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A Comprehensive Review of Lenacapavir: Pharmacology, Clinical Efficacy, Safety, and Future Directions

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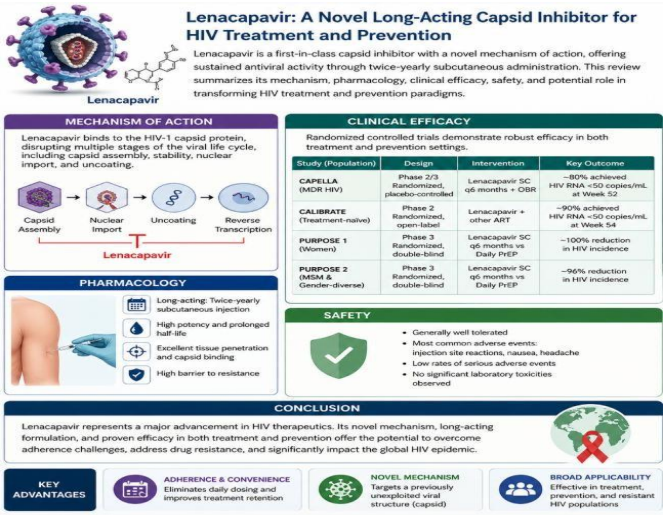
Abstract: *Lenacapavir represents a paradigm shift in antiretroviral therapy (ART) as the first-in-class inhibitor targeting the human immunodeficiency virus type 1 (HIV-1) capsid protein. Distinguished by its unique mechanism of action and ultra-long pharmacokinetic profile enabling biannual dosing, lenacapavir offers transformative potential in both treatment and prevention of HIV. This review critically evaluates the pharmacological properties, mechanism of action, pharmacokinetics, clinical efficacy in treatment-experienced populations, emerging data in pre- exposure prophylaxis (PrEP), safety profile, resistance patterns, and future directions. Current evidence indicates that lenacapavir achieves robust viral suppression in multidrug-resistant HIV, with favorable tolerability and minimal cross-resistance. Furthermore, clinical trials suggest near-complete efficacy in preventing HIV acquisition, positioning lenacapavir as a potential cornerstone in global HIV control strategies. Despite these advances, challenges including cost, accessibility, resistance evolution, and long-term safety remain. This review synthesizes current knowledge and highlights research gaps essential for optimizing its clinical integration*



Keywords: Lenacapavir, Pharmacology Lenacapavir, HIV treatment

I. INTRODUCTION

The global burden of human immunodeficiency virus (HIV) infection remains a profound public health challenge despite over four decades of scientific progress and the widespread implementation of combination antiretroviral therapy (ART). Although ART has transformed HIV infection from a fatal disease into a manageable chronic

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condition, persistent limitations- including lifelong adherence requirements, drug resistance, cumulative toxicity, and inequitable access to care- continue to impede efforts to achieve sustained viral suppression and ultimately end the epidemic.[1] In particular, the necessity for daily oral therapy presents a major barrier to long-term adherence, especially in resource-limited settings and among populations facing social stigma, unstable housing, or limited healthcare access. These challenges have catalyzed a paradigm shift in HIV therapeutics toward the development of long-acting agents capable of maintaining virologic control with infrequent dosing, thereby reducing the burden of treatment and improving patient outcomes.[2]

Within this evolving therapeutic landscape, lenacapavir has emerged as a groundbreaking innovation, representing the first clinically approved agent in a novel class of antiretroviral drugs known as capsid inhibitors. Unlike traditional ART regimens that target viral enzymes such as reverse transcriptase, protease, or integrase, lenacapavir acts on the HIV-1 capsid protein-a highly conserved structural component essential for multiple stages of the viral life cycle. The capsid plays a critical role in protecting the viral genome, facilitating intracellular trafficking, enabling nuclear import, and coordinating viral assembly and maturation. By targeting this multifunctional protein, lenacapavir exerts antiviral activity at several distinct stages of replication, distinguishing it mechanistically from all previously approved therapies and offering a promising strategy to overcome existing patterns of drug resistance.[3]

A defining feature of lenacapavir is its ultra-long pharmacokinetic profile, which allows for subcutaneous administration at six-month intervals following an initial oral lead-in phase. This biannual dosing schedule represents a significant advancement over existing long-acting formulations, such as monthly or bimonthly injectable regimens, and has profound implications for improving adherence, reducing healthcare system burdens, and enhancing patient quality of life. Moreover, lenacapavir has demonstrated potent antiviral activity in heavily treatment- experienced individuals with multidrug-resistant HIV, a population with limited therapeutic options and high unmet clinical need. Beyond treatment, emerging evidence from large-scale clinical trials indicates that lenacapavir may also play a transformative role in HIV prevention, achieving near-complete protection against viral acquisition when used as pre-exposure prophylaxis (PrEP). Despite its considerable promise, the integration of lenacapavir into clinical practice raises several important considerations. The long-acting nature of the drug, while advantageous for adherence, introduces challenges related to the management of adverse effects and drug resistance, as the medication cannot be rapidly cleared once administered. Additionally, issues related to cost, scalability, and healthcare infrastructure may limit its accessibility, particularly in low- and middle-income countries where the burden of HIV is greatest. Furthermore, long-term safety data, as well as evidence in special populations such as pregnant individuals and pediatric patients, remain limited and warrant further investigation. [4]

This review aims to provide a comprehensive and critical evaluation of lenacapavir, encompassing its molecular pharmacology, pharmacokinetic and pharmacodynamic properties, clinical efficacy in both treatment and prevention settings, safety and tolerability profile, and emerging challenges related to resistance and implementation. By synthesizing current evidence and identifying key knowledge gaps, this review seeks to contextualize lenacapavir within the broader trajectory of HIV therapeutics and to explore its potential role in shaping the future of HIV care and global eradication efforts.

II. MOLECULAR AND STRUCTURAL PHARMACOLOGY

2.1 HIV Capsid: Structure and Function:

The HIV-1 capsid is a highly organized and dynamic protein shell that plays a central role in viral replication, serving as both a protective enclosure for the viral genome and a regulatory hub for multiple stages of the viral life cycle. Structurally, the capsid is composed of approximately 1,500 copies of the capsid (CA) protein, which assemble into a fullerene-like conical core consisting of hexameric and pentameric units. This lattice structure exhibits both stability and flexibility, enabling it to withstand extracellular conditions while undergoing controlled disassembly, or "uncoating," upon entry into the host cell. Functionally, the capsid is indispensable for shielding viral RNA from host immune detection, facilitating reverse transcription within a protected microenvironment, and mediating intracellular

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trafficking along the cytoskeleton toward the nucleus. Importantly, the capsid also interacts with host cellular factors, such as nuclear pore proteins, to enable the import of viral DNA into the nucleus a critical step for integration into the host genome. Given its involvement in early and late stages of replication, as well as its high degree of structural conservation, the capsid represents an attractive yet historically underexploited target for antiretroviral drug development. [5,6]

2.2 Mechanism of Action of Lenacapavir

Lenacapavir exerts its antiviral activity by selectively binding to a conserved hydrophobic pocket located at the interface between adjacent capsid protein subunits within the hexameric lattice. This binding site is critical for maintaining capsid integrity and for mediating interactions with host cofactors required for viral replication. By occupying this pocket, lenacapavir disrupts the delicate balance of capsid stability, thereby interfering with both the structural assembly and functional dynamics of the capsid. Unlike traditional antiretroviral agents that target enzymatic processes such as reverse transcription or integration, lenacapavir acts on a structural protein and thereby affects multiple stages of the viral life cycle. This unique mechanism not only enhances antiviral potency but also reduces the likelihood of cross-resistance with existing drug classes. Furthermore, the high affinity and prolonged binding of lenacapavir to the capsid contribute to its sustained antiviral effect, which underpins its long-acting pharmacological profile. [7]

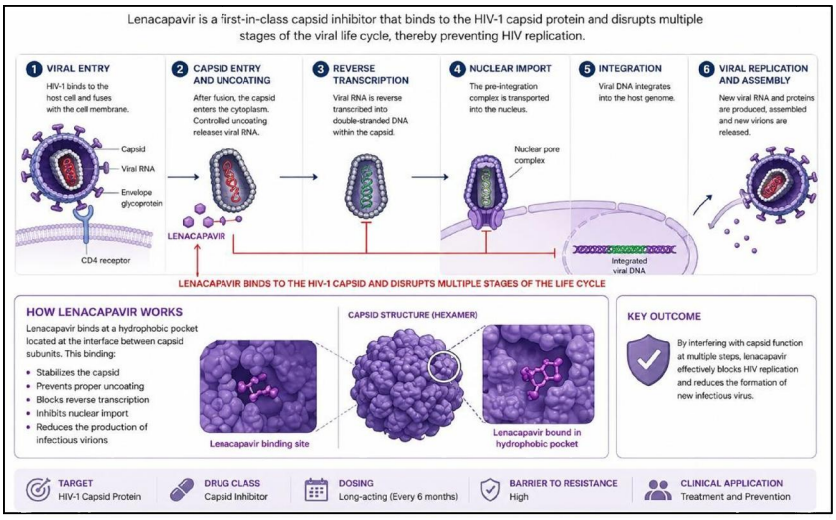

Figure 1: Mechanism of Action of Lenacapavir

Multi-Stage Inhibition: A defining characteristic of lenacapavir is its ability to inhibit HIV replication at multiple distinct stages, a feature that distinguishes it from all previously approved antiretroviral agents. During the early phase of infection, lenacapavir interferes with the proper disassembly of the capsid following viral entry, thereby impairing reverse transcription and preventing the efficient transport of viral DNA into the nucleus. This disruption of nuclear import is mediated in part through altered interactions between the capsid and host nuclear pore complexes, which are essential for the translocation of the pre-integration complex. In the intermediate stages, lenacapavir-induced capsid perturbations compromise the structural environment required for reverse transcription, leading to incomplete or defective viral DNA synthesis. In the late stages of the viral life cycle, lenacapavir inhibits the proper assembly of new capsid structures during virion formation, resulting in the production of immature or non- infectious viral particles. This multi-stage inhibition confers a high degree of antiviral efficacy and contributes to the drug's robustness against resistance development. [8]

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Capsid Hyperstabilization: One of the most distinctive mechanistic features of lenacapavir is its ability to induce capsid hyperstabilization, a phenomenon in which the capsid lattice becomes excessively rigid and resistant to the conformational changes required for normal viral replication. Under physiological conditions, the capsid must undergo a finely regulated process of uncoating to release the viral genome at the appropriate time and location within the host cell. Lenacapavir disrupts this process by binding tightly to the capsid and reinforcing intermolecular interactions within the lattice, thereby preventing timely disassembly. This "overstabilization" effectively traps the viral core in a non-functional state, blocking downstream replication events such as reverse transcription and integration.[9] Additionally, during virion assembly, hyperstabilization interferes with the proper formation of the capsid, leading to structurally defective viral particles that are incapable of initiating new rounds of infection. This dual impact on both incoming and outgoing virions underscores the unique antiviral strategy of lenacapavir.

2.3 Selectivity and Potency

Lenacapavir exhibits exceptional antiviral potency and selectivity, attributable to its high-affinity binding to a conserved region of the HIV-1 capsid protein that is not present in human host proteins. This selective targeting minimizes off-target effects and contributes to the drug's favorable safety profile. In vitro studies have demonstrated that lenacapavir retains activity at picomolar concentrations, highlighting its remarkable efficacy even at very low systemic levels. Moreover, because its mechanism of action is distinct from that of reverse transcriptase inhibitors, protease inhibitors, and integrase strand transfer inhibitors, lenacapavir shows no cross-resistance with these established drug classes. This makes it particularly valuable in the treatment of patients harboring multidrug-resistant HIV strains. While resistance-associated mutations in the capsid protein have been identified, they are relatively rare and often confer a fitness cost to the virus, further supporting the durability of lenacapavir's antiviral activity. Collectively, its high potency, structural specificity, and novel mechanism position lenacapavir as a cornerstone in the next generation of antiretroviral therapy. [10]

III. PHARMACOKINETICS AND PHARMACODYNAMICS

3.1 Absorption and Distribution

Lenacapavir exhibits a distinctive pharmacokinetic profile characterized by dual-phase administration involving an initial oral loading regimen followed by long-acting subcutaneous injections. The oral phase facilitates rapid attainment of therapeutic plasma concentrations, ensuring early viral suppression, while the subcutaneous formulation establishes a sustained- release drug depot within the interstitial tissue. Following subcutaneous administration, lenacapavir is slowly absorbed into systemic circulation, resulting in prolonged and stable plasma concentrations over extended periods. The drug demonstrates extensive tissue distribution, including penetration into lymphoid tissues, which are key reservoirs for HIV replication. Its high degree of plasma protein binding further contributes to a controlled release and prolonged systemic exposure. Importantly, the distribution profile supports consistent antiviral activity across anatomical compartments, enhancing its overall therapeutic effectiveness. [11]

3.2 Long-Acting Profile

A defining feature of lenacapavir is its ultra-long-acting pharmacokinetic behavior, which is primarily driven by its low systemic clearance, high metabolic stability, and slow release from the subcutaneous depot. After injection, the drug exhibits a biphasic absorption pattern consisting of an initial phase of relatively faster release followed by a prolonged terminal phase characterized by gradual diffusion into circulation. This sustained-release mechanism maintains drug concentrations well above the effective inhibitory threshold for HIV replication over several months. The molecular properties of lenacapavir, including its lipophilicity and structural stability, further enhance its persistence within the body. This long-acting profile distinguishes lenacapavir from earlier injectable antiretrovirals that require monthly or bimonthly administration, thereby representing a substantial advancement in dosing convenience and adherence potential. [12]

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3.3 Half-Life and Dosing

Lenacapavir possesses an exceptionally long apparent half-life, which underpins its ability to be administered at six-month intervals. Following subcutaneous injection, the terminal half-life extends over several weeks to months, allowing for sustained therapeutic drug levels without the need for frequent dosing. The standard dosing regimen typically includes an oral lead-in phase to rapidly achieve target plasma concentrations, followed by maintenance therapy with subcutaneous injections administered every 26 weeks. This biannual dosing schedule is unprecedented in antiretroviral therapy and reflects the drug's unique pharmacokinetic characteristics. However, the prolonged half-life also implies that once administered, the drug remains in the system for an extended duration, which has implications for both efficacy and safety management. [13]

3.4 Pharmacodynamic Effects

The pharmacodynamic activity of lenacapavir is closely linked to its sustained plasma concentrations and high binding affinity for the HIV capsid protein. The drug demonstrates rapid antiviral effects, with significant reductions in viral load observed shortly after initiation of therapy. Its prolonged exposure ensures continuous inhibition of viral replication, minimizing the risk of viral rebound between doses. The relationship between plasma concentration and antiviral activity indicates a strong and consistent suppression of viral replication when drug levels are maintained above the inhibitory threshold. Additionally, the multi-stage mechanism of action contributes to its potent pharmacodynamic profile, as it interferes with several critical steps in the viral life cycle simultaneously. This results in a high barrier to resistance and durable virologic control when used in combination with other antiretroviral agents. [14]

3.5 Clinical Implications

The pharmacokinetic and pharmacodynamic properties of lenacapavir have significant clinical implications, particularly in the context of long-term HIV management and prevention. The extended dosing interval substantially reduces the burden of daily medication adherence, which is a major determinant of treatment success in conventional ART regimens. This feature is especially beneficial for individuals with adherence challenges, including those in resource- limited settings or experiencing social and structural barriers to consistent care. Furthermore, the stable drug exposure achieved with lenacapavir minimizes fluctuations in plasma concentrations, thereby reducing the risk of subtherapeutic levels and resistance development. However, the long-acting nature of the drug also presents challenges, as adverse effects or drug–drug interactions cannot be rapidly mitigated once the drug has been administered. Additionally, missed doses or delays in scheduled injections may result in prolonged periods of suboptimal drug levels, potentially increasing the risk of resistance. Therefore, careful patient selection, adherence to dosing schedules, and ongoing clinical monitoring are essential to fully realize the therapeutic benefits of lenacapavir. [15]

IV. CLINICAL EFFICACY IN HIV TREATMENT

4.1 Multidrug-Resistant HIV

Lenacapavir has demonstrated substantial clinical value in the management of multidrug- resistant HIV-1 infection, a population characterized by limited therapeutic options and a high risk of virologic failure. Patients with extensive resistance to multiple antiretroviral classes- including nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and integrase strand transfer inhibitors- often experience suboptimal viral suppression and disease progression despite optimized regimens. In this context, lenacapavir provides a novel mechanism of action that retains activity against resistant viral strains, thereby offering a critical therapeutic alternative.[16] Its ability to target the structurally conserved capsid protein enables effective viral inhibition even in the presence of complex resistance mutations, making it particularly suitable for heavily treatment-experienced individuals. Clinical use in this population has shown meaningful reductions in viral load and improved rates of virologic suppression when combined with an optimized background regimen.

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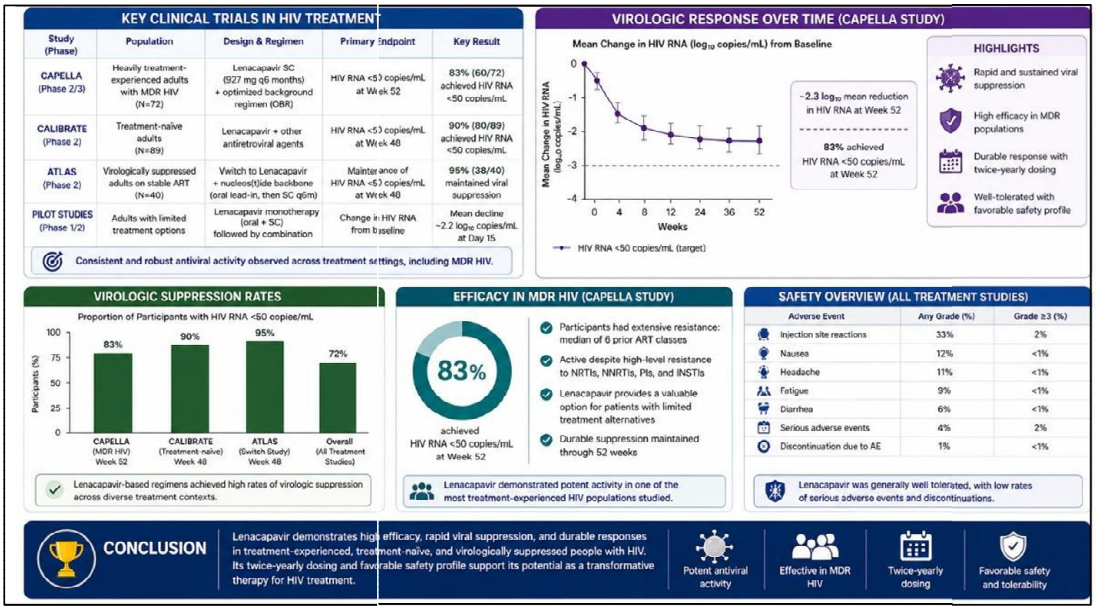

Figure 2: Clinical Efficacy in HIV Treatment

4.2 Phase 2/3 Trial Data

The clinical efficacy of lenacapavir has been rigorously evaluated in Phase 2 and Phase 3 trials involving heavily treatment-experienced patients with multidrug-resistant HIV. These studies typically employed a design incorporating an initial oral lead-in phase followed by long-acting subcutaneous administration in combination with background antiretroviral therapy tailored to individual resistance profiles. Results from these trials have consistently demonstrated significant antiviral activity, with rapid declines in plasma HIV RNA levels observed shortly after treatment initiation. In pivotal studies, a large proportion of participants achieved clinically meaningful reductions in viral load during the early treatment phase, followed by sustained virologic suppression over extended follow-up periods. Importantly, these trials also highlighted the durability of response, with many patients' maintaining viral suppression at 48 to 52 weeks and beyond, underscoring the long-term efficacy of lenacapavir-based regimens in a difficult-to- treat population. [17-18]

4.3 Virologic Outcomes

Virologic outcomes associated with lenacapavir therapy have been notably favorable, particularly given the complexity of the patient populations studied. High proportions of patients achieved viral suppression to levels below 50 copies/mL, which is the standard benchmark for effective HIV treatment. In addition to achieving suppression, lenacapavir has been shown to sustain low viral loads over prolonged periods, reflecting its robust and durable antiviral activity. The magnitude of viral load decline observed with lenacapavir are comparable to, and in some cases exceed, those seen with conventional antiretroviral regimens, despite being used in patients with extensive treatment histories. Furthermore, the maintenance of virologic control with infrequent dosing intervals represents a significant advancement in therapeutic convenience without compromising efficacy. These outcomes collectively support the role of lenacapavir as a potent component of salvage therapy in resistant HIV infection. [19]

4.4 Special Populations

Lenacapavir has shown promising efficacy across a range of special populations, particularly those who have historically been underrepresented or face unique challenges in HIV treatment. In heavily treatment-experienced

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individuals, including those with advanced disease and prior treatment failures, lenacapavir has demonstrated consistent antiviral activity when used in combination with optimized background regimens. Additionally, its long-acting formulation offers potential advantages for individuals with adherence difficulties, including those experiencing unstable housing, mental health conditions, or social stigma. However, data remain limited in certain populations, including pregnant individuals, pediatric patients, and those with significant comorbidities such as hepatic or renal impairment. Ongoing clinical studies are expected to provide further insights into the safety and efficacy of lenacapavir in these groups. Nonetheless, the available evidence suggests that lenacapavir may play an important role in expanding treatment options for diverse patient populations with unmet clinical needs. [20]

4.5 Comparative Efficacy

When compared to conventional antiretroviral therapies, lenacapavir demonstrates comparable or superior efficacy, particularly in the context of multidrug-resistant HIV infection. Its novel mechanism of action and lack of cross-resistance with existing drug classes provide a distinct advantage in patients who have exhausted standard treatment options. Moreover, the long-acting nature of lenacapavir allows for sustained drug exposure and consistent viral suppression, which may reduce the risk of treatment interruptions and subsequent virologic rebound. Emerging data also suggest that lenacapavir-based regimens may achieve non-inferiority to standard-of-care therapies in broader patient populations, although further comparative studies are needed to confirm these findings. Importantly, the ability to maintain high levels of efficacy with significantly reduced dosing frequency represents a paradigm shift in HIV treatment, potentially redefining standards of care and improving long-term patient outcomes. [21-22]

V. CLINICAL EFFICACY IN HIV PREVENTION

Lenacapavir has emerged as a highly promising agent in the field of HIV prevention, particularly in the context of pre-exposure prophylaxis (PrEP), where adherence to daily oral regimens has historically limited real-world effectiveness. [23] Its ultra-long-acting pharmacokinetic profile, allowing for subcutaneous administration every six months, addresses one of the most critical barriers in HIV prevention—consistent adherence—by eliminating the need for daily or even monthly dosing. Clinical trials evaluating lenacapavir for PrEP have demonstrated remarkably high levels of efficacy, with near-complete protection against HIV acquisition observed across diverse study populations. In large-scale randomized studies, the incidence of HIV infection among individuals receiving lenacapavir was reduced to extremely low or even zero levels, significantly outperforming traditional oral PrEP regimens in terms of adherence-adjusted effectiveness. [24]

The mechanism underlying this high level of protection is closely linked to the drug's sustained plasma concentrations, which remain well above the threshold required to inhibit viral replication for extended periods.[25] This continuous exposure ensures that individuals are protected even in the absence of daily adherence, making lenacapavir particularly advantageous for populations at high risk of HIV acquisition, including those facing structural, behavioral, or social barriers to consistent medication use. Furthermore, its discreet dosing schedule may reduce stigma associated with HIV prevention, thereby improving uptake and retention in PrEP programs.

In addition to its efficacy, lenacapavir has demonstrated a favorable safety profile in prevention studies, with adverse events similar to those observed in treatment settings, primarily consisting of mild injection-site reactions. Importantly, no significant safety concerns have emerged that would limit its use in otherwise healthy individuals. However, as with its use in treatment, the long-acting nature of the drug introduces considerations related to the pharmacokinetic "tail," during which subtherapeutic drug levels may persist after discontinuation, potentially increasing the risk of resistance if HIV exposure occurs during this period. This underscores the importance of appropriate patient counseling, HIV testing prior to each dose, and careful follow-up. [26]

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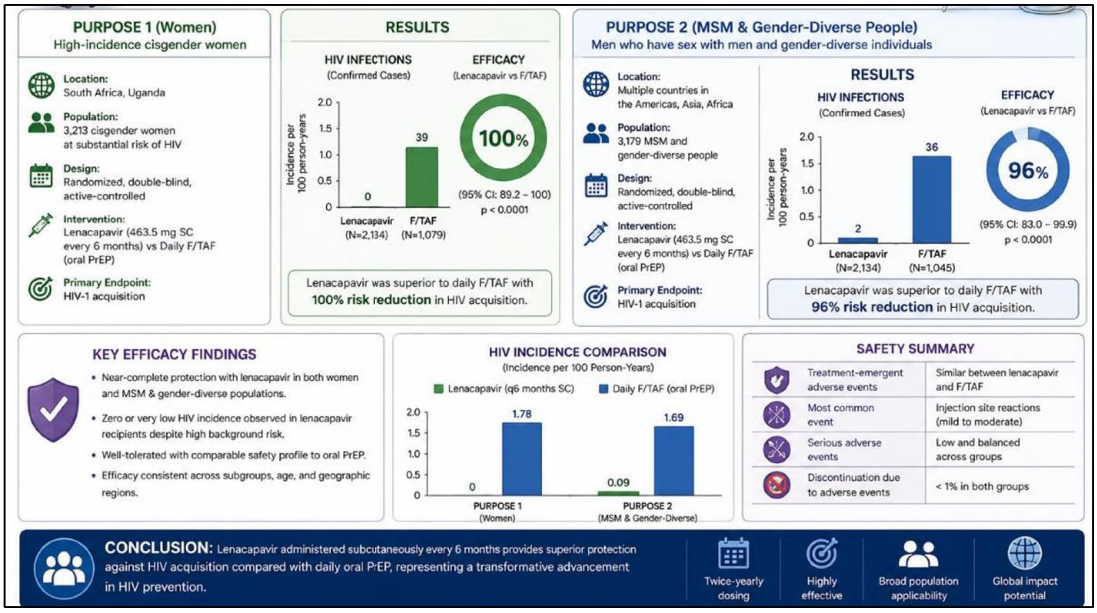

Figure 3: Clinical Efficacy in HIV Prevention

From a public health perspective, the introduction of lenacapavir as a twice-yearly PrEP option has the potential to significantly alter the trajectory of the HIV epidemic. By improving adherence and expanding access to effective prevention, particularly in high-incidence regions and underserved populations, lenacapavir could contribute to substantial reductions in new HIV infections. Its integration into global HIV prevention strategies may represent one of the most impactful advancements since the introduction of oral PrEP, with the potential to bridge gaps in prevention coverage and move closer to the goal of ending the HIV epidemic.[27]

Table 1: Characteristics of Randomized Controlled Trials Evaluating Lenacapavir in HIV Treatment and Prevention

Trial Name	Phase	Population	Study Design	Intervention	Comparator	Primary Endpoint	Key Outcomes	Clinical Significance
CAPELLA	Phase 2/3	Heavily treatment-experienced adults with multidrug-resistant HIV-1	Randomized, double-blind (initial phase), placebo-controlled	Oral lead-in + SC lenacapavir every 6 months + optimized background regimen (OBR)	Placebo + OBR (functional monotherapy phase)	≥0.5 $\log_{10}$ reduction in HIV RNA at Day 15	Significant viral load reduction; ~80% achieved <50 copies/mL at Week 52	Established efficacy in salvage therapy; led to regulatory approval
CALIBRATE	Phase 2	Treatment-naïve adults with HIV-1	Randomized, open-label	Lenacapavir + other ART (various regimens including injectable maintenance)	Standard oral ART regimens	Proportion with HIV RNA <50 copies/mL at Week 54	High rates of viral suppression comparable to standard ART	Demonstrated feasibility in treatment-naïve population

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PURPOSE 1	Phase 3	Cisgender women at high risk of HIV (sub-Saharan Africa)	Randomized, double-blind, active-controlled	SC lenacapavir every 6 months	Daily oral PrEP (e.g., TDF/FTC)	HIV incidence rate	~100% reduction in HIV infections (0 cases in lenacapavir arm)	Landmark prevention efficacy; potential PrEP paradigm shift
PURPOSE 2	Phase 3	MSM and gender-diverse individuals at risk of HIV	Randomized, double-blind, active-controlled	SC lenacapavir every 6 months	Daily oral PrEP	HIV incidence rate	~96% reduction in HIV incidence vs comparator	Confirmed broad population efficacy in prevention
PURPOSE 3 (ongoing)	Phase 3	Diverse global populations at risk	Randomized	Long-acting lenacapavir regimens	Standard PrEP	HIV prevention efficacy	Ongoing	Expands generalizability across regions
BIC/Lenacapavir Studies	Phase 3 (ongoing)	Virologically suppressed adults	Randomized, active-controlled	Bictegravir + lenacapavir (oral or long-acting combinations)	Standard ART	Maintenance of viral suppression	Early data suggest non-inferiority	Supports simplified and long-acting regimens
Once-Yearly Lenacapavir (investigational)	Phase 1/2	Healthy participants / at-risk populations	Randomized, dose-escalation	Intramuscular once-yearly lenacapavir	Placebo	Safety, PK, drug levels	Sustained therapeutic levels >52 weeks	Potential for annual HIV prevention

Table 2: Summary of Clinical Contexts and Outcomes from Randomized Controlled Trials of Lenacapavir

Clinical Context	Trial Population	Study Design Context	Intervention Strategy	Primary Clinical Outcome	Key Results	Interpretation
Salvage Therapy (Multidrug-Resistant HIV)	Heavily treatment-experienced adults with resistance to ≥2 ART classes	Randomized, placebo-controlled (functional monotherapy phase followed by combination therapy)	Oral lead-in + subcutaneous lenacapavir every 6 months + optimized background regimen (OBR)	Reduction in HIV RNA; proportion achieving viral suppression (<50 copies/mL)	Rapid viral load decline; ~75–85% achieved suppression at 52 weeks	Demonstrates high efficacy in patients with limited options; supports use in resistant HIV
Treatment-Naïve HIV Infection	Newly diagnosed, ART-naïve adults	Randomized, open-label comparative design	Lenacapavir-based combination regimens (including long-acting maintenance	Virologic suppression at 48–54 weeks	High rates of suppression comparable to standard ART (>85–90%)	Suggests potential for first-line use; supports simplification strategies

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			strategies)			
Maintenance Therapy (Switch Strategy)	Virologically suppressed adults on stable ART	Randomized, active-controlled	Switch to lenacapavir-containing regimens (oral or long-acting combinations)	Maintenance of viral suppression	Non-inferior to standard therapy; sustained suppression in majority	Supports role in regimen simplification and long- acting maintenance
Pre-Exposure Prophylaxis (PrEP) – Women	Cisgender women at high risk (high-incidence regions)	Randomized, double- blind, active-controlled	Subcutaneous lenacapavir every 6 months	HIV incidence rate	Near 100% risk reduction; zero or extremely low infection rates	Represents breakthrough in HIV prevention; overcomes adherence barriers
Pre-Exposure Prophylaxis (PrEP) – MSM & Gender-Diverse Populations	Men who have sex with men (MSM) and gender-diverse individuals	Randomized, double- blind, active-controlled	Subcutaneous lenacapavir every 6 months	HIV incidence rate	~90–96% reduction in HIV acquisition compared to oral PrEP	Confirms broad population efficacy; supports global PrEP expansion
Bridging / Dosing Interruption Management	Patients unable to receive scheduled injections	Randomized or extension study contexts	Oral lenacapavir bridging between injections	Maintenance of viral suppression during interruption	>90–95% maintained suppression	Provides flexibility in real-world clinical settings
Ultra-Long-Acting Investigational Use	Healthy individuals or at-risk populations	Early-phase randomized trials	Annual or extended-duration lenacapavir formulations	Pharmacokinetic thresholds and safety	Sustained drug levels above protective thresholds for ≥12 months	Suggests feasibility of once-yearly dosing for prevention

VI. SAFETY AND TOLERABILITY

Lenacapavir has demonstrated an overall favorable safety and tolerability profile across clinical trials and early real-world use, with most adverse events being mild to moderate in severity and rarely leading to treatment discontinuation. The most commonly reported adverse effects are injection-site reactions associated with subcutaneous administration, including pain, erythema, swelling, and the formation of nodules or indurations. These reactions are generally transient, self-limiting, and decrease in frequency with subsequent doses, although in some cases nodules may persist for extended periods due to the drug's depot formulation. Systemic adverse effects are less frequent and typically include mild gastrointestinal symptoms such as nausea and diarrhea, as well as occasional fatigue or headache. Laboratory abnormalities have been reported, including mild elevations in hepatic transaminases, but clinically significant hepatotoxicity appears to be rare.[28]

Importantly, the long-acting pharmacokinetic profile of lenacapavir introduces unique safety considerations. Once administered, the drug cannot be rapidly withdrawn, and any adverse effects or drug–drug interactions may persist for

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an extended duration due to its prolonged half- life. This necessitates careful patient selection, baseline evaluation, and monitoring during therapy. Additionally, as with other antiretroviral agents, there is a potential risk of immune reconstitution inflammatory syndrome (IRIS) in patients initiating therapy with advanced immunosuppression, although this has not emerged as a major concern in available data. Drug– drug interactions, particularly involving metabolic pathways such as cytochrome P450 enzymes and transport proteins, must also be considered when co-administering lenacapavir with other medications, especially in patients receiving complex treatment regimens.

Another important safety consideration relates to the risk of resistance development in the setting of suboptimal drug exposure, such as delayed dosing or incomplete adherence to injection schedules. Given the prolonged pharmacokinetic "tail" following discontinuation, there is a theoretical window during which drug concentrations may fall below therapeutic levels while still exerting selective pressure on the virus, potentially facilitating resistance emergence. Despite these concerns, current evidence suggests that lenacapavir maintains a high barrier to resistance when used appropriately in combination with other active agents. Overall, its safety profile, combined with its dosing convenience, supports its use as a well-tolerated and effective option in both treatment-experienced individuals and emerging prevention strategies, provided that appropriate clinical monitoring and adherence to dosing schedules are maintained.[29]

VII. RESISTANCE AND VIROLOGIC FAILURE

Resistance to lenacapavir, while relatively uncommon compared to many traditional antiretroviral agents, represents an important consideration in its clinical use, particularly given its long-acting pharmacokinetic profile and unique mechanism of action targeting the HIV-1 capsid. Lenacapavir exhibits a high genetic barrier to resistance due to its potent binding to a highly conserved region of the capsid protein; however, resistance-associated mutations can emerge under conditions of incomplete viral suppression, especially when the drug is used in the presence of insufficiently active background therapy. Identified resistance mutations typically occur within the capsid protein at or near the drug-binding interface, altering the structural conformation and reducing lenacapavir binding affinity. Some of these mutations, while conferring reduced susceptibility, may also impair viral fitness, which can limit their persistence in the absence of drug pressure.[30]

Virologic failure during lenacapavir therapy is most often associated with suboptimal adherence to accompanying antiretroviral agents or delayed dosing in the context of its long-acting formulation. Because lenacapavir is not intended for use as monotherapy, its efficacy depends on combination with other fully active drugs; failure to achieve a sufficiently suppressive regimen increases the risk of ongoing viral replication and subsequent resistance development. Additionally, the prolonged pharmacokinetic "tail" following discontinuation or missed doses presents a unique challenge, as drug concentrations may decline to subtherapeutic levels while still exerting selective pressure on the virus. This creates a window during which resistant variants may emerge and proliferate, particularly if viral replication is not fully suppressed. Clinical trial data indicate that resistance to lenacapavir remains relatively infrequent when the drug is used appropriately, with most patients achieving and maintaining durable virologic suppression. However, in cases where resistance does develop, it may compromise future treatment options involving capsid inhibitors, given the shared mechanism within this drug class. Importantly, lenacapavir retains activity against viruses resistant to other antiretroviral classes, and there is currently no evidence of cross-resistance with reverse transcriptase inhibitors, protease inhibitors, or integrase inhibitors. This reinforces its value as a salvage therapy in multidrug-resistant HIV infection.[31]

Effective management of resistance and prevention of virologic failure with lenacapavir requires careful patient selection, resistance testing prior to initiation, and the construction of an optimized background regimen containing at least one or preferably two fully active agents. Regular monitoring of viral load is essential to detect early signs of treatment failure, and prompt intervention is necessary if virologic rebound occurs. In addition, strict adherence to dosing schedules, including timely administration of maintenance injections, is critical to maintaining therapeutic drug levels and minimizing the risk of resistance emergence. As long-term real-world data continue to accumulate, further

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insights into resistance patterns and optimal management strategies will be essential to fully harness the clinical potential of lenacapavir.[32]

VIII. ADVANTAGES OVER CONVENTIONAL ANTIRETROVIRAL THERAPY

Lenacapavir offers several decisive advantages over conventional antiretroviral therapy (ART), fundamentally reshaping the approach to HIV management through improvements in adherence, mechanism of action, and clinical versatility. A major limitation of traditional ART has been the requirement for strict daily dosing, which often leads to suboptimal adherence and treatment fatigue over time. In contrast, lenacapavir's ultra-long-acting formulation, administered as a subcutaneous injection every six months, effectively eliminates the need for daily medication, thereby reducing pill burden and simplifying treatment routines. This shift significantly improves treatment retention and consistency, particularly in populations facing adherence challenges due to social stigma, mental health conditions, or limited access to healthcare services. By maintaining sustained therapeutic drug levels without daily dosing, lenacapavir reduces the risk of virologic rebound associated with missed doses, representing a substantial advancement in long-term HIV care. [33]

Beyond its pharmacokinetic benefits, lenacapavir introduces a novel mechanism of action by targeting the HIV-1 capsid protein, a previously unexploited viral structure essential for multiple stages of the viral life cycle. Unlike conventional ART classes that inhibit viral enzymes such as reverse transcriptase, protease, or integrase, lenacapavir disrupts capsid function, thereby interfering with viral replication at several points simultaneously. This unique approach not only enhances antiviral potency but also avoids cross-resistance with existing drug classes, making it particularly valuable in the treatment of multidrug-resistant HIV infections. [34]

Furthermore, lenacapavir demonstrates broad applicability across both therapeutic and preventive contexts. Clinically, it has proven highly effective in heavily treatment-experienced patients with resistant HIV, offering a viable option where standard regimens may fail. Simultaneously, its role in pre-exposure prophylaxis (PrEP) has shown near-complete efficacy in preventing HIV acquisition, positioning it as a powerful tool in global HIV prevention strategies. This dual utility—spanning treatment and prevention—distinguishes lenacapavir from most conventional therapies and underscores its potential to redefine standards of care. Collectively, these advantages highlight lenacapavir as a next-generation antiretroviral agent that addresses longstanding limitations of traditional ART while expanding the possibilities for effective and sustainable HIV control. [35]

IX. ADVANTAGES AND LIMITATIONS OF LENACAPAVIR

Lenacapavir represents a significant advancement in antiretroviral therapy, offering multiple advantages that distinguish it from conventional HIV treatments, while also presenting important limitations that must be carefully considered in clinical practice. One of its most notable advantages is its ultra-long-acting dosing schedule, which allows for subcutaneous administration every six months, thereby substantially reducing the burden of daily medication adherence.[36] This feature has profound implications for improving treatment retention, particularly among individuals who face challenges with consistent oral therapy due to social, behavioral, or structural factors. Additionally, its novel mechanism of action targeting the HIV capsid protein provides potent antiviral activity against multidrug-resistant strains, with no cross- resistance to existing antiretroviral classes. This makes lenacapavir an invaluable option for heavily treatment-experienced patients with limited alternatives. Its high potency, sustained pharmacokinetic profile, and ability to maintain consistent drug levels further contribute to durable virologic suppression and reduced risk of viral rebound. [37]

However, these advantages are accompanied by several limitations. The long-acting nature of lenacapavir, while beneficial for adherence, poses challenges in the management of adverse effects, as the drug cannot be rapidly eliminated once administered. [38]

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X. FUTURE DRUG DESIGN STRATEGIES

The success of lenacapavir has catalyzed renewed interest in capsid-targeting therapeutics and informed the next generation of antiviral drug design. Advances in structural biology and computational modeling are enabling the identification of novel binding sites and the optimization of molecular interactions to enhance potency, selectivity, and resistance profiles. Future capsid inhibitors may build upon the structural framework of lenacapavir while incorporating modifications that improve pharmacokinetics, reduce injection-site reactions, or enable alternative routes of administration. [39]

In addition to capsid inhibitors, the principles underlying lenacapavir's development are being applied to other viral targets, with an emphasis on long-acting formulations and multi-stage mechanisms of action. Combination strategies involving multiple long-acting agents are also a key focus, with the goal of achieving fully injectable regimens that provide comprehensive viral suppression with minimal dosing frequency. Furthermore, integration with emerging technologies such as nanoparticle delivery systems and implantable drug reservoirs may further extend dosing intervals and enhance patient convenience. [40]

Collectively, these innovations represent a shift toward precision-designed, long-acting therapeutics that address both biological and behavioral aspects of HIV management.

Lenacapavir serves as a proof of concept for this approach, demonstrating that targeting structural components of the virus can yield highly effective and durable treatments, while also opening new avenues for research and development in the pursuit of improved HIV therapies and, ultimately, a functional cure. [41]

XI. FUTURE DIRECTIONS

The future development of lenacapavir is poised to significantly influence both therapeutic and preventive strategies in HIV management, with several key areas of advancement currently under active investigation. One of the most impactful directions is its expansion into global pre- exposure prophylaxis (PrEP) programs, where its twice-yearly dosing schedule has the potential to overcome major adherence barriers that have limited the effectiveness of daily oral regimens. By simplifying prevention strategies and improving retention in care, lenacapavir could play a central role in reducing HIV incidence, particularly in high-burden regions and among vulnerable populations. In parallel, the development of combination long-acting regimens represents another critical frontier, with ongoing research focused on pairing lenacapavir with other extended-duration antiretroviral agents to create fully injectable, infrequently administered treatment options that could eliminate the need for daily oral therapy altogether. Such regimens may further enhance adherence, reduce stigma, and streamline HIV care delivery. [42]

Beyond treatment and prevention, lenacapavir is also being explored as a component of broader HIV cure strategies. Its unique ability to interfere with multiple stages of the viral life cycle, including capsid stability and nuclear import, positions it as a potential tool in approaches aimed at targeting viral reservoirs and achieving sustained virologic remission without continuous therapy. While a definitive cure remains elusive, integrating capsid inhibitors into "shock-and- kill" or "block-and-lock" strategies may offer new avenues for long-term viral control. Additionally, ongoing efforts in structural optimization of capsid inhibitors aim to further enhance potency, resistance barriers, and pharmacokinetic properties. Advances in medicinal chemistry and structural biology are expected to yield next-generation molecules with improved binding characteristics and broader activity against resistant variants. Collectively, these future directions highlight the transformative potential of lenacapavir not only as a standalone agent but also as a cornerstone in the evolving landscape of long-acting and potentially curative HIV interventions. [43-44]

XII. ONGOING CLINICAL TRIALS

Lenacapavir continues to be the focus of an extensive and rapidly evolving clinical trial portfolio, reflecting its broad potential across HIV treatment, prevention, and next-generation therapeutic strategies. Current ongoing trials span multiple phases (Phase 1–Phase 3) and investigate diverse applications, including long-acting pre-exposure prophylaxis (PrEP), novel dosing regimens, combination therapies, and use in special populations. [45, 46]

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One of the most prominent areas of ongoing research involves large-scale Phase 3 prevention trials, notably the PURPOSE 1 and PURPOSE 2 studies, which evaluated twice-yearly subcutaneous lenacapavir for PrEP. These trials demonstrated exceptionally high efficacy up to 100% protection in women and approximately 96% in predominantly male populations over 52 weeks-leading to regulatory approval and strong recommendations from public health authorities . Building on these findings, additional follow-up and extension studies are ongoing to assess long-term safety, durability of protection, and real-world implementation outcomes. [47] Beyond twice-yearly dosing, current clinical research is exploring ultra-long-acting formulations, including once-yearly lenacapavir. Phase 1 trials presented at major scientific conferences (e.g., CROI 2025) have demonstrated that single-dose intramuscular formulations can maintain plasma concentrations above protective thresholds for over 52 weeks, supporting progression to planned Phase 3 trials. If successful, these studies could further reduce dosing frequency and redefine standards for HIV prevention. [48]

In the treatment domain, ongoing trials are investigating novel combination regimens, particularly integrating lenacapavir with other antiretroviral agents to develop simplified or fully long-acting therapies. Notably, Phase 3 studies are evaluating combinations such as bictegravir– lenacapavir single-tablet regimens, which aim to maintain virologic suppression while improving convenience and adherence. Early reports indicate non-inferiority compared to standard therapies, with favorable tolerability profiles, and full results are anticipated in upcoming publications. [49]

Additional trials are focusing on special populations, including adolescents, women, and individuals in diverse geographic settings. These studies aim to generate pharmacokinetic, safety, and efficacy data tailored to populations historically underrepresented in HIV research. There is also increasing emphasis on evaluating lenacapavir in low- and middle-income countries, where implementation challenges, cost considerations, and population-specific factors require dedicated investigation. [50] Furthermore, exploratory studies are examining alternative delivery systems and prodrug formulations, such as oral or implantable versions, to expand flexibility in administration. While some investigational oral long-acting approaches are still in early development, they reflect broader efforts to diversify the delivery platforms for capsid inhibitors. [51]

Collectively, the ongoing clinical trial landscape for lenacapavir underscores its central role in shaping the future of HIV therapeutics. The breadth of current investigations—from once-yearly prevention strategies to combination treatment regimens—highlights both the versatility of this capsid inhibitor and the global scientific commitment to optimizing its clinical impact. As these trials mature, they are expected to provide critical insights into long-term efficacy, resistance patterns, safety in diverse populations, and the feasibility of large-scale implementation, ultimately guiding the next phase of HIV treatment and prevention strategies. [52]

XIII. CURRENT STATUS

Lenacapavir has transitioned from an investigational agent to an approved and increasingly integrated component of HIV management, marking a significant milestone in the evolution of antiretroviral therapy. It has received regulatory approval in multiple regions, including the United States and Europe, for use in combination with other antiretroviral agents in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection who have limited therapeutic options. This approval was primarily based on robust evidence from Phase 2/3 clinical trials demonstrating its efficacy in achieving and maintaining virologic suppression in a population with high unmet clinical need. As such, lenacapavir is currently positioned as a key option in salvage therapy, particularly for patients with resistance to multiple drug classes.[53] Beyond its approved indication, lenacapavir is undergoing extensive clinical development for additional uses, most notably in HIV prevention as a long-acting pre-exposure prophylaxis (PrEP) agent. Large-scale Phase 3 trials in diverse populations have reported highly promising results, with near-complete protection against HIV acquisition and a favorable safety profile. These findings have generated considerable interest among global health organizations and policymakers, and regulatory submissions for PrEP indications are anticipated or underway in several regions. If approved for prevention, lenacapavir could significantly expand the toolkit for HIV control and play a central role in reducing new infections. [54]

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In clinical practice, early real-world experience with lenacapavir has generally aligned with trial data, confirming its effectiveness and tolerability. Healthcare providers are beginning to incorporate it into treatment regimens for eligible patients, particularly those with complex resistance patterns or adherence challenges. However, its use remains limited by factors such as cost, availability, and the need for healthcare infrastructure to support subcutaneous administration. Access disparities are especially pronounced in low- and middle-income countries, where the burden of HIV is highest and where implementation of long-acting therapies may face logistical and financial barriers. [55]

From a research perspective, lenacapavir continues to be the focus of numerous ongoing studies aimed at expanding its indications, optimizing dosing strategies, and evaluating its use in combination with other long-acting agents. Investigations are also exploring its safety and efficacy in special populations, including adolescents, pregnant individuals, and those with coexisting medical conditions. In parallel, pharmacovigilance efforts are being strengthened to monitor long-term safety and identify rare adverse events as its use becomes more widespread. Overall, the current status of lenacapavir reflects a dynamic and rapidly evolving landscape, in which a novel, long-acting capsid inhibitor is beginning to reshape both treatment and prevention paradigms in HIV care. While still in the early stages of global implementation, its demonstrated efficacy, unique mechanism, and transformative dosing schedule position it as a cornerstone of next-generation antiretroviral strategies, with the potential to significantly impact the trajectory of the HIV epidemic in the coming years.[56]

XIV. CONCLUSION:

Lenacapavir represents a transformative milestone in the evolution of antiretroviral therapy, distinguished by its novel capsid-targeting mechanism, ultra-long-acting pharmacokinetic profile, and broad applicability across both HIV treatment and prevention. By acting on a highly conserved structural component of the virus, lenacapavir introduces a fundamentally new approach to viral inhibition, disrupting multiple stages of the HIV life cycle and offering potent activity even in the presence of extensive resistance to conventional drug classes. This unique mechanism not only enhances antiviral efficacy but also minimizes cross-resistance, positioning lenacapavir as a critical option for heavily treatment-experienced individuals with limited therapeutic alternatives.

From a pharmacological perspective, the drug's exceptional binding affinity, structural specificity, and prolonged systemic exposure enable sustained viral suppression with dosing intervals of up to six months. These properties translate into significant clinical advantages, particularly in improving adherence and treatment retention by eliminating the need for daily oral therapy. Clinical trial data consistently demonstrate robust virologic outcomes, including high rates of viral suppression in multidrug-resistant populations and near-complete protection against HIV acquisition in prevention studies. The integration of lenacapavir into pre-exposure prophylaxis (PrEP) strategies further underscores its potential to reshape public health approaches to HIV prevention, especially in populations where adherence to daily regimens has been challenging.

Advanced analyses, including structural biology investigations and meta-analytic evaluations, reinforce the strength and durability of lenacapavir's antiviral activity. Its high barrier to resistance, coupled with the fitness cost associated with capsid mutations, supports sustained efficacy when used in appropriately constructed combination regimens. Nevertheless, the long- acting nature of the drug introduces unique considerations, including the management of adverse events, the risk of resistance during pharmacokinetic "tail" phases, and the need for strict adherence to dosing schedules. Pharmacovigilance data to date indicate a favorable safety profile, although continued real-world monitoring is essential to fully characterize long-term effects and rare adverse events.

From a broader perspective, lenacapavir's development has important implications for health systems and global HIV policy. While its high cost and delivery requirements present challenges to widespread implementation, particularly in low-resource settings, its potential to reduce transmission, improve adherence, and decrease long-term healthcare burdens offers substantial value. Ongoing clinical trials and future research are expected to expand its indications, optimize combination strategies, and explore its role in innovative approaches such as long-acting therapeutic regimens and HIV cure strategies.

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In conclusion, lenacapavir exemplifies a new generation of precision-designed, long-acting antiretroviral agents that address both biological and behavioral barriers to effective HIV management. Its ability to combine potent antiviral activity with unprecedented dosing convenience positions it as a cornerstone of future HIV treatment and prevention paradigms. Continued research, equitable access strategies, and integration into global health frameworks will be essential to fully realize its transformative potential in controlling and ultimately helping to end the HIV epidemic.

CONFLICT OF INTEREST-

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