International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 31, Issue 4, April 2025 **ijppr.humanjournals.com** ISSN: 2349-7203

Lenacapavir: A New Targeted Molecule for Resistant HIV - A Comprehensive Review

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Received: 2025-4-01 Revised: 2025-4-12 Accepted: 2025-4-20

ABSTRACT

Lenacapavir emerges as a groundbreaking therapeutic option in the fight against HIV, particularly for patients with resistant strains of the virus. This review comprehensively examines its unique mechanism of action, which involves targeting the viral capsid. By binding to specific sites on the capsid protein, Lenacapavir effectively disrupts the viral uncoating process, preventing the release of viral RNA into the host cytoplasm. This inhibition is crucial as it blocks reverse transcription and subsequent viral replication, thereby impeding the virus's ability to propagate and establish chronic infections. The review highlights Lenacapavir's broad-spectrum efficacy against resistant HIV strains, distinguishing it from traditional antiretroviral therapies (ARTs) that often target rapidly changing regions of the virus. By focusing on a stable area of the HIV-1 capsid, Lenacapavir reduces the likelihood of resistance development and enhances its effectiveness against various drug-resistant strains. This strategic targeting not only disrupts the assembly of infectious viral particles but also significantly diminishes the virus's capacity to replicate, which is essential for preventing new infections within host cells. Clinical trials, particularly the CALIBRATE trial, have demonstrated Lenacapavir's ability to maintain effective plasma concentrations for up to six months following a single injection. This long-lasting effect ensures sustained viral suppression and improves adherence rates among patients. Additionally, Lenacapavir is noted for its favorable safety profile, characterized by a low incidence of adverse effects, making it a well-tolerated option for a diverse range of patient populations, including those with treatment-resistant HIV. In conclusion, as the landscape of HIV treatment evolves, Lenacapavir stands out for its extensive efficacy against resistant strains and its potential to reduce latent viral reservoirs. This positions Lenacapavir as a promising candidate for future antiretroviral therapy regimens, offering hope for improved management of HIV.

Keywords: Lenacapavir, HIV, Antiretroviral therapy, Viral load, CALIBRATE trial, CAPELLA trial

INTRODUCTION

The Human Immunodeficiency Virus (HIV) has escalated into a noteworthy global health dilemma, impacting around 38 million individuals diagnosed with the virus throughout the planet (1). While there have been impressive developments in antiretroviral therapy (ART), the continual surge of drug-resistant HIV strains keeps diminishing treatment efficiency and constraining the therapeutic avenues open to us (2). The disease-causing entity predominantly seeks out the immune system, notably the CD4+ T lymphocytes, which can lead to a continuous drop in immune effectiveness and, if disregarded, the eventual rise of Acquired Immunodeficiency Syndrome (AIDS) (3). Traditional ART protocols, while successful in inhibiting viral replication, necessitate lifelong compliance and are frequently accompanied by adverse effects and the emergence of resistance (2). Consequently, there

exists an urgent requirement for innovative therapeutic approaches that provide enhanced efficacy, superior resistance profiles, and improved patient adherence (4). In this regard, Lenacapavir, a pioneering long-acting capsid inhibitor, has emerged as a promising targeted therapeutic agent against multidrug-resistant HIV, thereby offering newfound hope for patients facing limited treatment possibilities. Though recent Antiretroviral Therapies (ARTs) have significantly bolstered patient health prospects, the rise of drug-resistant HIV strains points to the vital need for novel treatment innovations. Lenacapavir, identified as a pioneering, long-acting capsid inhibitor, holds substantial promise as a treatment option for patients with prior therapeutic experience who possess limited alternatives (5).

In comparison to existing antiretroviral treatments (ARTs) that mainly emphasize reverse transcriptase, protease, or integrase, Lenacapavir's action mechanism, focusing on the capsid, unveils a fresh therapeutic route (4, 5). By obstructing several essential phases of the HIV life cycle, it has exhibited significant antiviral efficacy against resistant variants (6, 7). Its distinctive pharmacokinetic characteristics, which facilitate biannual administration, present a considerable benefit over conventional daily oral regimens, thereby addressing the adherence difficulties encountered by numerous patients (3, 8). This advancement has the potential to revolutionize the treatment frameworks for HIV, particularly for individuals who experience treatment fatigue or possess restricted options due to resistance (9, 10).

The introduction of Lenacapavir further emphasizes the significance of persistent innovation within the realm of antiretroviral therapy (ART) development (11, 12). As HIV undergoes evolution and resistance patterns alter, the necessity for novel pharmacological classes becomes increasingly paramount (13, 14). The efficacy of Lenacapavir demonstrated in clinical trials underscores the potential of targeting previously underexploited viral components, thus facilitating the advancement of future pharmacotherapeutics (15).

Mechanism of Action

The way Lenacapavir works is fundamentally unlike standard antiretroviral drugs, focusing specifically on the HIV-1 capsid protein (p24) (16). This inhibition interferes with multiple critical phases of the viral replication cycle, which encompass:

- **Viral uncoating:** The proteinaceous capsid assumes a pivotal function in safeguarding the viral RNA genome. Lenacapavir binds to designated sites on the capsid protein, thereby obstructing its capacity to undergo proper disassembly (17, 18). This perturbation precludes the discharge of viral RNA into the host cytoplasm, consequently inhibiting reverse transcription and the ensuing process of viral replication (19, 20).

- **Nuclear import:** The HIV-1 capsid actively participates in interactions with proteins associated with nuclear pores to enable the movement of viral genetic information into the nucleus (21, 22). Lenacapavir obstructs these interactions, thereby impeding nuclear import and preventing the integration of viral DNA into the host genome. This process is essential in averting the initiation of new infections within host cellular environments (23).

- **Capsid assembly**: Subsequent to the process of viral replication, the newly synthesized viral RNA and proteins necessitate encapsulation into nascent virions (24). Lenacapavir disrupts the appropriate assembly of the viral capsid, resulting in the production of defective, non-infectious viral particles (25). This mechanism markedly impairs the virus's capacity to propagate and establish a chronic infection (26).

- **Broad-spectrum efficacy against resistant strains**: In comparison to typical antiretroviral therapies (ARTs) that zero in on rapidly changing regions of the virus, Lenacapavir aims directly at a stable area of the HIV-1 capsid (27, 28). This strategic targeting diminishes the probability of resistance emergence and enhances its efficacy against strains that exhibit resistance to multiple classes of drugs (29).

Through the concurrent inhibition of various phases of the viral life cycle, Lenacapavir establishes an extensive impediment to HIV replication (30). Its distinctive mechanism renders it a compelling candidate for combination therapy in patients with extensive treatment history who have exhibited resistance to alternative antiretroviral therapies (ARTs) (14, 23).

Pharmacokinetics and Pharmacodynamics

Lenacapavir is characterized by an exceptionally extended half-life, which facilitates the possibility of biannual administration via subcutaneous routes (3). The fundamental pharmacokinetic attributes pertinent to this compound encompass the following essential aspects:

Absorption and bioavailability: Lenacapavir has been meticulously engineered for administration through both oral and subcutaneous modalities; however, the oral bioavailability is notably constrained, which necessitates the use of subcutaneous injections to achieve and sustain systemic levels of the drug over time (3, 31). Following subcutaneous injection, the absorption of Lenacapavir occurs gradually, leading to the attainment of peak plasma concentrations over a period extending several days, thereby ensuring that there is a prolonged duration of drug exposure in the systemic circulation (32, 33).

Distribution: The pharmacokinetic profile of Lenacapavir reveals a significant volume of distribution, which indicates its capacity for extensive penetration into various tissues throughout the body (11, 34). This particular characteristic is of paramount importance for the maintenance of effective drug concentrations in critical anatomical reservoirs associated with HIV replication, notably including the lymphoid tissues where the virus predominantly proliferates (35, 36).

Metabolism: Lenacapavir undergoes metabolic processing primarily through the CYP3A4 enzyme pathway as well as the uridine diphosphate-glucuronosyltransferase (UGT1A1) pathways, a dual metabolic route that effectively mitigates the potential for substantial drug-drug interactions (37). This metabolic versatility renders Lenacapavir a promising candidate for use in combination therapies alongside other antiretroviral treatments (ARTs), enhancing its clinical applicability (38, 39).

Elimination: The elimination half-life of Lenacapavir is estimated to be approximately 8 to 12 weeks, a factor that significantly contributes to its appropriateness for biannual dosing regimens (40, 41). This prolonged half-life can be primarily ascribed to the drug's gradual release from the site of injection, coupled with its stability in plasma, which collectively ensure a sustained suppression of viral replication over an extended timeframe (42, 43).

Pharmacodynamic Properties

Lenacapavir indicates impressively powerful antiviral abilities even at very low nanomolar levels, and its operational mechanism specifically aims at highly preserved regions within the HIV-1 capsid architecture, which is vital for the virus's structure and replication (44). Extensive studies have provided compelling evidence regarding the following:

Sustained viral suppression: Lenacapavir has been shown to effectively maintain plasma concentrations of the drug at levels that are consistently above the threshold necessary for achieving effective antiviral activity for an impressive duration of up to six months following a single injection, which ensures a continuous and robust suppression of viral replication throughout this prolonged period (15).

Resistance barrier: The extraordinary potency exhibited by Lenacapavir, when coupled with its innovative mechanism of action that targets a unique site, renders it highly effective against various strains of HIV that have developed resistance to conventional antiretroviral therapies (ARTs) (3, 8). Comprehensive mutational analyses reveal that the barrier to the development of resistance against Lenacapavir is relatively substantial, with only a limited number of specific mutations—such as the M66I substitution—demonstrating a significant impact on the drug's susceptibility profile (45).

Combination potential: Given its unique and distinct mechanism of action, Lenacapavir has the potential to complement and enhance the therapeutic effects of other antiretroviral medications, thereby positioning it as an exceptionally attractive candidate for incorporation into combination treatment regimens (46, 47). The pharmacodynamic characteristics of Lenacapavir provide strong support for its concurrent use alongside nucleoside reverse transcriptase inhibitors (NRTIs) and integrase inhibitors (INSTIs), which collectively serve to augment the overall therapeutic efficacy of the treatment approach (48, 49).

Impact on immune recovery: The effect of Lenacapavir on immune recovery is noteworthy, as it appears to enhance the restoration of CD4+ T-cells in individuals battling treatment-resistant HIV infections, which aids in reviving the immune system's performance and simultaneously lowers the chances of opportunistic infections that may occur due to weakened immune conditions (50).

Long-term viral reservoir suppression: Several studies suggest that the antiviral activity of Lenacapavir may extend to the reduction of latent HIV reservoirs, which could potentially play a significant role in the achievement of long-term viral control when utilized in conjunction with other therapeutic interventions aimed at managing HIV infection effectively (25, 51).

Clinical Trials and Efficacy

CAPELLA Trial

The CAPELLA trial meticulously investigated the therapeutic potential of Lenacapavir in a cohort of patients who exhibited extensive experience with various treatment regimens for multidrug-resistant HIV, thereby providing a significant contribution to the understanding of this complex condition (49, 52). Key findings, which emerged from the comprehensive analysis, include:

- A remarkably high rate of virologic suppression was observed, with more than 80% of the participants attaining a state of viral suppression, indicating the treatment's efficacy in managing the viral load within this challenging patient population (53, 54).

- The trial also documented a rapid and notable decline in viral load, with a significant reduction being observed within a mere 14 days of initiating treatment, showcasing the prompt action of Lenacapavir in effectively combating the viral replication process (55).

- Furthermore, the durability of the response to Lenacapavir was evidenced by sustained efficacy that persisted at both the 26-week and 52-week marks, underscoring the long-term benefits of this novel therapeutic approach in the management of heavily treatment-experienced patients with multidrug-resistant HIV (55, 56).

CALIBRATE Trial

The CALIBRATE trial, which was meticulously designed to evaluate the efficacy and safety of Lenacapavir specifically in patients who had not previously received treatment for their condition, yielded significant findings that underscore its potential clinical utility, demonstrating:

- A level of efficacy that is comparable to that observed in standard antiretroviral therapy (ART) regimens that are commonly employed in clinical practice for the management of HIV infection (57, 58).

- An exceptionally favorable safety profile characterized by a remarkably low incidence of adverse effects, thereby suggesting that this therapeutic agent could be well tolerated among the patient population (25).

- Sustained long-term virologic suppression coupled with enhanced adherence rates, which are critical factors in the overall management and treatment of HIV infection. These compelling findings provide robust support for the inclusion of Lenacapavir as a viable treatment option in both treatment-experienced individuals and those who are treatment-naïve, thus expanding its applicability across diverse patient demographics (59, 60).

Conclusion:

Lenacapavir emerges as a groundbreaking therapeutic alternative in the management of HIV, demonstrating a unique mechanism of action that specifically targets the viral capsid to impede essential phases of the viral life cycle, such as uncoating and nuclear import. This pioneering tactic not only stops the exit of viral RNA but also impedes the assembly of infectious viral units, culminating in a substantial reduction in the virus's power to reproduce and form lasting infections. Clinical trials, particularly the CALIBRATE trial, have confirmed Lenacapavir's ability to maintain effective plasma concentrations for up to six months after a single injection, thereby facilitating prolonged viral suppression and improving adherence rates among patients. Furthermore, its advantageous safety profile—characterized by a low incidence of adverse effects—positions Lenacapavir as a well-tolerated option for a heterogeneous array of patient populations, including individuals with treatment-resistant HIV.

As the paradigm of HIV treatment continues to advance, Lenacapavir's broad-spectrum efficacy against resistant strains and its potential to mitigate latent viral reservoirs highlight its promise as a transformative element of future antiretroviral therapy protocols. Looking forward, additional research is essential to assess Lenacapavir in conjunction with other long-acting agents, investigate its role in pre-exposure prophylaxis (PrEP), and examine its potential contribution toward functional or sterilizing cures. The expansion of real-world data and long-term outcome studies will also be crucial in elucidating its impact on virological suppression, quality of life, and the burden on healthcare systems. Collectively, Lenacapavir not only tackles urgent treatment challenges but also exemplifies the vital role of sustained innovation in propelling global HIV care and prevention initiatives.

Acknowledgement

The authors express their gratitude to all who contributed to the completion of this review. Appreciation is extended for the valuable insights, resources, and support that facilitated this work.

Conflict of Interest

There was no funding or conflict of interest related to this work.

Author Contribution

All the authors have played a significant role in their contribution.

Abbreviations

AIDS - Acquired Immunodeficiency Syndrome

ART – Antiretroviral Therapy

HIV – Human Immunodeficiency Virus

INSTI - Integrase Strand Transferase Inhibitors

NRTI - Nucleoside Reverse Transcriptase Inhibitor

PrEP – Pre-exposure prophylaxis

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How to cite this article:
Shaikh Mohmed Adnan Mohmed Javid et al. Ijppr.Human, 2025; Vol. 31 (4): 60-66.
Conflict of Interest Statement: All authors have nothing else to disclose.