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Lenacapavir and Long-Acting HIV Therapeutics Pharmacological Mechanisms, Clinical Evidence from the PURPOSE Trials, and Future Directions in Antiretroviral Therapy

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ABSTRACT

Lenacapavir (Sunlenca for treatment; Yeztugo for prevention) is a first-in-class HIV-1 capsid inhibitor with an unprecedented pharmacokinetic profile enabling subcutaneous administration only twice yearly, representing a transformative advance in both HIV treatment and prevention.[2,3,23] The HIV capsid — the conical protein shell encasing the viral genome — performs essential functions across multiple stages of the viral life cycle (uncoating, reverse transcription, nuclear import, integration, and assembly), and lenacapavir's multi-stage inhibition of capsid function produces potent, durable antiviral activity with a novel mechanism distinct from all existing antiretroviral classes.[3,5,6] The 2024 PURPOSE 1 and PURPOSE 2 trials demonstrated remarkable efficacy of twice-yearly subcutaneous lenacapavir for HIV pre-exposure prophylaxis (PrEP): PURPOSE 1, conducted in cisgender women and adolescent girls in sub-Saharan Africa, demonstrated 100% efficacy (zero infections among approximately 2,134 participants receiving lenacapavir),[4] while PURPOSE 2, in cisgender men and gender-diverse individuals, demonstrated 96% efficacy versus background incidence.[9] These results — among the most striking in HIV prevention history — led to FDA approval of lenacapavir for PrEP in 2025,[23,56] offering the prospect of transforming HIV prevention through the convenience and adherence advantages of twice-yearly dosing. This review provides a comprehensive pharmacological analysis of lenacapavir and long-acting HIV therapeutics including the HIV capsid biology and the novel capsid inhibition mechanism, lenacapavir pharmacology and the engineering of its extraordinary half-life, the treatment indication for multidrug-resistant HIV (CAPELLA), the PURPOSE PrEP trial program, the comparison with long-acting injectable cabotegravir (and cabotegravir-rilpivirine for treatment), the broader long-acting antiretroviral pipeline, the access and equity considerations including generic licensing for low- and middle-income countries, the Indian HIV epidemiology and prevention context, and future directions including once-yearly formulations, combination long-acting regimens, and the potential impact on the global HIV epidemic.

Keywords: Lenacapavir; Sunlenca; Yeztugo; HIV capsid inhibitor; pre-exposure

prophylaxis; PrEP; PURPOSE; long-acting antiretroviral; cabotegravir; HIV prevention; twice-yearly dosing; multidrug-resistant HIV.

1. INTRODUCTION

Human immunodeficiency virus (HIV) infection remains a major global health challenge, with approximately 39 million people living with HIV worldwide and approximately 1.3 million new infections annually according to recent estimates. Despite remarkable progress in antiretroviral therapy (ART), which has transformed HIV from a uniformly fatal disease into a manageable chronic condition, and in pre-exposure prophylaxis (PrEP), substantial challenges remain. These include the requirement for lifelong daily oral therapy, adherence-related difficulties, persistent stigma associated with HIV infection and daily pill-taking, inadequate uptake and persistence of oral PrEP among populations at highest risk, and the continuing gap between available interventions and the goal of ending the HIV epidemic. Long-acting antiretroviral therapies have emerged as promising strategies to address many of these challenges. [1,2]

Lenacapavir, developed by Gilead Sciences, represents a transformative advance through two distinguishing features: a novel first-in-class mechanism as an HIV-1 capsid inhibitor and an unprecedented pharmacokinetic profile enabling subcutaneous administration only twice yearly (every six months). It was first approved in 2022 (Sunlenca®) for the treatment of multidrug-resistant HIV-1 infection in heavily treatment-experienced adults receiving optimized background antiretroviral therapy. Subsequently, its remarkable efficacy in HIV pre-exposure prophylaxis demonstrated in the PURPOSE clinical trial programme led to its approval in 2025 (Yeztugo®) for HIV prevention. [3–6]

The HIV-1 capsid is a conical protein shell composed of approximately 1,500 capsid protein monomers arranged in a fullerene-like lattice surrounding the viral RNA genome and associated proteins. Once regarded primarily as a structural component, the capsid is now recognized as a multifunctional regulator involved throughout the viral replication cycle, including protection of the viral genome, regulation of reverse transcription, nuclear import of the pre-integration complex, integration site selection, and viral assembly and maturation. Because of its indispensable role across multiple stages of the viral life cycle, the capsid has become an attractive therapeutic target, and lenacapavir interferes with several capsid-dependent processes during both the early and late phases of viral replication. [7–9]

The PURPOSE clinical trial programme produced some of the most remarkable findings in the history of HIV prevention. PURPOSE 1, conducted among cisgender women and adolescent girls aged 16–25 years in South Africa and Uganda, demonstrated complete protection against HIV infection with no HIV infections observed among participants receiving twice-yearly subcutaneous lenacapavir. PURPOSE 2, conducted among cisgender men, transgender women, transgender men, and gender-diverse individuals across multiple countries, demonstrated approximately 96% efficacy compared with background HIV incidence. These findings established lenacapavir as a potentially transformative HIV prevention strategy, largely because twice-yearly administration substantially minimizes adherence challenges associated with daily oral PrEP. [10]

This review provides a comprehensive pharmacological analysis of lenacapavir and long-acting HIV therapeutics. It discusses HIV capsid biology, the novel mechanism of capsid inhibition, the pharmacological properties and prolonged pharmacokinetic profile of lenacapavir, evidence from the CAPELLA trial, findings from the PURPOSE PrEP programme, and the future role of long-acting antiretroviral therapies in HIV treatment and prevention.

2. HIV Capsid biology and the Capsid inhibition mechanism

2.1 The HIV Capsid: Structure and Multi-Stage Function

The HIV-1 capsid is a conical structure assembled from approximately 250 hexamers and 12 pentamers of the capsid (CA) protein, a cleavage product of the Gag polyprotein, forming a fullerene cone that encloses the viral RNA genome, reverse transcriptase, integrase, and other viral proteins. Far from being a static container, the capsid is a dynamic, metastable structure that plays essential roles throughout the viral life cycle. During early infection, the intact capsid protects the viral genome from cytoplasmic sensors and nucleases, provides the environment necessary for reverse transcription, and traffics the pre-integration complex toward the nucleus. Interactions with host nuclear pore proteins (Nup358 and Nup153) and the host factor CPSF6 facilitate nuclear import and influence viral integration site selection. Controlled capsid uncoating is critical, as both premature and delayed disassembly impair viral infectivity. During late infection, correct capsid assembly and maturation are required for the production of infectious virions.

2.2 Lenacapavir's Multi-Stage Mechanism

Lenacapavir binds to a highly conserved hydrophobic pocket located at the interface between adjacent capsid protein subunits, the same binding site utilized by host proteins including CPSF6 and Nup153. By occupying this pocket, lenacapavir interferes with multiple capsid-dependent processes throughout the HIV replication cycle. During early infection, it disrupts capsid-mediated nuclear import, impairs reverse transcription, and alters the timing of capsid uncoating. During late infection, it interferes with capsid assembly and maturation, resulting in the production of structurally abnormal and non-infectious virions. This dual mechanism, targeting both early and late stages of viral replication, distinguishes lenacapavir from all currently approved antiretroviral drug classes and contributes to its potent antiviral activity against multidrug-resistant HIV-1 isolates. [11–13]

2.3 Resistance Considerations

Resistance to lenacapavir may emerge through amino acid substitutions within the capsid protein at the drug-binding interface, including M66I, Q67H, K70N/R/S, N74D, and T107N. However, because the capsid protein is highly conserved and many resistance-associated mutations reduce viral fitness, lenacapavir possesses a relatively high genetic barrier to resistance. In the treatment of multidrug-resistant HIV infection, lenacapavir should always be administered in combination with other fully active antiretroviral agents to minimize the risk of resistance associated with functional monotherapy. In the prevention setting, surveillance for breakthrough infections, resistance testing, and careful management of the prolonged pharmacokinetic tail are important considerations because declining subtherapeutic drug concentrations may theoretically facilitate the emergence of resistant viral variants. [14–16]

3. Lenacapavir Pharmacology

3.1 The Engineering of an Extraordinary Half-Life

Lenacapavir's defining pharmacological feature is its exceptionally long elimination half-life, enabling twice-yearly subcutaneous administration. This prolonged duration of action results from rational molecular design combining low aqueous solubility, high antiviral potency, metabolic stability, and sustained release from a subcutaneous depot formulation. Following subcutaneous injection, lenacapavir is gradually released into the systemic circulation over several months, maintaining plasma concentrations well above the antiviral target. The availability of both oral and subcutaneous formulations provides flexibility during treatment initiation and maintenance, and the successful development of a six-month dosing interval represents a major advance in long-acting drug delivery systems.

3.2 Pharmacokinetics and Administration

For the treatment of multidrug-resistant HIV-1 infection, lenacapavir therapy is initiated with oral loading doses followed by subcutaneous administration every six months. Similar dosing intervals have been adopted for HIV pre-exposure prophylaxis. Lenacapavir undergoes metabolism primarily through CYP3A and is also a substrate of P-glycoprotein and UGT1A1. Because it acts as a moderate CYP3A inhibitor, clinically significant drug-drug interactions should be considered during co-administration with susceptible medications. Following discontinuation, plasma concentrations decline gradually over an extended pharmacokinetic tail, an important consideration for resistance management and pregnancy planning. Injection-site reactions, including nodules, induration, erythema, and pain, are generally mild to moderate and represent the most frequently reported adverse events.

3.3 Drug Interactions and Special Populations

Strong CYP3A inducers, including rifampin and certain anticonvulsants, substantially reduce systemic exposure to lenacapavir and should generally be avoided. Conversely, moderate inhibition of CYP3A by lenacapavir may increase exposure to concomitant CYP3A substrates. The prolonged elimination half-life complicates the management of adverse drug reactions because complete drug clearance requires several months. Current evidence indicates that dose adjustment is generally unnecessary in patients with mild-to-moderate renal or hepatic impairment, although clinical experience in severe organ dysfunction remains limited. Additional data regarding pregnancy exposure continue to accumulate, and the prolonged pharmacokinetic tail should be considered during reproductive planning.

4. Treatment of multidrug-resistant HIV: CAPELLA

Lenacapavir received its first regulatory approval in 2022 (Sunlenca®) for the treatment of multidrug-resistant HIV-1 infection in heavily treatment-experienced adults with limited remaining therapeutic options, in combination with an optimized background antiretroviral regimen. Clinical evidence from the CAPELLA study demonstrated that the addition of lenacapavir resulted in marked reductions in plasma HIV-1 RNA levels, with the majority of patients achieving virologic suppression (HIV-1 RNA <50 copies/mL) at Weeks 26 and 52, accompanied by meaningful recovery in CD4+ T-cell counts. Owing to its unique capsid-targeting mechanism and lack of cross-resistance with existing antiretroviral classes, lenacapavir provides an important therapeutic option for patients with extensive treatment failure. The phase II CALIBRATE study further demonstrated sustained virologic suppression and good tolerability of lenacapavir-containing regimens in treatment-naïve adults with HIV-1 infection. [17–21]

Although the current treatment indication is limited to heavily treatment-experienced individuals, the broader significance of lenacapavir lies in its potential to transform long-acting HIV therapy. Ongoing clinical research is evaluating combination regimens incorporating lenacapavir with other long-acting antiretroviral agents to develop complete maintenance regimens that may eventually replace lifelong daily oral therapy. [22]

5. The PURPOSE PrEP Trial program

5.1 PURPOSE 1: Cisgender Women in Sub-Saharan Africa

PURPOSE 1 was a multinational Phase III clinical trial conducted among cisgender women and adolescent girls aged 16–25 years in South Africa and Uganda, populations with a high incidence of HIV infection and well-recognized adherence challenges with daily oral PrEP. Participants received twice-yearly subcutaneous

lenacapavir or daily oral PrEP regimens. The study demonstrated complete protection against HIV infection among participants receiving lenacapavir, with no incident HIV infections reported during the primary analysis period. The exceptional efficacy observed resulted in early termination of the trial because the predefined efficacy criteria had been exceeded, highlighting the considerable promise of long-acting HIV prevention strategies. [23]

5.2 PURPOSE 2: Men and Gender-Diverse Individuals

PURPOSE 2 evaluated twice-yearly subcutaneous lenacapavir among cisgender men, transgender women, transgender men, and gender-diverse individuals across multiple countries in the Americas, Africa, and Asia. The trial demonstrated a substantial reduction in HIV incidence compared with background population incidence and showed superior preventive efficacy relative to daily oral tenofovir disoproxil fumarate/emtricitabine. Together, PURPOSE 1 and PURPOSE 2 established the effectiveness of twice-yearly lenacapavir across diverse populations and supported its subsequent approval for HIV pre-exposure prophylaxis. [24]

5.3 The Adherence Advantage and Implementation

The outstanding efficacy of lenacapavir for HIV prevention is largely attributable to the adherence benefits associated with twice-yearly dosing. Although daily oral PrEP is highly effective when taken consistently, real-world adherence remains suboptimal in several high-risk populations. Administration of only two injections per year substantially reduces the burden of daily medication use and may improve long-term persistence with preventive therapy. Successful implementation will depend on healthcare infrastructure capable of delivering scheduled injections, effective management of the prolonged pharmacokinetic tail following treatment discontinuation, equitable access, affordability, and integration into national HIV prevention programmes.

6. Long-acting cabotegravir and the long-acting landscape

6.1 Cabotegravir for PrEP

Long-acting injectable cabotegravir (Apretude), an integrase strand transfer inhibitor, was the first long-acting injectable PrEP agent, approved in 2021 based on the HPTN 083 and HPTN 084 trials. Cabotegravir is administered intramuscularly every 2 months (after oral lead-in and initial injections). HPTN 083 (in cisgender men and transgender women who have sex with men) and HPTN 084 (in cisgender women in sub-Saharan Africa) both demonstrated superiority of long-acting cabotegravir over daily oral F/TDF for HIV prevention, establishing the value of long-acting injectable PrEP. Cabotegravir's every-2-month dosing, while more frequent than lenacapavir's twice-yearly, established the long-acting injectable PrEP paradigm that lenacapavir extends. [25–27]

6.2 Cabotegravir-Rilpivirine for Treatment

Long-acting cabotegravir combined with rilpivirine (Cabenuva), administered intramuscularly every 1-2 months, was approved (2021) as the first complete long-acting injectable regimen for HIV treatment (maintenance of virologic suppression in virologically suppressed adults). The ATLAS, FLAIR, and ATLAS-2M trials demonstrated non-inferiority to daily oral therapy for maintaining viral suppression. Cabotegravir-rilpivirine offers freedom from daily oral therapy for treatment, addressing pill fatigue, stigma, and adherence, though the every-1-2-month dosing requires regular healthcare encounters. The combination represented the first proof that complete HIV treatment could be delivered via long-acting injection. [28–30]

6.3 The Broader Long-Acting Pipeline

The long-acting antiretroviral field is expanding rapidly. Long-acting formulations

and combinations in development include: lenacapavir combined with other long-acting agents (long-acting islatravir, broadly neutralizing antibodies) to enable complete long-acting treatment regimens potentially dosed every 6 months; once-yearly lenacapavir formulations in development; long-acting capsid inhibitor successors; broadly neutralizing antibodies (bNAbs) for prevention and treatment; and various long-acting oral and implantable approaches. The goal of complete, infrequently-dosed long-acting HIV treatment and prevention — potentially annual — would represent a further transformation. Islatravir (a nucleoside reverse transcriptase translocation inhibitor) development was affected by lymphocyte count concerns but continues in modified form. [31–33]

7. Access, Equity, and Generic licensing

The transformative potential of lenacapavir for ending the HIV epidemic depends critically on access in the low- and middle-income countries (LMICs) that bear the greatest HIV burden, particularly sub-Saharan Africa and parts of Asia. The originator price of lenacapavir in high-income countries (approximately USD 40,000+ per year for treatment) is incompatible with global access. Recognizing this, and following substantial advocacy, Gilead announced voluntary licensing agreements in 2024 with multiple generic manufacturers (including several Indian companies) to produce generic lenacapavir for 120 low- and middle-income countries, with the aim of dramatically reducing the price (analyses suggest generic production could eventually cost as little as USD 40-100 per year per person). The access strategy for lenacapavir PrEP is considered critical to its potential epidemic impact.

The role of Indian generic manufacturers is central to global lenacapavir access. India's generic pharmaceutical industry has historically been the primary supplier of affordable antiretrovirals to LMICs, producing the vast majority of generic ARVs used in global HIV programs (through mechanisms including the Medicines Patent Pool and voluntary licenses). Several Indian companies (including those that have produced generic versions of other Gilead antiretrovirals) are party to the lenacapavir voluntary licensing agreements and are positioned to produce affordable generic lenacapavir for global distribution. This Indian manufacturing capability is critical to translating lenacapavir's clinical promise into global public health impact.

Access considerations include not only the drug price but also the healthcare delivery infrastructure required for twice-yearly injections, the cold chain and supply logistics, the integration into existing HIV prevention and treatment programs, the financing through global mechanisms (PEPFAR, Global Fund), and the political and regulatory pathways for adoption in each country. The combination of generic licensing, advocacy, and global health financing will determine whether lenacapavir achieves its potential to transform the global HIV epidemic. WHO has moved to issue guidance on long-acting PrEP including lenacapavir to support implementation. [34–38]

8. Indian HIV Context

India has the third-largest HIV epidemic globally, with an estimated 2.4 million people living with HIV (adult prevalence approximately 0.2%, low overall but with substantial absolute numbers and concentrated epidemics among key populations). India's National AIDS Control Programme (NACP), through the National AIDS Control Organisation (NACO), provides free antiretroviral therapy and has made substantial progress in expanding treatment access and reducing new infections. HIV in India is concentrated among key populations — men who have sex with men, transgender people, female sex workers, people who inject drugs, and migrant populations — with substantial regional variation (higher prevalence in some southern and northeastern states). [39-41]

Pre-exposure prophylaxis in India has had limited rollout to date. Daily oral PrEP (tenofovir-based) has been introduced in pilot programs and is recommended for key populations, but uptake and access remain limited. The advent of long-acting PrEP — cabotegravir and especially twice-yearly lenacapavir — offers substantial potential for the Indian context, where the adherence advantages and reduced healthcare-encounter frequency could improve prevention among key populations facing barriers to daily oral PrEP and stigma. The availability of affordable generic lenacapavir (through Indian manufacturing under the voluntary licensing agreements) is critical for Indian access.

Indian generic manufacturers are positioned to play a central role in lenacapavir access — both for the domestic Indian market and for global supply to LMICs. India's status as the 'pharmacy of the developing world' for antiretrovirals, the established generic ARV manufacturing infrastructure, and the inclusion of Indian companies in the lenacapavir voluntary licensing agreements together position India centrally in the global lenacapavir access strategy. For the domestic Indian HIV program, the incorporation of long-acting PrEP and (eventually) long-acting treatment into NACP guidelines, the development of healthcare delivery infrastructure for injectable administration, and the financing of these interventions represent key considerations.

Indian research and education priorities related to long-acting HIV therapeutics include: implementation research on long-acting PrEP delivery among Indian key populations; characterization of lenacapavir pharmacology and any population-specific considerations; the role of Indian generic manufacturing in global and domestic access; integration of long-acting agents into NACP guidelines and infrastructure; pharmacovigilance for the Indian population; addressing stigma and barriers to HIV prevention and treatment; and pharmacology education addressing the novel capsid inhibition mechanism, the long-acting therapeutic paradigm, the PURPOSE trial results, and the access and equity dimensions. The combination of India's substantial HIV burden, its central role in global ARV manufacturing, and the transformative potential of lenacapavir makes long-acting HIV therapeutics a distinctively important topic for Indian pharmacology and public health.

9. Tables

Table 1. Pharmacological Profile of Lenacapavir

Parameter	Description
Generic name	Lenacapavir
Brand names	Sunlenca® (treatment); Yeztugo® (HIV PrEP)
Manufacturer	Gilead Sciences
Pharmacological class	First-in-class HIV-1 capsid inhibitor
Mechanism of action	Inhibits multiple stages of the HIV-1 replication cycle, including capsid uncoating, nuclear import, virion assembly, and capsid maturation
Dosage regimen	Oral loading followed by subcutaneous administration every 6 months
Approved indications	Multidrug-resistant HIV-1 infection (2022); HIV pre-exposure prophylaxis (2025)
Metabolism	Primarily metabolized by CYP3A; substrate of P-glycoprotein (P-gp) and UGT1A1; moderate CYP3A inhibitor
Key clinical advantage	Twice-yearly dosing with activity against multidrug-resistant HIV-1 strains
Major resistance-associated mutations	M66I, Q67H, K70N/R/S, N74D, T107N (capsid gene)

Table 2. PURPOSE Trial Program Evaluating Lenacapavir for HIV Pre-Exposure Prophylaxis

Trial	Study Population	Comparator	Key Findings	Status
PURPOSE 1	Cisgender women and adolescent girls (16–25 years) in South Africa and Uganda	Daily oral F/TAF or F/TDF	No HIV infections reported in the lenacapavir group; demonstrated superior efficacy compared with daily oral PrEP	Completed
PURPOSE 2	Cisgender men, transgender, and gender-diverse individuals	Daily oral F/TDF	Two HIV infections in the lenacapavir group; approximately 96% risk reduction compared with background HIV incidence and superior efficacy versus daily oral PrEP	Completed
PURPOSE 3	Cisgender women in the United States	Not applicable	Ongoing evaluation of twice-yearly lenacapavir for HIV prevention	Ongoing
PURPOSE 4	People who inject drugs	Not applicable	Designed to evaluate the effectiveness of lenacapavir in a key at-risk population	Planned/Ongoing

Table 3. Comparison of Long-Acting Antiretroviral Agents for HIV Prevention and Treatment

Feature	Lenacapavir	Cabotegravir
Drug class	HIV-1 capsid inhibitor	Integrase strand transfer inhibitor (INSTI)
Target	HIV-1 capsid protein	HIV integrase enzyme
Approved use	HIV treatment and pre-exposure prophylaxis (PrEP)	HIV treatment and pre-exposure prophylaxis (PrEP)
Route of administration	Oral loading followed by subcutaneous injection	Intramuscular injection
Maintenance dosing	Every 6 months	Every 2 months
Mechanism of action	Inhibits multiple stages of the viral life cycle	Inhibits viral DNA integration into the host genome
Major clinical advantage	Twice-yearly dosing with prolonged antiviral activity	Established long-acting regimen with proven efficacy
Resistance considerations	Capsid-associated mutations (e.g., M66I, Q67H, K70N/R/S, N74D, T107N)	Integrase-associated resistance mutations may occur
Clinical role	Long-acting therapy and HIV prevention, including multidrug-resistant HIV-1	Long-acting therapy and HIV prevention

Table 4. Major Classes of Antiretroviral Drugs and Their Molecular Targets

Antiretroviral Class	Molecular Target	Representative Drugs	Stage of HIV Life Cycle
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)	Reverse transcriptase	Tenofovir, Emtricitabine, Abacavir	Reverse transcription
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Reverse transcriptase (allosteric site)	Efavirenz, Rilpivirine, Doravirine	Reverse transcription
Integrase Strand Transfer Inhibitors (INSTIs)	HIV integrase	Dolutegravir, Bictegravir, Cabotegravir	Viral DNA integration
Protease Inhibitors (PIs)	HIV protease	Darunavir, Atazanavir, Lopinavir	Viral maturation
Entry and Fusion Inhibitors	CCR5, gp41, or gp120	Maraviroc, Enfuvirtide, Fostemsavir, Ibalizumab	Viral entry
Capsid Inhibitors	HIV-1 capsid protein	Lenacapavir	Multiple stages (uncoating, nuclear import, assembly, and maturation)

Table 5. Current Landscape of HIV Prevention and Treatment in India

Parameter	Current Status in India
People living with HIV	Approximately 2.4 million individuals
Epidemic pattern	Concentrated among key populations, including MSM, transgender persons, female sex workers, people who inject drugs, and migrants
National HIV programme	National AIDS Control Programme (NACP) implemented through the National AIDS Control Organization (NACO)
Daily oral PrEP	Limited implementation, primarily through pilot programmes for key populations
Long-acting cabotegravir	Limited availability
Lenacapavir	Voluntary licensing agreements include Indian manufacturers to facilitate future access
Generic antiretroviral manufacturing	India is a leading global producer and supplier of generic antiretroviral medicines
Implementation considerations	Expansion of long-acting injectable therapy requires appropriate healthcare infrastructure and delivery systems

10. Future directions

Several developmental directions will shape the future of long-acting HIV therapeutics. First, once-yearly lenacapavir formulations are in development, which would further reduce dosing frequency to a single annual injection—a remarkable prospect for both treatment and prevention that could further transform adherence and implementation. Second, complete long-acting treatment regimens combining lenacapavir with other long-acting agents (long-acting islatravir, broadly neutralizing antibodies, or other partners) are being developed to enable fully long-acting HIV treatment, potentially dosed every 6 months, replacing daily oral therapy for people living with HIV.

Third, broadly neutralizing antibodies (bNAbs)—antibodies targeting conserved HIV envelope epitopes—are advancing for both prevention and treatment, potentially in combination with lenacapavir, offering infrequent dosing and additional mechanisms. Fourth, the implementation science of long-acting PrEP and treatment—optimizing delivery, adherence to injection schedules, management of the pharmacokinetic tail, and integration into health systems—will determine real-world impact. Fifth, the access and equity agenda—translating generic licensing into actual affordable global supply, financing through global mechanisms, and integration into national programs—is critical for epidemic impact.

Sixth, for the Indian context, the priorities include the role of Indian generic manufacturing in global and domestic lenacapavir supply, the incorporation of long-acting PrEP and treatment into NACP guidelines and infrastructure, implementation research among Indian key populations, and the financing of these interventions. Seventh, the potential population-level impact of widely accessible twice-yearly (or annual) lenacapavir PrEP on HIV incidence—potentially a major tool toward ending the HIV epidemic—represents one of the most significant prospects in global health. The combination of transformative efficacy, the novel mechanism, the long-acting convenience, and (critically) the generic access strategy positions lenacapavir as potentially one of the most important advances in the history of HIV prevention.

11. CONCLUSION

Lenacapavir represents a transformative advance in HIV therapeutics through its first-in-class capsid inhibition mechanism and its unprecedented twice-yearly subcutaneous dosing. The HIV capsid, performing essential multi-stage functions across the viral life cycle, is an attractive antiviral target, and lenacapavir's multi-stage inhibition produces potent, durable antiviral activity with a mechanism distinct from all existing antiretroviral classes — active against all-class-resistant HIV and with a high barrier to

resistance. The engineering of lenacapavir's extraordinary half-life, enabling a 6-month dosing interval, represents a pharmaceutical milestone.

The 2024 PURPOSE trials produced among the most striking results in HIV prevention history: PURPOSE 1 demonstrating 100% efficacy (zero infections) in cisgender women and adolescent girls in sub-Saharan Africa, and PURPOSE 2 demonstrating 96% efficacy in men and gender-diverse individuals. These results, reflecting the adherence advantage of twice-yearly dosing over daily oral PrEP, established lenacapavir as a potentially transformative HIV prevention tool and led to FDA approval for PrEP in 2025. Lenacapavir's treatment indication for multidrug-resistant HIV (CAPELLA) addresses an important but smaller population, while the prevention indication and the broader promise of long-acting treatment regimens offer transformative potential.

The realization of lenacapavir's transformative potential depends critically on access in the low- and middle-income countries bearing the greatest HIV burden. The voluntary licensing agreements enabling generic manufacturing (with Indian companies central to the strategy) and the potential for dramatic price reduction are essential to translating clinical promise into global public health impact. India's status as the 'pharmacy of the developing world' for antiretrovirals positions Indian generic manufacturing centrally in the global lenacapavir access strategy, both for global supply and for the substantial Indian HIV epidemic.

For the Indian context, with the third-largest HIV epidemic globally (~2.4 million people living with HIV), concentrated among key populations, the advent of long-acting PrEP and treatment offers substantial potential to improve prevention and care among populations facing barriers to daily oral therapy and stigma. Pharmacology educators should emphasize lenacapavir and long-acting HIV therapeutics as a foundational example illustrating the novel capsid inhibition mechanism, the engineering of long-acting formulations, the transformative PURPOSE trial results, the long-acting therapeutic paradigm (alongside cabotegravir), and critically the access and equity dimensions and India's central role in global ARV manufacturing. The lenacapavir era — combining mechanistic novelty, transformative efficacy, long-acting convenience, and a deliberate generic access strategy — represents one of the most important and hopeful advances in the global effort to end the HIV epidemic.

Declaration by Authors

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