CODEN: WJAPAC Impact Factor: 3.87 ISSN: 3049-3013

World Journal of Advance Pharmaceutical Sciences

Volume 2, Issue 4. Page: 157-165 Research Article www.wjaps.com

LENACAPAVIR: A NOVEL CAPSID INHIBITOR TRANSFORMING HIV MANAGEMENT

***Mohammad Mujtaba and Dr. Rahila Tarannum**

Department of Pharmacy, MESCO College of Pharmacy.

How to cite this Article *Mohammad Mujtaba and Dr. Rahila Tarannum (2025). LENACAPAVIR: A NOVEL CAPSID INHIBITOR TRANSFORMING HIV MANAGEMENT, 2(4), 157-165.

Article Info

Article Received: 18 October 2025,

Article Revised: 08 November 2025,

Article Accepted: 28 November 2025.

DOI: https://doi.org/10.5281/zenodo.17766928

***Corresponding author:**

***Mohammad Mujtaba**

Department of Pharmacy, MESCO College of Pharmacy.

ABSTRACT

Lenacapavir (GS-6207, brand Sunlenca/Yeztugo) is an anti-Retroviral drug developed by Gilead Sciences as one of very first class of HIV capsid inhibitor. Its discovery has been built upon decades of NIH (National Institute of health)-funded structural biology research showing the HIV capsid (p24) as a critical, druggable target. Structure-based design in the 2010s led to GS-CA1 and later lenacapavir, which binds between capsid subunits and "molecularly glues" them together. Researchers found lenacapavir disrupts the capsid by binding CA proteins, preventing the virus from entering the nucleus or replicating. In 2019 the FDA granted Breakthrough Therapy designation. The pivotal Phase 2/3 CAPELLA trial in heavily treatment-experienced (HTE) patients with multi-drug-resistant HIV was launched (NCT04150068) and later supported global regulatory filings. By Aug 2022 the EMA granted marketing authorization (EU) for lenacapavir in multi-drug-resistant HIV, followed by US FDA approval (Sunlenca) in Dec 2022 and Canadian approval soon after. On June 18, 2025, the U.S. Food and Drug Administration (FDA) approved Yeztugo (lenacapavir) for use as PrEP to reduce the risk of sexually-acquired HIV-1 infection in adults and adolescents weighing ≥ 35 kg. The drug is given via subcutaneous injection every 6 months (twice-yearly), making it the first FDA-approved HIV prevention option with that dosing frequency.

KEYWORDS: Lenecapavir, Anti-retroviral drug, NIH, HIV, PrEP, GS CA1, FDA.

BACKGROUND

AIDS was first clinically diagnosed in the year 1981, after an outbreak of new cases reported in injection drug users and gay men with no known history of impaired immunity conditions showing symptoms of a rare opportunistic infection which are prominent in individuals with severely compromised immune system, known as pneumocytis pneumonia. Some individuals also showed development of rare skin cancer called Kaposi's sarcoma. These cases prompted CDC (centres for disease control and prevention) to monitor the outbreak and form a committee to evaluate the causes and study the reported outbreaks. In 1982 AIDS was coined for this newly discovered disease. By 1983, Montagnier, Barré-Sinoussi, Gallo, and Levy independently discovered the causative retrovirus. Initially named LAV, HTLV-III, and ARV, it was unified under the name HIV in 1986.

HUMAN IMMUNODEFICIENCY VIRUS, also known as HIV are a group of retrovirus belonging to genus of retrovirus called lentivirus. It is a virus that destroys CD4+ T lymphocytes, progressively weakening the immune system leading to AIDS (Acquired Immunodeficiency Syndrome).[5] Currently there are two main types of HIV which are region specific namely, HIV-1, the most common and globally dominant and

HIV-2, which is mainly specific to western Africa and is relatively less transmissible than HIV-1.[6]

Structurally, HIV is an enveloped RNA virus and carries two copies of single-stranded RNA, several enzymes like reverse transcriptase, integrase. Protease and capsid protein.[5] Capsid protein also happens to be target for new drugs, leading to development of drugs which specifically acts on capsid, such as **Lenacapavir.**[7]

The virus lifecycle includes attachment, fusion, reverse transcription, integration, transcription/translation, assembly, and maturation — all key drug targets. Pathogenesis progresses from acute infection with flu-like symptoms, through a long asymptomatic latency, to AIDS marked by opportunistic infections and cancers once CD4 counts fall below ~200.[5]

Diagnosis relies on 4th-generation antigen/antibody tests, confirmed by nucleic acid testing; window periods range from 10–45 days depending on method. Signs and symptoms vary: acute fever, rash, and sore throat; chronic lymphadenopathy or weight loss; and advanced opportunistic infections like TB, PCP, or cryptococcal meningitis.[8]

Treatment now starts immediately at diagnosis with antiretroviral therapy (ART), usually a dolutegravir-based triple regimen; newer two-drug regimens (DTG/lamivudine) are also effective in selected patients.[10] Modern classes include NRTIs, NNRTIs, INSTIs, protease inhibitors, entry/fusion inhibitors, and the newer capsid inhibitors such as lenacapavir.[7] Long-acting injectables, such as cabotegravir (every 2 months) and lenacapavir (every 6 months), are major advances for both treatment and prevention.[9]

Prevention relies on combination strategies: condoms, harm reduction for injection drug use, voluntary male circumcision, **PrEP** (daily oral TDF/FTC or long-acting injectables like cabotegravir and lenacapavir), **PEP** (3-drug regimen within 72 hours for 28 days), and **TasP (Treatment as Prevention)** where virally suppressed people cannot transmit HIV (U=U).[11]

Success rates are high: oral PrEP reduces risk by ~99% with adherence, injectables are highly effective, and most ART regimens achieve sustained viral suppression; globally, ~73% of people with HIV are suppressed. Challenges remain, including adherence fatigue, side effects (e.g., weight gain with INSTIs), drug interactions, resistance (especially with long-acting drugs if infection occurs), co-infections like TB or HBV, and stigma and access barriers.[13]

Ongoing monitoring includes viral load, CD4 counts, and safety labs. Global targets aim for **95-95-95 by 2030**: 95% diagnosed, 95% on treatment, and 95% virally suppressed.[12]

INTRODUCTION

The FDA approved Gilead's Yeztugo (lenacapavir) based on results from two Phase 3 trials, PURPOSE 1 and PURPOSE 2.[7] In PURPOSE 1, conducted among 2,134 cisgender women in Sub-Saharan Africa, zero HIV infections occurred in the Yeztugo group, demonstrating 100% protection and superiority over daily oral Truvada. In PURPOSE 2, involving 2,179 cisgender men and gender-diverse people globally, only two HIV infections occurred, showing 99.9% protection and superiority over Truvada. Across both trials, Yeztugo was well-tolerated, with no new safety concerns identified, and consistently demonstrated superiority over both Truvada and background HIV incidence.[7]

PrEP (Pre-Exposure Prophylaxis)

Over the past decade, PrEP (Pre-Exposure Prophylaxis) has emerged as one of the most powerful biomedical tools in HIV prevention. Unlike post-exposure interventions, PrEP is taken *before* potential exposure to HIV, so that the body maintains protective drug levels that can intercept the virus early and prevent it from establishing a permanent infection. Its role is particularly important for individuals at higher risk (e.g., serodiscordant couples, men who have sex with men, people who inject drugs, sex workers).

As of 2025, newer long-acting injectable forms are expanding PrEP's reach by overcoming some limitations of daily pills. In July 2025, the World Health Organization formally recommended **injectable lenacapavir** as an additional PrEP option.[14]

Mechanism & Rationale

PrEP works by keeping antiretroviral (ARV) drug levels in blood and tissues such that, if HIV exposure happens, the virus is blocked early in its life cycle (reverse transcription / integration). In other words, PrEP provides a pharmacologic shield.[15]

The key is consistent drug levels — missing doses may allow HIV to replicate and escape. Hence, adherence (taking drugs as prescribed) is critical to PrEP success.[16]

One modeling and practical insight is that for oral PrEP, it takes about **7 days** of consistent use to reach optimal protection for receptive anal sex, and about **21 days** for vaginal sex. Because PrEP acts before infection, if HIV is already acquired (especially recently), PrEP alone is not sufficient; that's why confirming HIV-negative status before initiation is essential.[13]

Approved & Emerging PrEP Options

Oral PrEP

- **TDF + FTC (emtricitabine/tenofovir disoproxil fumarate)**: the classic daily oral PrEP regimen for individuals at risk via sex or injection drug use. It is well studied and considered safe in many populations.[13]

TAF + FTC (emtricitabine/tenofovir alafenamide; marketed as Descovy in some settings): also FDA-approved for PrEP, but **not recommended for receptive vaginal exposure** because of limited data in that context.[13] In a 2025 analysis, TAF/FTC usage showed an 89% risk reduction in cisgender women who had biomarker evidence of ≥2 doses/week, which supports its careful use in select cases.[17]

Long-Acting Injectable PrEP

- **Cabotegravir (CAB-LA):** intramuscular injection every 2 months. Previously approved (in many countries) as a PrEP option, offering an alternative to daily pills.
- **Lenacapavir (LEN):** a novel long-acting **capsid inhibitor**, administered **twice yearly** (every 6 months). In June 2025, the U.S. FDA approved lenacapavir (brand name Yeztugo) for PrEP.[7]
  - Clinical trials (PURPOSE 1, PURPOSE 2) reported efficacy at **100% in females** and **96% in primarily male populations** over one year, compared with expected HIV incidence. The most common adverse events were mild to moderate injection site reactions.[7]
  - Lenacapavir demonstrated **superior efficacy** to daily oral F/TDF in head-to-head or comparative settings, even in settings of relatively good adherence.[1]
  - The WHO now recommends injectable lenacapavir as an additional PrEP choice in its 2025 guideline update.[1]
  - Notably, Indian drugmakers Dr Reddy's, Hetero to sell generic HIV prevention drug for $40 a year. lenacapavir has also been licensed via voluntary agreements to generic manufacturers for distribution in 120 low- and middle-income countries (from 2027 onward), a major access measure.[18]

A recent review describes lenacapavir as offering considerable advantages in adherence, privacy, and reducing stigma associated with daily medication, though challenges remain in access, cost, and implementation at scale.[7]

Evidence of Efficacy & Real-World Outcomes

- Oral PrEP (TDF/FTC) is extremely effective when taken consistently: reduces HIV sexual transmission risk by **~99%**, and risk from injection drug use by **≥74%** in adherent users.[13]
- However, in real-world settings, **adherence declines over time** — many users discontinue or miss doses within 6–12 months.[12]

 The two injectable trials (PURPOSE 1 & 2) for lenacapavir report very high efficacy (96–100%) over 52 weeks with no major safety issues.

 Modeling studies suggest that both cabotegravir and lenacapavir could have substantial impact and be cost-effective in HIV prevention at population scale, assuming availability and uptake.

 But rollout of long-acting PrEP agents has been slow, hampered by regulatory, cost, manufacturing, and delivery constraints.

Pharmacology of Lenacapavir

Lenacapavir is a novel, first-in-class **HIV-1 capsid inhibitor** that represents a significant advancement in antiretroviral therapy. It is a small-molecule compound with the molecular formula $\mathbf{C_{39}H_{32}ClF_{10}N_7O_5S_2}$ and a molecular weight of approximately **968.28 Da**. Unlike most conventional HIV drugs that act on viral enzymes such as reverse transcriptase, integrase, or protease, Lenacapavir specifically targets the **capsid protein**, an essential structural component that encases the viral RNA and enzymes critical for replication.[1]

By binding to the capsid, Lenacapavir interferes with multiple key stages of the HIV life cycle, thereby preventing the formation of mature and infectious viral particles.[2] This distinctive mechanism has established Lenacapavir as an important therapeutic and preventive option, particularly for long-acting **pre-exposure prophylaxis (PrEP)** and for treatment in cases of multidrug-resistant HIV-1 infection.

Lenacapavir's pharmacological profile is characterized by **its long duration of action** and **broad antiviral potency.[1]** It is available both as an **oral formulation** and as a **subcutaneous injectable.[1]** The extended duration and slow-release properties of the injectable form make it especially advantageous for improving treatment adherence and patient outcomes in HIV management.[1] However, despite these pharmacological benefits, there remain challenges related to cost, accessibility, and equitable distribution, particularly in low-resource regions.[1]

Mechanism of Action

Lenacapavir acts by targeting the **HIV-1 capsid core**, disrupting essential processes that occur during the viral replication cycle.[2] It affects several stages of the virus's life, including **capsid assembly**, **nuclear import**, and **viral maturation.[2]**

During normal viral assembly, the HIV capsid is formed by approximately 200–250 hexamers and 12 pentamers arranged into a cone-shaped shell.[2] Lenacapavir binds to the interface between neighboring capsid subunits through hydrophobic and electrostatic interactions.[2] This abnormal interaction promotes **premature capsid oligomerization**, leading to the formation of **defective, unstable capsid structures.[2]** Consequently, the virus releases malformed and non-infectious particles, effectively blocking further replication.[2]

The second mechanism involves the **inhibition of nuclear translocation.[2]** Following infection, the HIV capsid normally facilitates the transport of viral DNA into the host cell nucleus by interacting with cellular proteins such as **nucleoporin 153 (NUP153)** and

cleavage and polyadenylation specificity factor 6 (CPSF6).[2] Lenacapavir competitively inhibits these interactions, preventing the viral DNA from entering the nucleus and integrating into the host genome, a vital step in establishing persistent infection.[2]

Finally, Lenacapavir interferes with **viral maturation** by altering the structural dynamics of the **Gag** and **Gag-Pol** polyproteins, which are responsible for forming mature viral particles.[2] This disruption produces immature virions that lack infectivity. By simultaneously targeting these three processes, Lenacapavir exerts a **multi-stage antiviral effect**, reducing the likelihood of resistance development and enhancing its therapeutic potential.[2]

Pharmacokinetics and Pharmacodynamics

Lenacapavir demonstrates unique pharmacokinetic characteristics that support its use as a **long-acting therapeutic and prophylactic agent.**[1,2] Following **oral administration**, the drug reaches its maximum plasma concentration within approximately **four hours** and has a half-life of **10 to 12 days.**[2] When administered **subcutaneously**, Lenacapavir exhibits an even more prolonged half-life of **8 to 12 weeks**, enabling dosing intervals of up to **six months.**[1] This long duration of action makes Lenacapavir particularly suitable for sustained HIV suppression and long-term PrEP regimens.

The pharmacokinetic profile of Lenacapavir is defined by **biphasic absorption kinetics**, characterized by an initial rapid absorption phase followed by a slow-release phase.[2] In both animal and human studies, subcutaneous injection has been shown to produce a gradual and sustained release of the drug into systemic circulation, maintaining therapeutic plasma concentrations for extended periods.[2]

In terms of pharmacodynamics, Lenacapavir exhibits **exceptionally high potency** against HIV-1. In vitro studies have shown inhibitory concentration (IC_{50}) values around **200 picomolar**, while effective concentration (EC_{50}) values in human immune cells were recorded at **32 picomolar in $CD4^+$ T cells** and **56 picomolar in macrophages.**[2] These results confirm Lenacapavir's strong antiviral efficacy across multiple HIV-1 strains.[2]

However, Lenacapavir shows **reduced potency against HIV-2**, with susceptibility levels approximately tenfold lower than those observed for HIV-1.[2] Clinical data indicate that while Lenacapavir-based therapy can achieve viral suppression in some cases of multidrug-resistant HIV-2, its overall efficacy in this subgroup is limited.[2]

The drug displays **high plasma protein binding**, with a free fraction of about **1.46%** in human plasma.[2] Lenacapavir undergoes minimal metabolic transformation, and no major circulating metabolites have been identified.[2] It is primarily excreted through the **intestinal route**, with fecal elimination being predominant, while renal excretion plays only a minor role.[2]

Lenacapavir is metabolized mainly by the **cytochrome P450 (CYP3A)** enzyme system, which indicates potential for **drug–drug interactions.**[1] Co-administration with CYP3A inhibitors or inducers may alter its plasma concentration, necessitating clinical monitoring and potential dose adjustments.[1]

Methods

A comprehensive literature search was conducted in **PubMed** using the keywords *"lenacapavir," "pre-exposure prophylaxis,"* and *"HIV."* Studies published up to **September 2024** were included, with no restrictions on the start date.[1] Only **full-text English-language clinical studies (Phase I–III)** were considered.[7] Data on **safety outcomes** (serious adverse drug reactions) and **efficacy endpoints** (HIV incidence reduction) were extracted and synthesized into a **narrative review** format.[1]

RESULTS

Efficacy of Lenacapavir

Early-phase trials primarily investigated lenacapavir among **HIV-positive individuals** to evaluate its antiviral efficacy and safety.

- In the **Phase Ib trial**, lenacapavir demonstrated a **statistically significant ($p < 0.0001$)** reduction in **HIV-1 RNA** compared with placebo.
- In the **Phase II CALIBRATE study**, treatment-naïve participants achieved **viral suppression rates of 92–100% by week 28**, which remained sustained through **week 54 in 85–92%** of subjects.[1]
- Lenacapavir was generally **well tolerated**, with most adverse events limited to **mild injection-site reactions** and no major safety issues reported.[1]

Expanding its application, the **Gilead PURPOSE clinical program** has nearly assessed lenacapavir as a **long-acting PrEP (Pre-Exposure Prophylaxis)** option across diverse at-risk populations, including **cisgender women, MSM, transgender, and non-binary individuals.**[7] Through PURPOSE trials in which 1 & 2 has successfully concluded.

PURPOSE 1 (Phase III)

This study evaluated **twice-yearly subcutaneous lenacapavir** as PrEP in **HIV-negative women** at high risk of infection. Results revealed a **100% reduction in HIV incidence** among participants receiving lenacapavir.[1] Compared with **oral TAF/FTC** and **TDF/FTC**, lenacapavir showed **complete prevention** (incidence rate ratio = 0.00; $p < 0.001$), while oral PrEP arms exhibited incidences of **2.02 per 100 person-years** (TAF/FTC) and similar background rates for TDF/FTC.[1] Adherence emerged as a major determinant of efficacy, particularly for the oral regimens, whereas

lenacapavir's long-acting formulation eliminated adherence-related failures.

PURPOSE 2 (Phase III)
Conducted among **3,273 participants** (cisgender men, transgender, and non-binary individuals having sex with men), this study found **two HIV infections among 2,180 lenacapavir recipients**, equating to **0.10 per 100 person-years.**[1] Lenacapavir provided a **96% relative risk reduction** versus background incidence (2.37 per 100 person-years) and an **89% higher efficacy** compared with **daily TDF/FTC (0.93 per 100 person-years; rate ratio 0.11, p = 0.00245).**[1] Overall, **99.9% of participants** receiving lenacapavir remained HIV-negative.[1]

The findings underscore lenacapavir's superiority in both **biological efficacy and real-world adherence** compared to traditional oral PrEP.[1]

Additional studies under the PURPOSE umbrella include:

- **PURPOSE 3**: PrEP use among U.S. cisgender women, particularly **Black and minority women.**[1]
- **PURPOSE 4**: Evaluating lenacapavir in **people who inject drugs** in the U.S.[1]
- **PURPOSE 5**: The first **European Phase II** PrEP trial (France and UK).[1]

Clinical Efficacy of Lenacapavir in HIV-1 Treatment
Multiple randomized trials have confirmed lenacapavir's **potent antiviral activity** in both **treatment-naïve** and **heavily treatment-experienced** individuals with HIV-1 infection. Virological suppression was defined as **HIV-1 RNA < 50 copies/mL.**[2]

- **ARTISTRY-1 (Phase II)**: Combined lenacapavir (25 mg or 50 mg) with bictegravir (75 mg) in virologically suppressed adults. By **week 24**, suppression rates were **96.1–96.2%**, comparable to control regimens.
- **CALIBRATE (Phase II)**: Evaluated four lenacapavir-based regimens in treatment-naïve adults. At **week 28**, viral suppression was **93–100%** across groups; at **week 54**, rates remained **85–92%**.
- **Oral lenacapavir + islatravir (Phase II)** achieved **94–98% suppression** at weeks 12–48, comparable to the standard **BIC + FTC + TAF** combination [NCT05052996].
- **CAPELLA (Phase III)**: In multidrug-resistant HIV-1 patients, lenacapavir produced rapid suppression—**88% within 15 days** compared with **17% for placebo**. Sustained suppression was **81–83% at week 26**, **72–83% at week 52**, and **56–69% at week 104**, with only mild injection-site reactions reported.

Clinical Efficacy of Lenacapavir for PrEP
Lenacapavir's long-acting protection is being tested across five major PURPOSE trials:

PURPOSE 1–5, representing various demographics and risk groups. Currently, **PURPOSE 1 and 2** have reported results, while **PURPOSE 3–5** remain ongoing.[2] A recent **Phase I open-label study** also demonstrated the feasibility of **once-yearly intramuscular lenacapavir**, maintaining therapeutic concentrations for **over 56 weeks.**[2]

- **PURPOSE 1 (Adolescent girls & young women, NCT04994509):** Among 5,338 participants, **no HIV cases** occurred in the lenacapavir group (0.0 per 100 person-years), compared with **2.02** (TAF/FTC) and **1.69** (TDF/FTC).[2] Injection-site reactions were common (68.8%), but only **0.2% discontinued** treatment.[1,2]
- **PURPOSE 2 (MSM & gender-diverse adults, NCT04925752):** In 3,265 participants, **two infections** were reported in the lenacapavir arm (**0.1 per 100 person-years**) compared with **nine in the TDF/FTC arm (0.93 per 100 person-years).**[2] The **infection risk ratio was 0.11 (p = 0.002)**, confirming lenacapavir's **statistical superiority.**[2]

Safety Profile of Lenacapavir
Across all trials—ARTISTRY-1, CALIBRATE, CAPELLA, PURPOSE 1 & 2—lenacapavir demonstrated a **consistent safety profile**. The most frequent adverse events were **injection-site reactions (pain, nodules, erythema)**, **nausea**, and **diarrhea**, typically mild to moderate in severity.[2] In PrEP trials, adverse event rates were **similar to oral PrEP arms**, and most reactions resolved without intervention.[2] Lenacapavir is **safe in mild hepatic or renal impairment**, though caution is advised with drugs metabolized by **CYP3A**, **P-gp**, or **BCRP**, as lenacapavir is a **moderate CYP3A inhibitor** and may increase systemic exposure to co-administered agents.[2]

Viral Resistance
Lenacapavir targets the **HIV-1 capsid**, and resistance arises from **mutations near the capsid-binding pocket** (e.g., **L56I, M66I, Q67H, K70H/N, N74D**).[2] While resistance mutations remain **rare (<1%) among drug-naïve individuals**, they have been detected in **treatment-experienced** patients with poor adherence or suboptimal background therapy.

Commonly reported resistance substitutions include **M66I, Q67H/K/N, K70H/N/R/S, N74D/H/K, A105S/T, and T107A/C/N.**[2] The **N74D** mutation notably reduces lenacapavir's binding affinity **20-fold** and viral susceptibility **10-fold.**[2] Similar resistance patterns (e.g., **N73D in HIV-2**) have been linked to viral rebound.[2] Hence, lenacapavir should always be combined with **at least one fully active antiretroviral** to prevent monotherapy-induced resistance.[2]

Antiretroviral Combinations
Lenacapavir is **not approved as monotherapy** and is indicated only in **combination regimens** for **multidrug-resistant HIV-1.**[2]

- **Lenacapavir + Cabotegravir:** Achieved **90% viral suppression (<75 copies/mL)** within 8 weeks among 34 treatment-experienced patients. Ongoing **CALENDULA (Phase II)** trial is assessing this dual long-acting combination [NCT06657885].[2]
- **Lenacapavir + Bictegravir:** In oral combination therapy, achieved **96.2% virological suppression** at 24 weeks in adults with HIV-1 RNA < 50 copies/mL.[2]
- **Lenacapavir + Islatravir:** Weekly regimen achieved **96.2% suppression** at week 48.[2]
- **Lenacapavir + Broadly Neutralizing Antibodies (bNAbs):** Co-administration with **teropavimab** or **zinlirvimab** maintained suppression for **≥26 weeks.[2]**
- **Lenacapavir + UB-421:** In multidrug-resistant HIV-1, this combination led to **sustained viral suppression.[2]**

Given its pharmacokinetic profile, lenacapavir's full potential is realized when paired with other **long-acting companion drugs**, enabling **durable, low-burden ART regimens.[2]**

Clinical Trials of Lenacapavir for HIV Pre-Exposure Prophylaxis (PrEP)

Phase 3 PURPOSE 1 Trial

The PURPOSE 1 trial (NCT04994509) evaluated the safety and efficacy of **twice-yearly injectable lenacapavir** for HIV prevention in cisgender women aged 16–26 years across 25 sites in South Africa and three sites in Uganda.[3] The trial was a multicenter, double-blind, active-controlled, randomized study, comparing lenacapavir to **once-daily oral Descovy®** (emtricitabine/tenofovir alafenamide) and a secondary comparator, **once-daily oral Truvada®** (emtricitabine/tenofovir disoproxil fumarate).[3] Participants were randomized in a 2:2:1 ratio to receive lenacapavir, Descovy, or Truvada, respectively.[3] A placebo arm was not included due to ethical considerations in populations where effective PrEP is available; background HIV incidence (bHIV) served as the primary comparator.[3]

Interim results from PURPOSE 1 demonstrated **zero HIV infections in the lenacapavir group**, corresponding to **100% efficacy** compared to background HIV incidence (0/100 person-years; 95% CI, 0.00–0.19) and superior prevention relative to daily Truvada (IRR 0; 95% CI, p<0.0001).[3] In contrast, HIV incidence in the Truvada group was 1.69/100 person-years, and in the Descovy group, 2.02/100 person-years.[3] Adherence to lenacapavir was consistently high, with 91.5% of participants receiving on-time injections at 26 weeks and 92.8% at one year.[3] Conversely, adherence to daily oral Descovy and Truvada was low and declined over time, reflecting previously observed challenges in daily oral PrEP adherence among cisgender women, particularly younger women.[3]

Safety outcomes were favorable. Lenacapavir and Descovy were generally well tolerated, with **injection site reactions (ISRs)** being the most common adverse events. Other frequently reported events included headache, urinary tract infection, chlamydia infection, and nausea. Serious adverse events were rare (2.8% in the lenacapavir group vs 4.0% in Descovy and 3.3% in Truvada).[3] Notably, lenacapavir demonstrated safety in **pregnant and lactating women**, marking the first adult HIV prevention trial to intentionally include this population.[3] Among 510 pregnancies, zero HIV infections occurred in the lenacapavir group.[3]

Phase 3 PURPOSE 2 Trial

The PURPOSE 2 trial (NCT04925752) extended the investigation of lenacapavir to **cisgender men, transgender individuals, and gender-diverse participants** aged ≥16 years across 88 sites in Argentina, Brazil, Mexico, Peru, South Africa, Thailand, and the United States.[4] Participants were randomized in a 2:1 ratio to lenacapavir or Truvada, with background HIV incidence as the primary comparator.[4]

Results from PURPOSE 2 showed that lenacapavir **reduced HIV infections by 96% relative to background incidence**, with only two incident cases among 2,179 participants, translating to **99.9% of participants remaining HIV-negative.[4]** Compared with daily Truvada, lenacapavir reduced HIV incidence by 89% (IRR 0.11; 95% CI, 0.02–0.51; p=0.00245).[4] Adherence to the twice-yearly injections remained high, with 91% of participants receiving on-time injections at six months and 92.8% at one year.[4] In contrast, adherence to Truvada declined over time, with high or medium adherence in only 62% of participants at one year.[4] All nine HIV infections in the Truvada group were observed in participants with low or no adherence.[4]

Safety and Tolerability

Lenacapavir was well tolerated in PURPOSE 2, with adverse events generally mild to moderate. ISRs were common but non-serious, and plasma concentrations of lenacapavir in the two participants who acquired HIV were within expected ranges.[4] No delayed HIV diagnoses were reported, and overall safety was comparable to other PrEP agents.[4]

Mechanism and Advantages

Lenacapavir inhibits HIV at **multiple stages of the viral life cycle**, distinguishing it from currently approved antiretroviral agents and minimizing cross-resistance.[4] Its long-acting, twice-yearly subcutaneous administration may address challenges with daily oral PrEP, improving adherence and persistence in high-risk populations.[3,4]

Regulatory Status and Access

Gilead Sciences has initiated regulatory submissions for lenacapavir for PrEP, with FDA **Breakthrough Therapy Designation** and rolling review underway.[3,4]

Access strategies prioritize **rapid availability in high-incidence, resource-limited countries**, including voluntary licensing agreements to manufacture low-cost formulations for over 120 countries.[3,4] Participants in ongoing trials continue to have access to open-label lenacapavir until commercial availability.[4]

CONCLUSION

The PURPOSE 1 and 2 trials establish lenacapavir as a **highly effective, safe, and long-acting option for HIV prevention**, with significant potential to improve PrEP adherence and uptake. Its inclusion of diverse populations, including adolescents and pregnant women, underscores its relevance for broad, real-world application in HIV prevention strategies globally.

FDA Approval of Yeztugo® (Lenacapavir): A Landmark Advancement in HIV Prevention

In a groundbreaking development for HIV prevention, the U.S. Food and Drug Administration (FDA) has approved **Yeztugo® (lenacapavir)**, developed by **Gilead Sciences, Inc.**, as the **first and only twice-yearly injectable pre-exposure prophylaxis (PrEP)** for the prevention of HIV-1 infection in adults and adolescents weighing at least 35 kilograms.[7] This milestone marks a major step forward in the global fight against HIV, offering a long-acting, convenient alternative to daily oral PrEP regimens.[7]

While Gilead pioneered the first PrEP medication in 2012, data from the **Centers for Disease Control and Prevention (CDC)** indicate that by 2022, only 36% of eligible individuals in the United States were using PrEP.[7] Uptake remains especially low among **women, Black/African American and Hispanic/Latino communities**, and in southern regions of the U.S. where new infections are disproportionately high.[7] These disparities are often attributed to **adherence challenges, social stigma, and lack of awareness** surrounding PrEP options. The introduction of Yeztugo, administered just twice a year, could address many of these barriers by reducing the burden of daily medication and potentially improving both adherence and acceptance.

Clinical data supporting Yeztugo's approval were derived from the large-scale **Phase 3 PURPOSE 1 and PURPOSE 2 trials**, both of which demonstrated remarkable efficacy.[7] In the **PURPOSE 1 study (NCT04994509)**, involving 2,134 cisgender women in sub-Saharan Africa, **no new HIV infections** occurred among participants receiving Yeztugo, confirming **100% efficacy** compared to daily oral **Truvada® (TDF/FTC).**[7] Similarly, the **PURPOSE 2 trial (NCT04925752)**, which enrolled 2,179 participants including cisgender men, transgender, and gender-diverse individuals, reported only **two HIV infections**, demonstrating that **99.9% of participants remained HIV-negative.**[7] These findings highlight Yeztugo's superior protective effect over existing PrEP options and underscore its consistency across diverse populations. Both trials also found Yeztugo to be **generally well tolerated**, with no significant safety concerns reported.[7]

The significance of these results was recognized widely in the scientific community. The trial findings were published in **The New England Journal of Medicine**, and **Science magazine** named lenacapavir the **2024 "Breakthrough of the Year."** Yeztugo also received **FDA Priority Review** and **Breakthrough Therapy Designation**, further emphasizing its clinical and public health importance.[7]

To ensure equitable access, Gilead announced a comprehensive **U.S. access strategy.**[7] The company is collaborating with insurance providers to secure full coverage and has established **assistance programs** to reduce out-of-pocket costs to zero for eligible patients.[7] Additionally, uninsured individuals may receive Yeztugo free of charge through Gilead's **medication assistance program**, reflecting the company's commitment to addressing cost-related barriers to HIV prevention.[7]

Beyond the United States, Gilead is actively pursuing **global regulatory approvals**. Applications are under review by the **European Medicines Agency (EMA)** and regulatory authorities in **Australia, Brazil, Canada, and South Africa**, with further submissions planned in countries that recognize FDA approval, including **Argentina, Mexico, and Peru.**[7] At present, Yeztugo remains the only PrEP formulation of lenacapavir approved for use, exclusively in the U.S., though its global expansion is anticipated in the coming years.[7]

Lenacapavir itself is a **first-in-class HIV-1 capsid inhibitor**, already approved in multiple countries for use in combination therapy for **multi-drug-resistant HIV infections**. The compound acts at **multiple stages of the HIV lifecycle**, displaying no known cross-resistance with existing antiretroviral classes. This unique mechanism supports its use for both treatment and prevention. Ongoing research is exploring **long-acting oral and injectable formulations** to further individualize HIV management and enhance accessibility.[7]

Yeztugo is supplied as a **463.5 mg/1.5 mL subcutaneous injection** and is indicated for **HIV-negative adults and adolescents weighing ≥35 kg.**[7] HIV testing must be conducted before initiation and prior to each subsequent injection to prevent inadvertent use in undiagnosed HIV-positive individuals, which could lead to **drug resistance.**[7] The product carries a **boxed warning** for this risk, emphasizing that individuals who acquire HIV-1 while on Yeztugo must immediately begin a complete HIV treatment regimen.[7]

The **recommended initiation regimen** consists of two 463.5 mg subcutaneous injections (total 927 mg) on **Day 1**, accompanied by oral loading doses of **lenacapavir 600 mg** on **Day 1 and Day 2.**[7] Maintenance dosing

involves a **single 927 mg subcutaneous injection every six months** (±2 weeks).[7] If an injection is delayed by more than two weeks, **oral lenacapavir (300 mg weekly)** can be used temporarily to maintain drug levels.[7] In cases where more than 28 weeks have elapsed since the last dose without oral bridging, the full initiation schedule must be restarted.[7] Dosage adjustments are necessary when co-administering with **strong or moderate CYP3A inducers**, as such agents can significantly alter lenacapavir exposure.[7]

Common **adverse reactions** include mild **injection site reactions, headache, and nausea** (≥5% incidence). Serious injection-site complications such as **necrosis or ulceration** are rare but can occur if the injection is improperly administered.[7] Residual lenacapavir can remain in systemic circulation for up to **12 months**, underscoring the importance of strict adherence to the biannual dosing schedule. Furthermore, **drug interactions** are an important consideration; **CYP3A inducers** can reduce lenacapavir levels, while certain **CYP3A or P-glycoprotein inhibitors** may elevate concentrations of co-administered drugs for up to nine months following injection.[7]

Overall, the approval of Yeztugo represents a transformative advancement in HIV prevention, combining **high efficacy, long duration of action, and convenient twice-yearly dosing.[7]** By overcoming challenges of adherence and stigma associated with daily oral PrEP, lenacapavir has the potential to greatly expand access and uptake among populations most at risk, marking a pivotal milestone in global efforts toward an HIV-free generation.[7]

REFERENCES

1. Goswami, S., Veeramachaneni, S., & Masurkar, P. P. (2025). Lenacapavir for HIV PrEP: Narrative review of clinical trials and implications for patient access. *Current Treatment Options in Infectious Diseases, 17*(5). https://doi.org/10.1007/s40506-024-00281-2
2. De Clercq, E., Zhang, Y., Li, G., Deng, Y., Khouri, R., Růžek, D., Król, E., & Tan, L. (2025). Lenacapavir: A capsid inhibitor for HIV-1 treatment and prevention. *Biochemical Pharmacology, 240:* 117125. https://doi.org/10.1016/j.bcp.2025.117125
3. Gilead Sciences. (2024). *Full efficacy and safety results for Gilead investigational twice-yearly Lenacapavir for HIV prevention presented at AIDS 2024.* https://www.gilead.com/news/news-details/2024/full-efficacy-and-safety-results-for-gilead-investigational-twice-yearly-lenacapavir-for-hiv-prevention-presented-at-aids-2024
4. Gilead Sciences. (2024). *Gilead presents full PURPOSE 2 data results for twice-yearly Lenacapavir for HIV prevention at HIV Glasgow.* https://www.gilead.com/news/news-details/2024/gilead-presents-full-purpose-2-data-results-for-twice-yearly-lenacapavir-for-hiv-prevention-at-hiv-glasgow
5. World Health Organization. (2024). *HIV and AIDS.* https://www.who.int/news-room/fact-sheets/detail/hiv-aids
6. Swinkels, H. M., Nguyen, A. D., & Gulick, P. G. (2025). *HIV and AIDS.* In *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK534860/
7. Gilead Sciences. (2025). *Yeztugo® (Lenacapavir) is now the first and only FDA-approved HIV prevention option offering 6 months of protection.* https://www.gilead.com/news/news-details/2025/yeztugo-lenacapavir-is-now-the-first-and-only-fda-approved-hiv-prevention-option-offering-6-months-of-protection
8. HIV.gov. (n.d.). *HIV testing overview.* https://www.hiv.gov/hiv-basics/hiv-testing/learn-about-hiv-testing/hiv-testing-overview
9. U.S. Department of Health and Human Services. (n.d.). *Guidelines for the use of antiretroviral agents in adults and adolescents with HIV.* https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/what-start-initial-combination-regimens
10. Cento, V., & Perno, C. F. (2021). Dolutegravir plus lamivudine two-drug regimen: Safety, efficacy, and diagnostic considerations for its use in real-life clinical practice—A refined approach in the COVID-19 era. *Diagnostics, 11*(5): 809. https://doi.org/10.3390/diagnostics11050809
11. ViiV Healthcare. (n.d.). *HIV prevention: Everything you should know.* https://viivhealthcare.com/about-hiv/hiv-prevention/#
12. World Health Organization. (2025). *HIV data and statistics.* https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/strategic-information/hiv-data-and-statistics
13. HIV.gov. (n.d.). *Pre-exposure prophylaxis.* https://www.hiv.gov/hiv-basics/hiv-prevention/using-hiv-medication-to-reduce-risk/pre-exposure-prophylaxis
14. World Health Organization. (2025, July 14). *WHO recommends injectable Lenacapavir for HIV prevention.* https://www.who.int/news/item/14-07-2025-who-recommends-injectable-lenacapavir-for-hiv-prevention
15. National Institutes of Health. (n.d.). *Pre-exposure prophylaxis (PrEP).* https://hivinfo.nih.gov/understanding-hiv/fact-sheets/pre-exposure-prophylaxis-prep
16. Centers for Disease Control and Prevention. (2025). *Clinical guidance for PrEP.* https://www.cdc.gov/hivnexus/hcp/prep/index.html
17. Landovitz, R. J., Molina, J., Buchbinder, S. P., & International Antiviral Society–USA (IAS–USA) Panel. (2025). Preexposure prophylaxis for HIV: Updated recommendations from the 2024 International Antiviral Society–USA Panel. *JAMA,*

334(7): 638–639. https://doi.org/10.1001/jama.2025.1141.
18. Reuters. (2025, September 24). Indian drugmakers Dr. Reddy's, Hetero to sell generic HIV prevention drug for $40 a year. https://www.reuters.com/business/healthcare-pharmaceuticals/indian-drugmakers-dr-reddys-hetero-sell-generic-hiv-prevention-drug-40-year-2025-09-24/