

Revolutionizing HIV treatment: unveiling the new frontiers of HIV capsid research

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ABSTRACT

The HIV-1 capsid protein (CA) plays a crucial role in viral replication by orchestrating nuclear entry through interactions with host nuclear pore complexes (NPCs). Recent research has revealed that HIV-1 CA actively disrupts NPC architecture via phenylalanine-glycine (FG)-repeat nucleoporin interactions, thereby enabling nuclear translocation of viral components. This mechanistic insight has driven the development of lenacapavir, the first-in-class CA inhibitor approved for multidrug-resistant HIV-1. Lenacapavir competitively blocks CA-NPC binding, stabilizes cytoplasmic capsids, disrupts viral maturation, and demonstrates pan-stage antiviral efficacy and long-acting pharmacokinetics. Clinical trials have indicated its 100% prophylactic efficacy and potential to decrease global HIV incidence. Advances in structural biology, molecular dynamics simulations, and nanotechnology are expected to further inform next-generation therapeutic strategies targeting CA-host interactions. These findings not only redefine HIV-1 treatment paradigms but also have broader implications for combating CA-dependent viruses.

Keywords: HIV-1 Capsid Protein, Lenacapavir, Nuclear Pore Complex, Nuclear Translocation, Drug Design

Human immunodeficiency virus (HIV), particularly HIV-1, is the primary cause of the global AIDS pandemic. Each year, millions of new HIV infections and hundreds of thousands of AIDS-related deaths occur, thus posing a critical public health issue. Although antiretroviral therapy (ART) has improved survival and quality of life, its long-term efficacy is limited by several factors [1]. HIV-1's genetic variability leads to drug-resistant variants, thereby often causing treatment failure. Additionally, the complex lifelong regimens required for ART pose substantial physical and psychological burdens on patients, and decrease therapeutic adherence and success. These challenges increase the risk of emergence and spread of multidrug-resistant strains. Therefore, developing next-generation therapies that prevent resistance through targeting new mechanisms is essential.

The HIV-1 capsid protein (CA) is a critical structural component that governs multiple stages of the viral life cycle, and orchestrates essential processes in viral replication and infectivity. During early infection, CA stabilizes the viral core within the cytoplasm; facilitates

nuclear transport through interactions with nucleoporins, such as NUP358 and NUP153; and guides viral DNA integration into host chromatin by binding the host factor Cleavage and polyadenylation specificity factor 6 (CPSF6) [2]. In late stages, CA mediates virion assembly and maturation, and proteolytic cleavage of the Gag polyprotein enables formation of the infectious conical capsid. Disrupting CA stability or maturation abolishes viral infectivity and therefore has therapeutic potential. In 2022, the U.S. Food and Drug Administration approved lenacapavir (LEN), the first-in-class CA inhibitor, for treating multidrug-resistant HIV-1 infections. This approval marked an important milestone in CA-based antiviral therapy and has spurred increased scientific investigation of CA's functional mechanisms during HIV-1 infection.

A recent landmark study by Martin Beck and Gerhard Hummer (*Cell*, 2025) has elucidated how HIV-1 CA exploits the nuclear pore complex (NPC), thereby facilitating nuclear entry (Figure 1A) [3]. Using super-resolution microscopy and cryo-electron tomography, the team demonstrated that intact CA hexamers accumulate at

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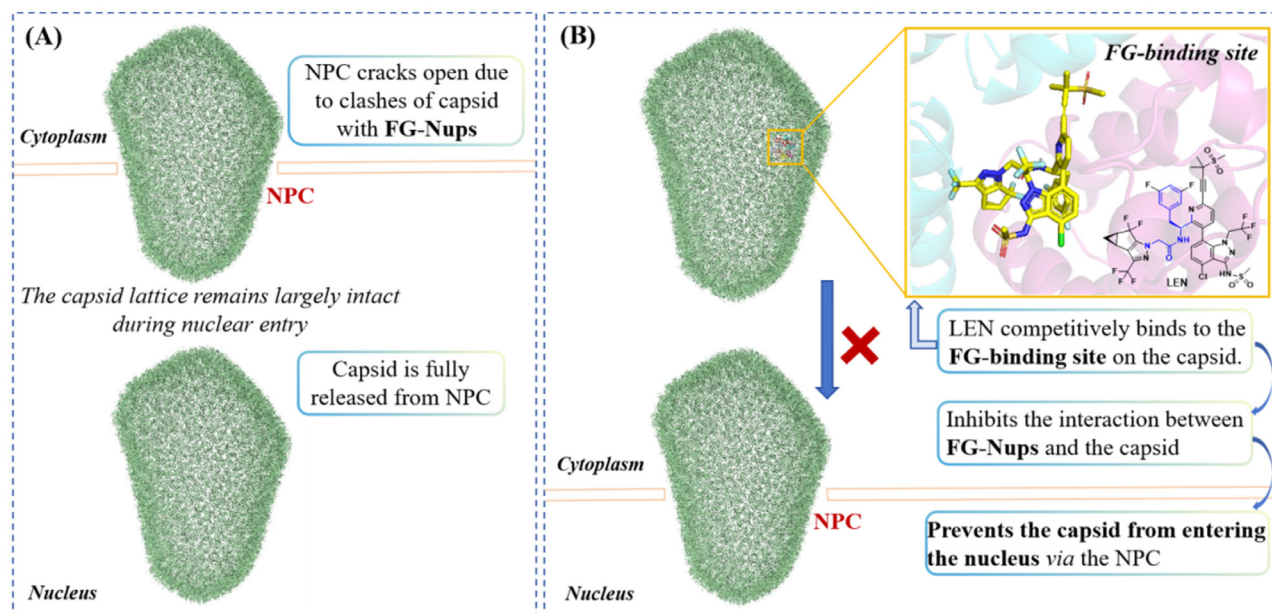


Figure 1 | (A) HIV-1 CA enters the nucleus through interaction with FG-Nups; (B) LEN prevents CA from entering the nucleus via the NPC. These figures were made in PyMOL, ChemDraw, and Microsoft Office PowerPoint (PPT).

NPCs and induce structural disruption during translocation. At 24–48 hours post-infection, a substantial number of CA-associated signals appeared in the nuclear envelope and within the nucleus, and 89% of nuclear-envelope-associated CA signals were closely associated with NPCs. This discovery suggests that the virus interacts with host cell structures in a dynamic process facilitating viral translocation through the nuclear envelope.

During traversal of the nuclear pore, the scaffold ring of the NPC undergoes structural disruption, particularly when the proximal (broader) end of the HIV-1 CA penetrates the central channel. Infected cells exhibited a markedly higher frequency of NPC rupture than uninfected controls. Therefore, HIV-1 CA actively disrupts rather than passively traverses NPC architecture, and uses its unique geometric and biomechanical properties to facilitate nuclear entry. This active disruption by HIV-1 CA demonstrates that an aggressive targeted viral strategy is necessary to overcome cellular barriers—a process critically dependent on the virus's unique geometric and biomechanical properties to achieve nuclear entry, an essential phase of the viral life cycle. According to molecular dynamics simulations, phenylalanine-glycine (FG)-repeat nucleoporins (Nups) induce expansion of the CA diameter during NPC transit. Intact NPCs sterically hinder CA passage, whereas structurally compromised or dilated NPCs permit translocation. The simulations further indicate energy minima transitions and tilting dynamics during CA-NPC interactions. This study provides novel insights into the mechanism of HIV-1 infection, highlighting the importance of the interplay between viral and host factors in the viral entry process.

Understanding these detailed mechanisms may potentially guide the development of therapeutic strategies that inhibit viral replication and spread by targeting the interaction between HIV-1 and the host cell's nuclear transport machinery.

Understanding this mechanism also has implications for the development of new diagnostic methods. The NPC disruption caused by HIV-1 CA might potentially serve as a biomarker for early HIV-1 infection, thereby enabling earlier intervention and treatment initiation, and improving patient prognosis. Moreover, this discovery might lead to the development of host-directed therapies. Instead of directly targeting the virus, these therapies would focus on strengthening the cell's defense mechanisms against viral invasion, such as by enhancing the integrity of the NPC or modulating the expression of host factors involved in the viral entry process.

LEN exemplifies the translational effects of such discoveries. By competitively binding FG-Nup interaction sites on CA, LEN blocks nuclear translocation and stabilizes the capsid in the cytoplasm, thereby preventing premature disassembly and shielding viral RNA from immune detection (Figure 1B). Additionally, by stabilizing CA integrity through multivalent binding, LEN prevents premature CA disassembly in the cytoplasm and shields viral genomic material from host immune surveillance. LEN demonstrates pan-stage antiviral activity, by additionally interfering with late-stage viral maturation through impairing proper Gag polyprotein processing, and consequently suppressing virion assembly and release. Furthermore, CA stabilization paradoxically potentiates

host innate immune responses *via* sustained exposure of viral nucleic acids to pattern recognition receptors. This multimodal mechanism confers broad-spectrum efficacy against resistant strains. Notably, as the pioneer long-acting CA inhibitor, LEN combines exceptional pharmacokinetic properties with high clinical efficacy. After its initial European Commission approval in August 2022, the agent received accelerated U.S. Food and Drug Administration authorization in December 2022 [4]. Recognized as a 2024 scientific breakthrough and ranked among the year's top ten scientific advancements globally, LEN has gained international scientific consensus support and revolutionized HIV therapeutics. Most recently, in January 2025, the China National Medical Products Administration (NMPA) granted marketing authorization for both tablet and injectable formulations, thus offering new salvage therapy options for adults with multidrug-resistant HIV-1 infections, particularly virologically uncontrolled patients in whom existing regimens have failed. LEN's approval in multiple regions has also spurred international collaborative research efforts aimed at further optimizing treatment regimens, and combining LEN with other antiretroviral agents in different sequences and dosages. These efforts are expected to explore the maximization of antiviral efficacy and minimization of potential adverse effects, and to address drug resistance more effectively. Additionally, real-world studies are being conducted to evaluate the long-term safety and effectiveness of LEN in diverse patient populations, including those with co-morbidities, such as hepatitis B or C viral infections, which are common among HIV-positive patients.

In vitro studies have demonstrated that LEN at picomolar concentrations exhibits potent antiviral activity markedly surpassing that of clinical ART agents (efavirenz and dolutegravir) [5]. Pharmacokinetic profiling revealed LEN's low predicted hepatic clearance and poor aqueous solubility—characteristics that facilitated its development as a long-acting, subcutaneously administered anti-HIV agent. Pharmacodynamic analyses have indicated that a single 927 mg subcutaneous dose achieves therapeutic plasma concentrations that are sustained for ≥ 6 months, owing to its extended elimination half-life. This parenteral administration approach bypasses solubility constraints while extending therapeutic duration. The compound is a promising candidate for HIV prevention strategies, because its prolonged-action profile significantly diminishes treatment burden and increases adherence. Future research may explore combinations of LEN with other antiviral agents to create more effective and safer treatments. Overall, LEN's unique profile signals a positive shift in managing multidrug-resistant HIV-1, and ongoing research will further clarify its role in the ever-evolving landscape of HIV treatment.

In a critical phase 3 trial in 2,500 adolescent girls and young women in sub-Saharan Africa, LEN has shown exceptional efficacy as a pre-exposure prophylaxis for HIV. The trial, conducted over a 24-month period,

reported zero seroconversions among participants receiving LEN, thus indicating a remarkable 100% efficacy rate (95% CI: 100–100). These findings not only highlight LEN's potential to substantially decrease global HIV incidence but also underscore its potential role in addressing the specific challenges faced by high-risk populations. Although LEN demonstrates exceptional clinical efficacy, the long-term risk of drug resistance remains a critical consideration. *In vitro* studies examining prolonged LEN exposure have identified rare CA mutations (e.g., M66I, Q67H, N74D, K70H, K70N, A105T, and T70N) that modestly decrease drug susceptibility while impairing viral fitness by destabilizing the CA hexamer lattice. Clinically, no emergent resistance has been observed in patients adherent for 48 weeks—a finding attributed to LEN's high genetic barrier, multi-stage mechanism (disrupting nuclear translocation and late-stage maturation), and long-acting pharmacokinetics that minimize subtherapeutic troughs. However, vigilance is warranted regarding compensatory mutations or alternative nuclear import pathways. Preclinical data highlight synergistic suppression of resistance when LEN is combined with integrase or reverse transcriptase inhibitors. Ongoing trials (e.g., NCT04825743) and future research should prioritize structural characterization of resistance mutations, real-world surveillance, and development of non-overlapping CA-targeting agents to further mitigate resistance risks.

Martin Beck's team has made a seminal contribution to the field by elucidating a groundbreaking mechanism through which HIV-1 actively subverts the structure of NPC and thereby achieves nuclear entry. This discovery not only resolves the long-standing mystery surrounding HIV-1's translocation across the NPC but also highlights the dynamic plasticity of NPC function, and suggests broad implications for understanding the nuclear transport mechanisms of macromolecular complexes, thus extending its relevance beyond HIV-1. In conjunction with the clinical advancements observed with LEN, this research provides a comprehensive analysis of the pharmacological design and biological strategies against HIV-1. As a pioneering long-acting HIV-1 CA inhibitor, LEN demonstrates significant therapeutic and prophylactic potential in combating HIV-1 infection. Its innovative mechanism of action provides critical insights for developing long-acting formulations targeting other viruses with a CA structure. The strategic design of LEN, which incorporates electron-withdrawing groups within a metabolically stable and conformationally constrained macrocyclic framework, enhances metabolic stability and decreases hepatic clearance, thereby enabling prolonged release through subcutaneous administration. This structural design serves as a valuable template for the development of next-generation long-acting therapeutics.

In summary, the convergence of mechanistic insights into HIV-1 CA biology and innovative drug design has ushered in a new era of antiviral therapy. Leveraging

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the distinctive mechanism of LEN and the profound biological insights regarding the interaction between HIV-1 CA and the NPC, future drug design efforts may focus on modulating the stability and maturation of the viral CA. Future drug design may also consider the use of nanotechnology. Nanoparticle-based drug delivery systems could be engineered to specifically target HIV-infected cells, thereby increasing the bioavailability and efficacy of anti-HIV drugs. For example, nanoparticles could be designed to encapsulate LEN or other potential CA-targeting drugs, and protect them against degradation in the body while enhancing their delivery to infection sites. Additionally, computational drug design techniques may be further optimized. Advanced molecular docking and simulation methods are expected to enable more accurate prediction of the binding affinity of potential drugs to the CA and NPC, and therefore accelerate the drug discovery process. Strategies aimed at either enhancing the structural integrity of CA to prevent its disassembly or disrupting its interaction with NPC may be used to inhibit nuclear import. Capitalizing on the advanced understanding of the virus-host interface and the dynamic responses of NPCs to viral components may enable the development of drugs that precisely target these interactions. This targeted approach to inhibiting viral replication and limiting its spread represents a new frontier in antiviral therapeutic development. Furthermore, these findings have major implications for the broader class of CA-enclosed viruses. The HIV-1 CA serves as a paradigmatic model, and the principles elucidated herein may be applicable to other viruses that rely on CA for their lifecycle. Understanding the mechanisms through which these viruses interact with host cellular structures such as NPCs, and developing drugs that disrupt these interactions, may open new avenues for

combating a range of viral infections. Consequently, the insights gained from studying HIV-1 CA and its interaction with the NPC may have far-reaching consequences with the potential to transform approaches to antiviral therapy across multiple viral diseases.

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CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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