

Review

Pre-Exposure Prophylaxis for HIV: Emerging Role of Lenacapavir – A Comprehensive Review

Rajesh Deshwal

Associate Professor

Department of Emergency Medicine
Pacific Medical College and Hospital, Udaipur, Rajasthan, Bharat

Corresponding Author Email: drrajeshdeshwal@gmail.com

ABSTRACT

HIV continues to pose a substantial public health burden, with over 1.3 million new cases globally in 2023. Pre-exposure prophylaxis (PrEP) has transformed the HIV prevention landscape. However, oral PrEP regimens suffer from adherence challenges, resistance, and stigma. The 2025 FDA approval of Lenacapavir, a novel capsid inhibitor with biannual subcutaneous administration, introduces a promising long-acting PrEP option. This review provides a comprehensive appraisal of PrEP evolution, current regimens, the pharmacology and clinical efficacy of Lenacapavir; implementation barriers, and future directions, with a focus on its potential in the Indian context.

KEYWORDS: HIV, Pre-exposure prophylaxis, Lenacapavir

INTRODUCTION

Despite widespread ART rollout, HIV remains a pressing global concern, particularly in sub-Saharan Africa and Southeast Asia. India, with approximately 2.4 million people living with HIV, continues to witness transmission among key populations such as MSM, sex workers, and transgender individuals¹. PrEP offers a biomedical shield against HIV, with studies showing a reduction in risk by up to 99% when taken consistently².

However, traditional oral PrEP regimens demand daily adherence, often challenging in real-world settings. Lenacapavir, the first-in-class HIV capsid inhibitor approved on 18 June 2025 for PrEP use, offers a long-acting alternative with subcutaneous administration every six months.

Evolution of HIV Pre-Exposure Prophylaxis

Historical Background

Initial evidence for PrEP emerged from macaque models and transitioned into human trials such as iPrEx (2010), which showed 44% risk reduction among MSM using TDF/FTC³. This led to FDA approval of TDF/FTC (Truvada) for PrEP in 2012. Subsequent trials (PROUD, IPERGAY, HPTN-083/084) validated PrEP across various populations and geographies, but real-world effectiveness was often limited by poor adherence⁴⁻⁶.

Global and Indian Burden

- In 2023, 1.3 million new HIV infections occurred globally¹.
- In India, new infections were ~63,000, predominantly among high-risk groups⁷.
- PrEP remains underutilized in India due to cost, lack of awareness, and implementation gaps.

Current PrEP Modalities

Table 1: Approved PrEP Agents

Regimen	Drug Class	Route	Dosing Frequency	Approval Year	Populations
TDF/FTC	NRTI	Oral	Daily	2012	All adults and adolescents
TAF/FTC	NRTI	Oral	Daily	2019	MSM and TGW only
Cabotegravir LA	INSTI	Intramuscular	Every 2 months	2021	All adults
Lenacapavir	Capsid Inhibitor	SC	Every 6 months	2025	Women (cisgender)

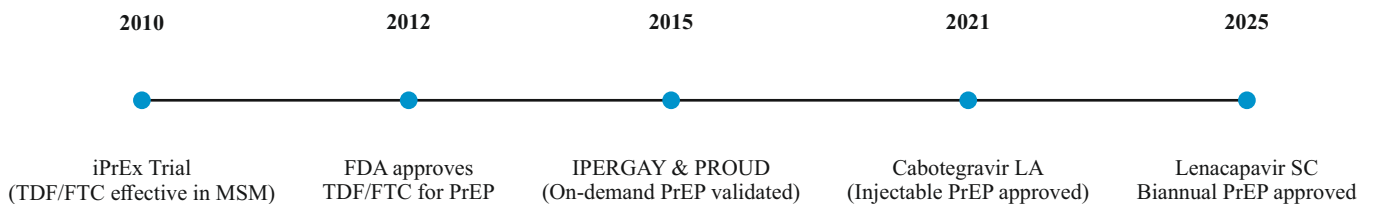


Figure 1: Timeline: Evolution of PrEP Strategies (Updated)

Lenacapavir: A Novel Long-Acting Agent

Mechanism of Action

Lenacapavir targets the HIV-1 capsid (p24), disrupting several essential viral processes:

- Uncoating of viral capsid
- Nuclear import of viral genome
- Integration into host DNA
- Virion assembly and maturation

This multi-step inhibition provides a strong resistance barrier and prevents cross-resistance with other ART classes⁸.

Pharmacokinetics

- **Bioavailability:** High after SC administration
- **Half-life:** 12–16 weeks
- **Time to steady state:** 4–6 weeks

- **Metabolism:** CYP3A4 and UGT1A1

- **Therapeutic levels:** Maintained >6 months post-dose⁹

Clinical Efficacy: Key Trials

PURPOSE 1 Trial (2024)

- Phase 3 RCT in 5,300 cisgender women (South Africa & Uganda)¹⁰
- Arms: Lenacapavir SC q6 months vs daily oral TDF/FTC vs placebo

Findings

- **Lenacapavir:** 0 HIV infections
- **TDF/FTC:** 16 infections
- **Placebo:** 39 infections

1. Entry inhibition

Lenacapavir prevents viral uncoating & entry into nucleus,

2. Reverse Transcription

HIV RNA → DNA Process is indirectly affected due to capsid instability

3. Nuclear Import Block

Lenacapavir inhibits capsid-mediated nuclear transport of viral genome

4. Virion Assembly

Prevents proper virion assembly, blocking new infections

Figure 2: Mechanism of Action of Lenacapavir

Lenacapavir acts at multiple stages of the HIV lifecycle—including entry, reverse transcription, nuclear import, and assembly—by inhibiting the capsid protein (p24).

- Efficacy vs placebo: **100%**
- Mild injection site erythema in <5%

PURPOSE 2 Trial (Ongoing)

- Targeting MSM, TGW, non-binary individuals
- Interim data suggest >95% efficacy¹¹
- Final results expected late 2025

Comparative Profile of PrEP Agents

Table 2: Comparative Features

Feature	TDF/FTC	Cabotegravir LA	Lenacapavir
Dosing	Daily	Every 2 months	Every 6 months
Route	Oral	Intramuscular	Subcutaneous
Mechanism	Reverse Transcriptase inhibitor	Integrase inhibitor	Capsid inhibitor
Adherence Needs	High	Moderate	Low
Resistance Risk	Present	Low	Minimal (PrEP use)
Cold Chain	No	Yes	No

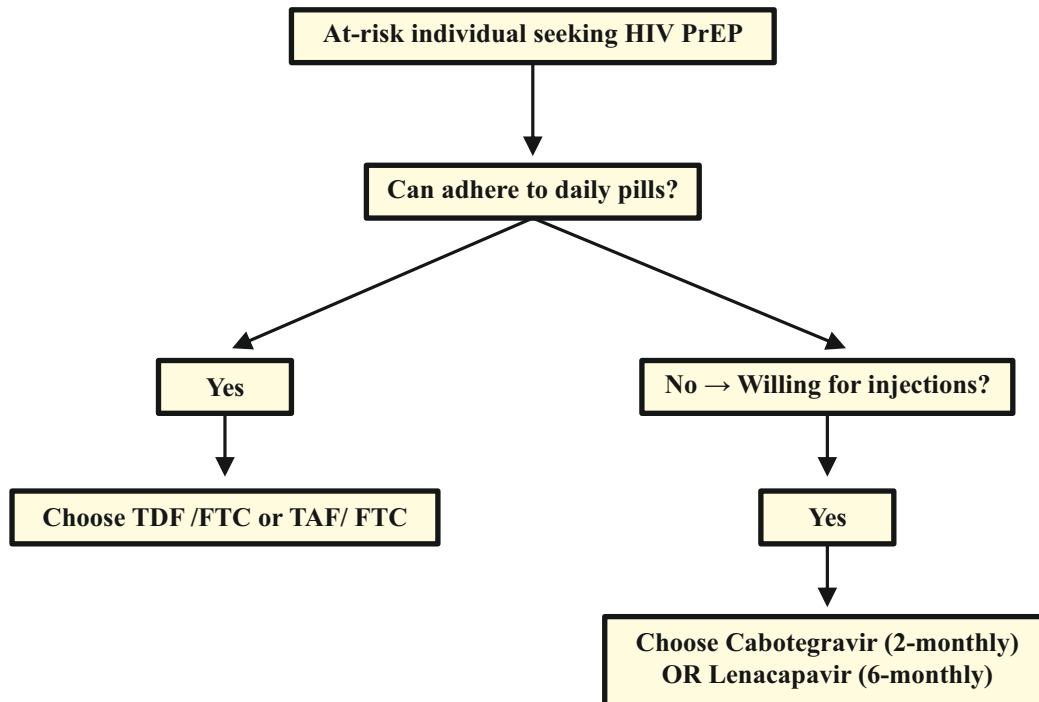


Figure 3: Flowchart: Choosing the Right PrEP Agent

Safety and Resistance Considerations

- **Resistance:** No significant mutations reported in PrEP use
- **Tolerability:**
 - No renal or hepatic toxicity
 - Mild injection site reactions
- **Drug Interactions:**
 - Avoid with strong CYP3A4 inducers (e.g., rifampicin)

Special Populations**Table 3:** Lenacapavir in Special Populations

Group	Efficacy/Safety	Current Recommendation
Women (cisgender)	Proven in PURPOSE 1	FDA approved
MSM and TGW	Awaiting full results	PURPOSE 2 ongoing
Pregnant/Breastfeeding	Limited safety data	Not recommended
Adolescents	Trials ongoing	No approval yet
Renal Impairment	Safe	No adjustment required
Hepatitis Co-infection	No hepatotoxicity	Monitor LFTs if HBV/HCV co-infected

Implementation Challenges in India**Barriers**

- No formal PrEP rollout in national HIV programs
- Lenacapavir is not yet approved in India
- High cost (INR 3–3.5 lakh per injection globally)

Opportunities

- Community-based PrEP via nurse-led models
- Integration with NACO and maternal-child health programs
- Long-acting profile is ideal for rural and mobile populations

BARRIERS	PRACTICAL SOLUTIONS
Barrier: Lack of regulatory approval (DCGI)	Solution: Fast-track regulatory review via ICMR/NACO
Barrier: High cost per injection (~INR 3-3.5 lakh)	Solution: Pooled procurement & subsidy schemes
Barrier: Low awareness among providers and users	Solution: Mass sensitization & CME programs
Barrier: No integration in NACO/NACP framework	Solution: Inclusion in National HIV prevention policy
Barrier: Criminalization of high-risk groups	Solution: Community-based & NGO-led delivery models

Figure 4: India-Specific Barriers and Solutions for Implementing Lenacapavir PrEP

Future Directions

- **Combination therapies:** Lenacapavir + islatravir trials underway
- **New delivery technologies:** Implants, microneedle patches
- **WHO prequalification:** Anticipated by late 2025
- **Public health modeling:** Assessing impact and cost-effectiveness in Low to middle Income Countries(LMICs)

CONCLUSION

Lenacapavir represents a milestone in the evolution of HIV prevention. With high efficacy, biannual dosing, and a novel mechanism of action, it addresses major limitations of daily oral PrEP. For India, the integration of Lenacapavir into prevention frameworks could offer a discrete, adherence-friendly option for high-risk individuals—provided challenges related to access, regulation, and cost are resolved.

CONFLICT OF INTEREST: None

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