

# Lenacapavir: A Novel Long-Acting Capsid Inhibitor Transforming HIV Management

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**Abstract**—Lenacapavir (GS-6207) represents a groundbreaking advancement in antiretroviral pharmacotherapy. As the first-in-class HIV-1 capsid inhibitor, it demonstrates unique multistage antiviral activity across the HIV replication cycle. Unlike conventional enzyme-targeting antiretrovirals, lenacapavir interferes with capsid assembly, nuclear import, and virion maturation. This review consolidates the molecular pharmacology, pharmacokinetics, resistance mechanisms, safety profile, and clinical efficacy of lenacapavir based on recent Phase II and III evaluations. The drug's long half-life enabling subcutaneous dosing every six months positions it at the forefront of long-acting antiretroviral therapy and HIV pre-exposure prophylaxis, addressing adherence challenges and expanding therapeutic potential against multidrug-resistant (MDR) HIV-1 strains.

**Index Terms**—Lenacapavir, HIV-1, Capsid inhibitor, Pharmacokinetics, Resistance, Long-acting therapy, PrEP.

## I. INTRODUCTION

The persistent global burden of human immunodeficiency virus type 1 (HIV-1) infection highlights the need for improved antiretroviral strategies. Despite significant advances in combination antiretroviral therapy (cART), issues of resistance, drug interactions, and adherence remain major impediments to achieving sustained viral suppression. Lenacapavir, a small-molecule capsid inhibitor developed by Gilead Sciences, introduces a fundamentally distinct mechanism of action targeting the viral capsid—a structural component essential to viral replication and genome encapsidation. Its dual application in both treatment and prevention broadens the landscape of long-acting therapy options.

## II. MECHANISM OF ACTION

Lenacapavir binds to a conserved interface between HIV-1 capsid protein hexamers, inducing structural instability that disrupts several critical replication stages. These include inhibition of capsid-mediated nuclear import, interference with Gag/Gag-Pol polyprotein assembly, and impaired capsid core formation. This multistage interference differentiates lenacapavir from classical enzyme inhibitors such as reverse transcriptase or integrase inhibitors, marking it as a distinct antiviral class with exceptional potency (EC<sub>50</sub> values ranging from 30–190 pM in primary CD4<sup>+</sup> T-lymphocytes). Such multi-targeted capsid inhibition confers lower risk of cross-resistance with existing antiretroviral classes.

## III. PHARMACOKINETICS AND PHARMACODYNAMICS

Lenacapavir exhibits highly favorable pharmacokinetics characterized by nonlinear absorption and long elimination phases. Oral bioavailability ranges from 6–10%, necessitating an initial oral loading phase followed by subcutaneous maintenance doses every 6 months. Median plasma half-lives are 10–12 days (oral) and 8–12 weeks (subcutaneous). The drug is primarily metabolized via CYP3A4 and UGT1A1 pathways, with minimal renal clearance and negligible influence from dialysis. Lenacapavir's slow depot release ensures sustained plasma concentrations adequate for therapeutic efficacy, aligning with the emerging model of low-frequency, long-term pharmacotherapy.

#### IV. CLINICAL EFFICACY

Clinical data from CAPELLA and CALIBRATE trials have reaffirmed lenacapavir's virologic efficacy. In heavily treatment-experienced individuals with MDR HIV-1, co-administration of lenacapavir with optimized background therapy achieved sustained viral suppression. Monotherapy phases demonstrated a mean 1.4–2.3 log<sub>10</sub> reduction in HIV-1 RNA after a single injection over 10 days, confirming intrinsic antiviral potency comparable to that of integrase inhibitors. Phase 3 PURPOSE-1 and PURPOSE-2 trials assessing PrEP efficacy further demonstrated up to 100% prevention of HIV acquisition in cisgender women and over 96% risk reduction in diverse populations receiving subcutaneous lenacapavir every 26 weeks.

#### V. RESISTANCE AND MUTATIONAL IMPACT

Resistance to lenacapavir arises from mutations within the capsid protein gene (notably M66I, Q67H, and K70H). These mutations can reduce susceptibility by 15–265 fold; however, such variants typically emerge under conditions of suboptimal adherence or functional monotherapy. Importantly, lenacapavir retains full activity against viral strains resistant to existing nucleoside, non-nucleoside, protease, and integrase inhibitors, underscoring its orthogonal mechanism and value in salvage regimens.

#### VI. SAFETY AND TOLERABILITY

In extensive clinical evaluation, lenacapavir demonstrated an excellent safety profile. The most frequent adverse events are localized injection-site reactions (pain, erythema, nodule formation, induration), generally mild and transient. Systemic events such as nausea, constipation, or headache occur infrequently and are not dose-limiting. No significant hepatic or renal toxicity has been observed across trials, and laboratory abnormalities were rare and clinically insignificant. Co-administration with strong CYP3A4 or P-gp inducers remains contraindicated to prevent subtherapeutic exposures.

#### VII. THERAPEUTIC ROLE AND FUTURE PROSPECTS

Lenacapavir's unique properties—multi-stage capsid inhibition, long-acting pharmacokinetics, and preserved activity against resistant variants—position it as a critical component of next-generation HIV therapy. Its integration into fixed-dose or combination regimens with other long-acting agents such as cabotegravir could significantly enhance durability and adherence. Moreover, its potential role in prophylactic programs across resource-limited settings reinforces its global public health relevance.

#### VIII. CONCLUSION

Lenacapavir exemplifies a paradigm shift in HIV pharmacotherapy by introducing structural-targeted, long-acting antiretroviral intervention. Its dual therapeutic and prophylactic capabilities, substantial antiviral potency, and tolerability align with the emerging needs of precision and sustained HIV management. Ongoing research into combination strategies and resistance dynamics will further define its role in achieving durable viral suppression and epidemic control.

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