A. M., et al. Lenacapavir: A novel injectable HIV-1 capsid inhibitor. Int J Antimicrob Agents 2024; 63 (1):107009. DOI: 10.1016/j.ijantimicag.2023.107009.

¿Sabías que ....?

Las proteínas GPCR (acrónimo del inglés, “G-protein Coupled Receptor”) acoplan la activación de un receptor por su agonista a una vía de señalización implicada en la actividad celular. Las GPCR de la subclase A son receptores del tipo rodopsina; poseen un sitio ortostérico incluido en un segmento intramembrana, un sitio alostérico para el sodio y los dominios terminales N y C.