Emerging Role of Lenacapavir in Hiv Therapy: A Review of Its Pharmacology, Efficacy

Nandini Rompicharla [1], Pavithra Gadde[2] Prasanna Thumpati[3], Veeranki Meghana[4],
Siva Gowri Tanuja Ramanadham[5], Dr. Garlapati Usha Kiran[6]
Professor, HOD Department of Pharmacology, NRI College Of Pharmacy, Pothavarappadu, Agiripalli, Eluru district.

***Abstract*—Human immunodeficiency virus (HIV) is a type of retrovirus that spreads through blood, sexual contact, childbirth, or breastfeeding. It specifically targets CD4+ T lymphocytes, which are crucial for a healthy immune system. Among the strains, HIV-1 is the most prevalent and aggressive, while HIV-2 progresses more slowly and is primarily found in West Africa. The life cycle of HIV includes several key steps: gp120 binds to CD4 receptors, gp41 facilitates fusion, reverse transcription occurs, the virus integrates into the host's genome, and finally, infectious virions are produced. Lenacapavir is a groundbreaking HIV-1 capsid inhibitor that takes a fresh approach to tackle resistant infections. It attaches to the capsid protein subunits, effectively blocking early processes like nuclear import and reverse transcription, as well as later stages such as assembly and maturation, which results in the production of defective viruses. This drug is particularly effective against multidrug-resistant strains and shows minimal cross-resistance. With its extended pharmacokinetics, Lenacapavir allows for subcutaneous dosing every six months after an initial oral loading dose, which helps improve patient adherence. Clinical trials have shown significant reductions in viral load, making it a promising option for those dealing with resistant and hard-to-treat HIV cases.**

***Index Terms*—Capsid inhibitor, Lenacapavir, Antiretroviral therapy, Multidrug-resistant HIV, Nuclear import inhibition, Long-acting therapy, Patient adherence.**

I. INTRODUCTION

HIV also known as the human immunodeficiency virus, is a blood-borne infection that is commonly transmitted through sexual contact, intravenous drug equipment, childbirth, or human milk. HIV infection is caused by Lentiviruses, which are members of the Retroviridae family [(1).]

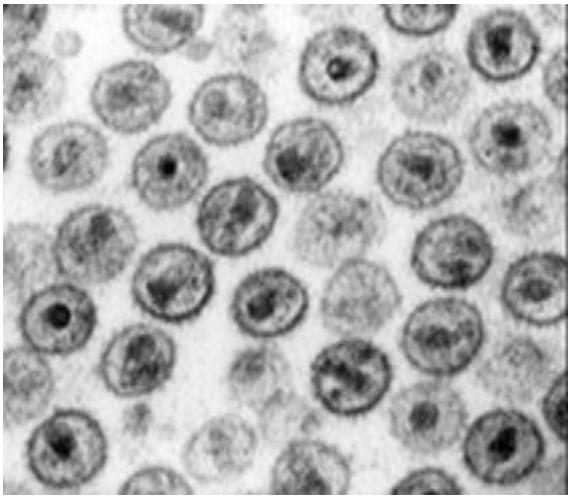


Fig.1 Electron microscopy of HIV virus-1 virions

Type of HIV viruses
Human immunodeficiency virus (HIV) includes HIV-1 and HIV-2. The immune system's white blood cell, CD4, is the target of both viruses. If left untreated, HIV can lead to HIV compromised CD4 cells that weaken the immune system.

HIV-1: HIV-1, a type of retrovirus, is responsible for approximately 95% of all HIV-related infections worldwide.

In addition, there are four groups of HIV-1 virus strains known as M (class M) and O (Class M), N (Natural

Varieties) or P (Proteomics). The likelihood of developing AIDS is higher in individuals who contract HIV through HIV-1.

HIV-2: One of the retroviruses, HIV-2, can also result in the onset of HIV. West African individuals are commonly infected with HIV due to this virus. With the exception of being a rare cause of HIV, this strain of the virus has slowed down its progression and is typically less aggressive than HIV-1. There are eight groups of HIV-2, with A and B being the ones that can cause epidemics [2].

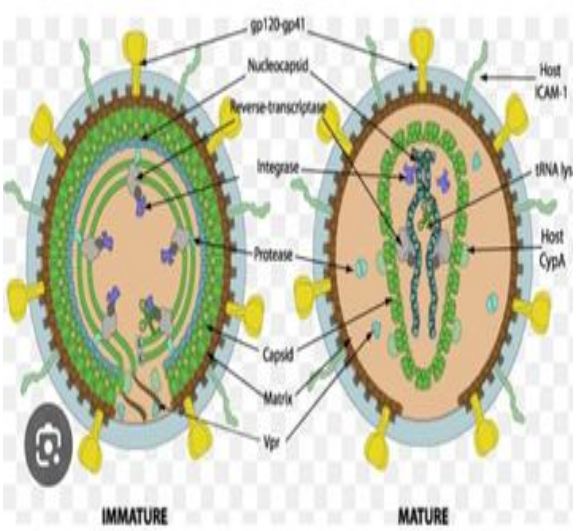


Fig2:Types of Hiv

II. PATHOPHYSIOLOGY

Knowing about the pathophysiology of the HIV virus when it enters into our body. For the viral glycoprotein gp120 to attach to that cell, it must interact with the CD4 cellreceptor. This binding causes a series of conformational changes that reveal V3domain and adjacent regions, which form the binding domain of gp120 to chemokine recep-tors. The structure of gp41 undergoes changes due to the second interaction, resulting in the appearance of an extremely hydrophobic domain at the N-terminal, which is anchored into the plasma membrane and causes binding. In this process, the host and viral membranes approach and combine [3].

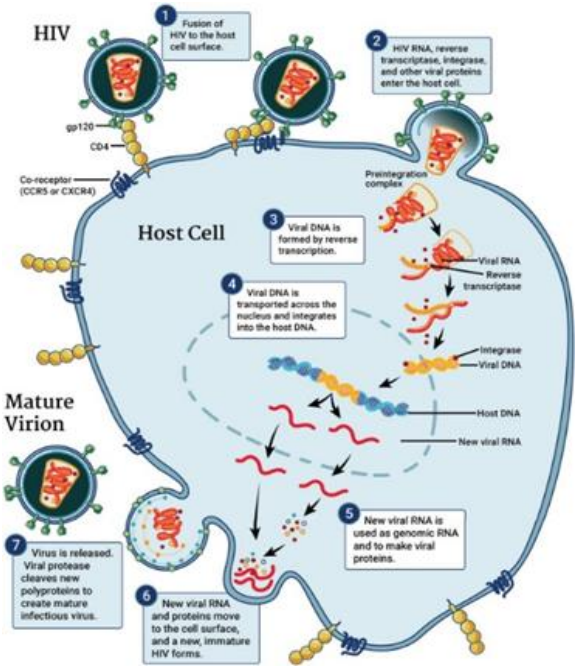
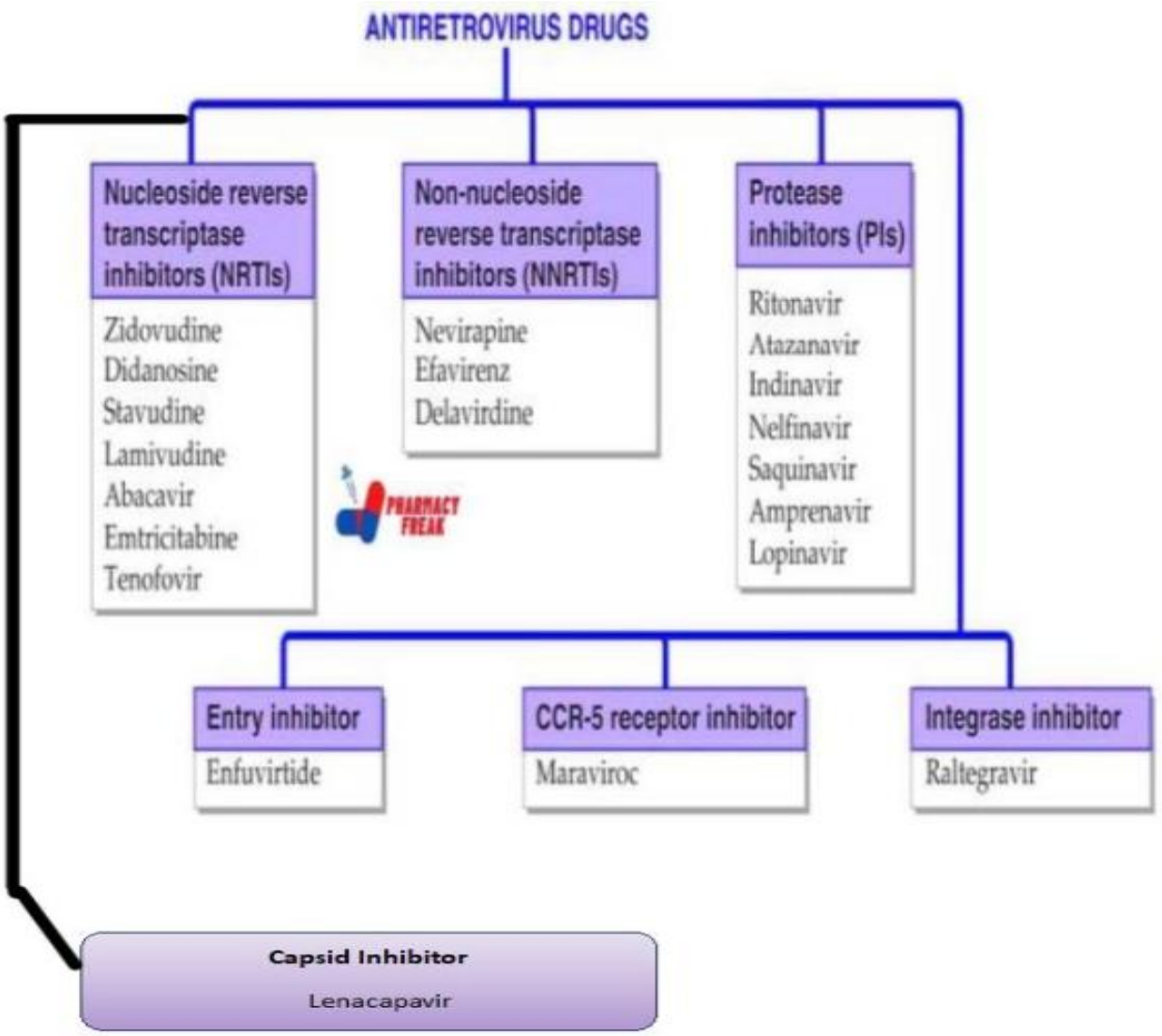


Fig3: Release of Virions

The viral genome is then decapsed and released after the nucleocapsid has been internalised. This occurs in stages. TRIM5, a restriction factor that alters the capsid's stability, is required for the virus to function by inhibiting it. The reverse transcriptase activity commences at this stage to initiate DNA from RNA. Activated or resting cells can be infected by the virus, but retro transcription of these cells is incomplete in restive lymphocytes. The absence of proofreading control activity in reverse transcriptase enables the constant production of mutants or quasi-espèces. The preintegration complex of proviral DNA is a combination of cellular factors and viral proteins (IN, RT, P17, and V pr) that are transported to the nucleus and integrated into the genome by viral integrase, leading to an evolution of HIV. This process is known as pre-integratiogenesis. For replication to begin, the viral genome must undergo transcription, which is influenced by various factors such as cellular proteins, Tat proteins (which regulate immune recognition), and Rev proteins that increase transcription. The protease inhibitors play a crucial role in helping virions assemble from human cells. When virions are replicated, they cloak our cell membranes, making it difficult for the immune system to recognize them. As a result, they emerge as viral cells wrapped in a protective capsid [4].

III. CLASSIFICATION



DRUG PROFILE
Drug name: Lenacapavir
Weight: 968
Chemical Formula:
C39H32ClF10N7O5S2
Therapeutic Categories
Human Immunodeficiency Virus 1 Capsid Inhibitor
Mechanism of Action:
Gag-Pol polyprotein (Human immunodeficiency virus type 1 group M subtype B (isolate HXB2)) Inhibitor

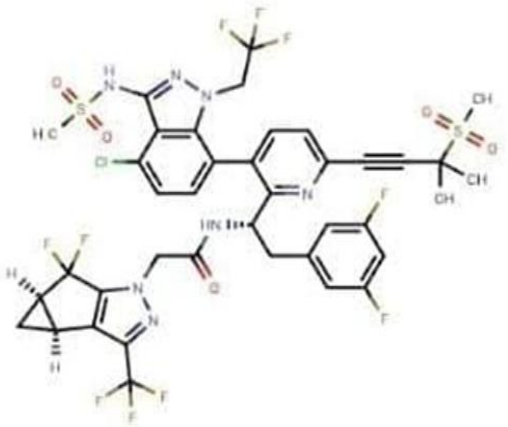


Fig 4: Structure of Lenacapavir

Background

HIV/AIDS remains an area of concern despite the introduction of numerous successful therapies, mainly due to the emergence of multidrug resistance and patient difficulty in adhering to treatment regimens.1,2 Lenacapavir is a first-in-class capsid inhibitor that demonstrates picomolar HIV-1 inhibition as a monotherapy in vitro, little to no cross-resistance with existing antiretroviral agents, and extended pharmacokinetics with subcutaneous dosing[5].

Pharmacodynamics

Lenacapavir is an antiviral drug with an extended pharmacokinetic profile. Lenacapavir works against the HIV-1 virus by inhibiting viral replication: it interferes with a number of essential steps of the viral lifecycle, including viral uptake, assembly, and release.6 Single subcutaneous doses ≥100 mg in healthy volunteers resulted in plasma concentrations exceeding the 95% effective concentration (EC95) for ≥12 weeks while doses ≥300 mg exceeded the EC95 for ≥24 weeks. In treatment-naive HIV-1-infected patients, a single subcutaneous dose of 20-450 mg resulted in a mean maximum log10-transformed reduction in plasma HIV-1 RNA of 1.35-2.20 by the ninth-day post-injection[6].

IV. MECHANISM OF ACTION

Action of lenacapavir by stopping the production of virions

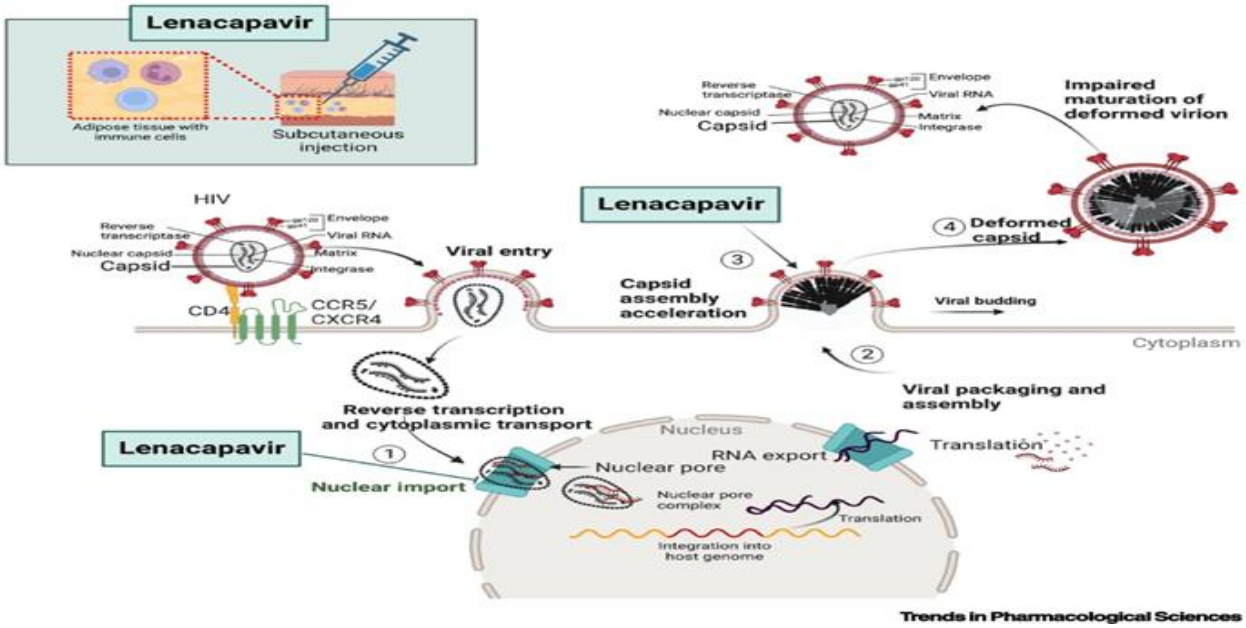


Fig5: Mechanism of Lenacapavir

Lenacapavir disrupts several phases of the HIV life cycle. By binding to two adjacent subunits of the HIV capsid protein, it interferes with their interactions that are crucial for several phases of viral replication. This includes the capsid-mediated nuclear uptake of preintegration complexes, the production of virions, and the proper formation of the capsid core. Viruses produced in the presence of lenacapavir have misshapen capsids that can enter new target cells but are unable to replicate[7].

Inhibition of Early Replication Stages

Lenacapavir works by blocking the nuclear import and reverse transcription processes, which stops the viral genome from integrating into the host DNA.

Inhibition of Late Replication Stages

Inhibition of the later stages of replication disrupts the assembly of the capsid and the maturation of the virion, leading to the production of viruses that can't infect.

Resistance Profile

This treatment is effective against strains that are resistant to various classes of HIV drugs, and it has low cross-resistance thanks to its unique mechanism [8].

V. PHARMACOLOGICAL ACTIONS

Let's talk about how lenacapavir is administered. When we look at the plasma concentrations after taking it orally (a) versus subcutaneously (b), we see some interesting differences.

For the subcutaneous route: When lenacapavir is given subcutaneously, it releases slowly and steadily, with the amount absorbed increasing proportionally up to 927 mg. This gradual release from the injection site leads to a unique absorption pattern, characterized by delayed and first-order absorption kinetics. As a result, the time to reach maximum concentration is around 77 to 84 days after the dose, and the half-life franges from 8 to 12 weeks.

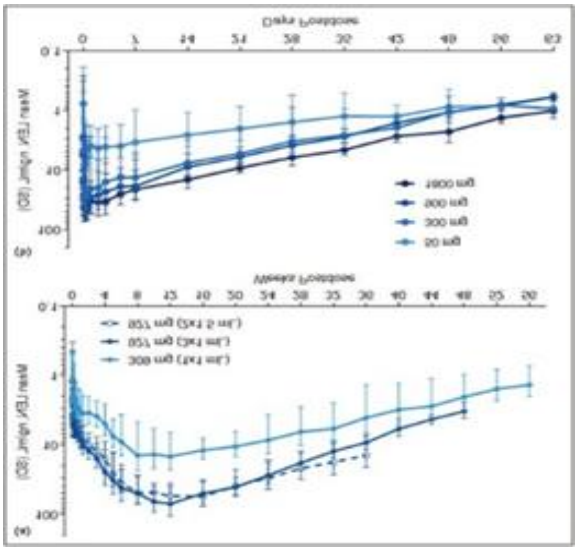


Fig 6: Subcutaneous administration of Lenacapavir

ORAL: The half-life of oral lenacapavir is approximately 10 to 12 days, and its absorption is unaffected by meal intake. In current clinical trials, oral lenacapavir is used for initial pharmacokinetic loading before transitioning to subcutaneous dose every six months. This is based on the estimated pharmacokinetics of phase 2/3 oral and subcutaneous combination regimens in healthy volunteers. Adapted from [9].

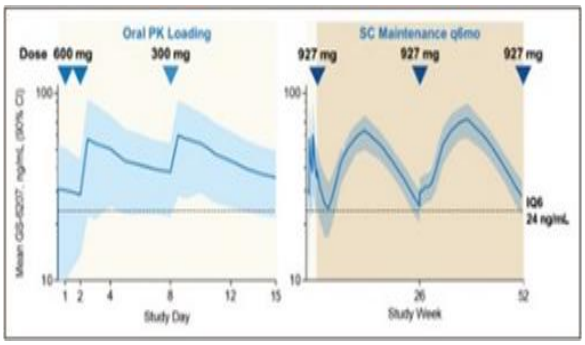


Fig 7: Oral administration of Lenacapavir

REFERENCES

[1] Justiz Vaillant AA, Naik R. HIV-1 Associated Opportunistic Infections. Stat Pearls. 2022 Jan.

[2] Peng Y, Zong Y, Wang D, et al. Current drugs for HIV-1: from challenges to potential in HIV/AIDS. Front Pharmocol. 2023; 14:1294966. doi:10.3389/fphar.2023.1294966.

[3] Matreyek KA, Engelman A. Viral and cellular requirements for the nuclear entry of retroviral preintegrationnucleoprotein complexes. Viruses 2013; 5:2483511.

[4] Yang H, et al. Structural insight into HIV-1 capsid recognition by rhesus TRIM5α. Proc Natl Acad Sci U S A2012;109:1837.

[5] Zhuang S, Torbett BE: Interactions of HIV-1 Capsid with Host Factors and Their Implications for Developing Novel Therapeutics. Viruses. 2021 Mar 13(3). pii: v13030417. doi: 10.3390/v13030417.

[6] Link JO, Rhee MS, Tse WC, Zheng J, Somoza JR, Rowe W, Begley R, Chiu A, Mulato A, Hansen D, Singer E, Tsai LK, Bam RA, Chou CH, Canales E, Brizgys G, Zhang JR, Li J, Graupe.

[7] Rhee MS, Tse WC, et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. Nature 2020; 584:614–618.PubMed | CrossRef | Google Scholar.

[8] Gilead Sciences, Sunlenca (Lenacapavir) Prescribing Information, 2022
NIH ClinicalInfo Database.

[9] Begley R, Rhee M, West SK, et al. PK, food effect, and safety of oral GS-6207, a novel HIV-1 capsid inhibitor. 2020 Conference on Retroviruses and Opportunistic Infections; Boston, Massachusetts, USA; March 8–11, 2020.