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A Review of Lenacapavir Act as Caspid Inhibitor

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Abstract: *HIV is an infection that targets the immune system of the body, specifically the CD4 cells, which are white blood cells to prevent the spread of the virus by using medications that alter the HIV genome. The rise of drug-resistant viruses has rendered all antiretroviral medications, including emerging drug classes, largely or completely inert. The HIV capsid, a protein shell that protects the virus's genetic material and replication-related enzymes, is the family of inhibitors that lenacapavir belongs to. HIV cannot function correctly in the presence of capsid inhibitors. HIV capsid can be damaged by capsid inhibitors at several stages of the viral life cycle. HIV levels can be lowered and its spread can be halted as a result. It is recommended to use Lenacapavir in combination with other antiretroviral to treat HIV-1 infection in adults with extensive treatment experience who have multidrug-resistant HIV-1 infection and are not responding to their current antiretroviral regimen due to resistance, intolerance, or safety concerns. Metabolic studies, pharmacodynamics, pharmacokinetics, mechanism of action, adverse effects, Pre-clinical studies, Clinical trial are all included in this review article.*

Keywords: Lenacapavir, Mechanism of Action, Adverse effects, Clinical Trials

I. INTRODUCTION

HIV infection is a serious public health concern. HIV-1 and HIV-2 are two genetically different variants of the virus. With a frequency of almost 95%, HIV-1 is more common than HIV-2 worldwide. Out of an estimated 38.4 million people globally, about 28.7 million are on antiretroviral therapy (also called ART for their HIV-1 infection. A person with AIDS has a compromised immune system as a result of infection with HIV-1, which can lead to illness. A CD4+ T-cell count of less than 200 cells per microlitre or HIV infection with related conditions such as lymphomas, Kaposi's sarcoma, cryptococcal meningitis, tuberculosis, etc., are indicators of AIDS. HIV infection is a serious public health concern. HIV-1 and HIV-2 are two genetically different variants of the virus. A high HIV-1 viral load and a low CD4+ T-cell count are classic indicators of HIV-1 infection progression and treatment failure. An uncontrolled HIV-1 infection might become rather serious [1, 2].

Drug resistance, especially multi-drug resistance (MDR), has increased in recent years as a result of the introduction of antiretroviral therapy (ART). Unmanaged drug resistance reduces the effectiveness of antiretroviral therapy (ART), raising the risk of infection with HIV and HIV-related death rates. Since traditional antiretroviral therapy is unsuccessful against MDR HIV-1 infection, new drugs must be developed to fulfil unmet medical needs. the US Food and Drug Administration (USFDA) in recent years. Lenacapavir (LEN) is the first capsid inhibitor in its class to receive a licence after being approved by the European Medicines Agency (EMA) and Health Canada as a treatment for drug-resistant HIV-1 infection [3, 4].

II. LENACAPAVIR SODIUM

Chemical name: sodium (4-chloro); Molecular formula: $C_{39}H_{31}ClF_{10}N_7NaO_5S_2$; Molecular Weight: 990.264; IUPAC:1h-Cyclopropa (3,4) Cyclopenta(1,2-C) Pyrazole-1-Acetamide, N-((1s)-1-(3-(4-Chloro-3-((Methylsulfonyl)Amino)-1-(2,2,2-Trifluoroethyl)-1h-Indazol-7-Yl)-6-(3-Methyl-3-(Methylsulfonyl)-1-Butyn-1-Yl)-2-Pyridinyl)-2-(3,5-Difluorophenyl) Ethyl)-5,5-Difluoro-3b,4,4.

Sunlenca's active ingredient has a two-year shelf life, a pka of 6.8, and a partition coefficient (log P) of 5.1. There are eight stereoisomers of LEN, and each one has three chiral centres. The (2S,3bS,4aR)-isomer is the primary isomeric

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active ingredient in Sunlenca. There are several different forms of LEN, including crystalline in nature amorphous, solvates, etc. Sunlenca uses crystalline LEN sodium because of its biopharmaceutical qualities, durability against the effects of hydrolysis, oxidation, and photolysis, also as well as its consistency and usefulness.

Sunlenca injection is a sterile, preservative-free, transparent, yellowish-brown solution that also contains additional ingredients such as water for injection and polyethylene glycol 300. The film-coated, beige, capsule-shaped Sunlenca tablet contains a variety of other non-medicinal ingredients [5, 6].

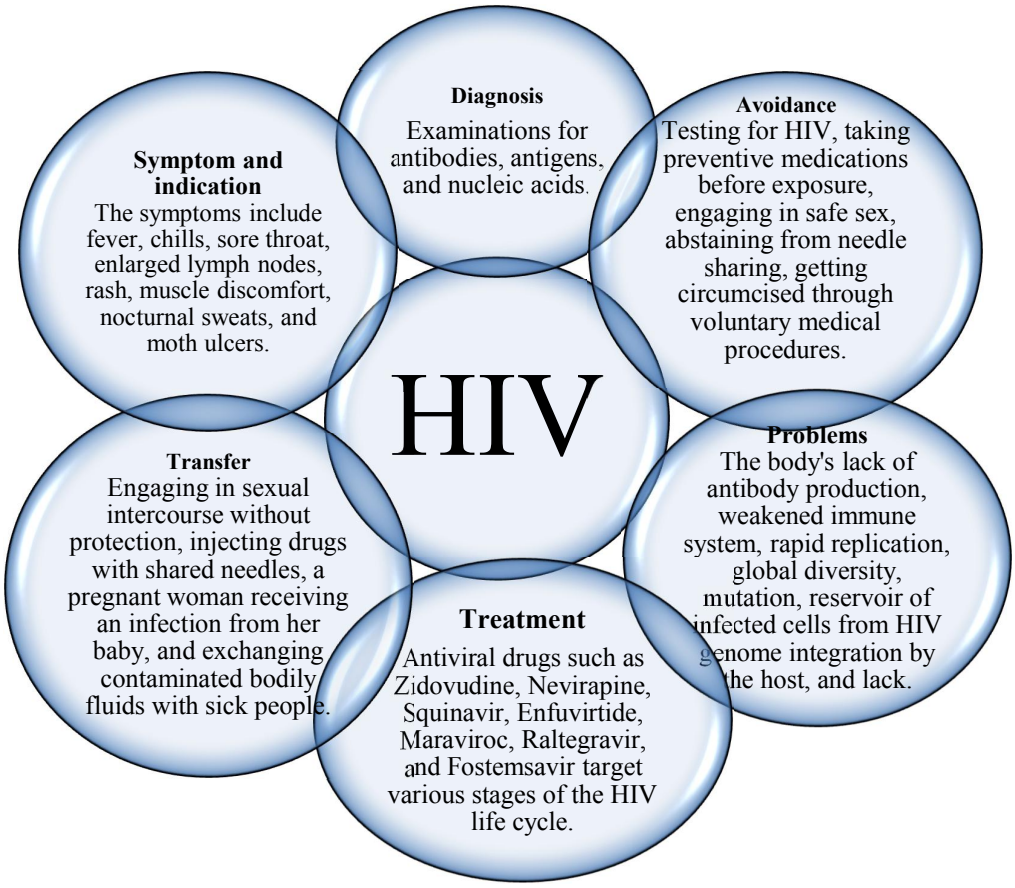

Fig 1: Overview of HIV

III. MECHANISM OF ACTION OF LEN

The retrovirus known as HIV-1 is encased in a shell. Within the protein shell of the HIV-1 capsid are reverse transcriptase, integrase, nucleocapsid, and viral RNA. HIV-1 performs numerous vital functions during its various replication phases, including mobility, interacting with the host cell, shielding, and the release within the viral DNA inside the host cell. The capsid's normal functions, including as nuclear absorption and viral DNA integration, impede the HIV-1 virus life cycle in a number of ways. Because of these characteristics, the HIV-1 capsid is a favourable target for treatment [7, 8].

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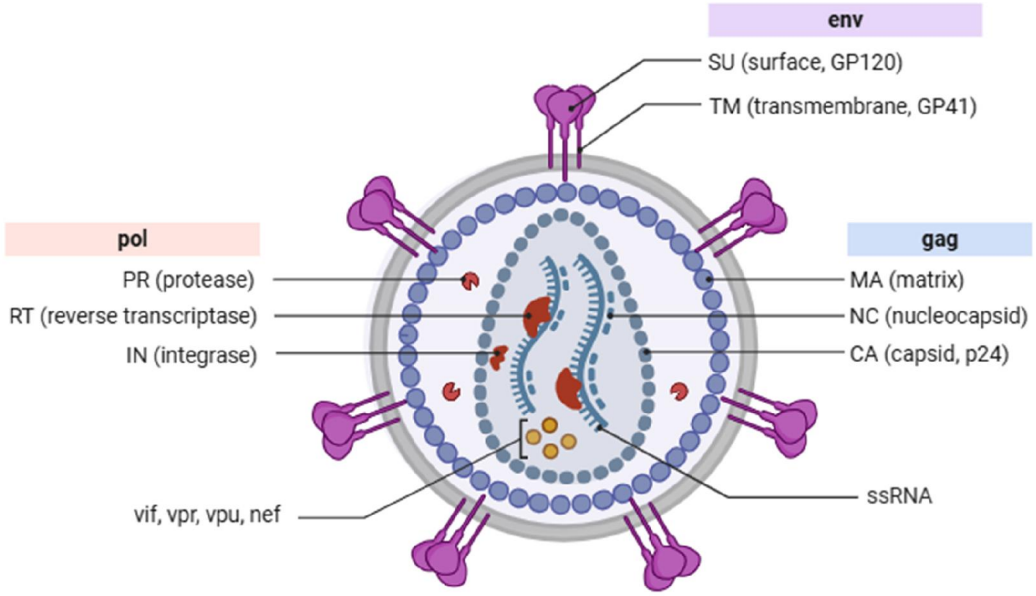

Fig 2: HIV Viron

HIV-1's protein shell is composed of repeating subunits known as protomers (hexamers). LEN specifically interacts with the HIV-1 capsid at the boundary between two hexamer subunits, involving one residue (N74) from the N-terminal region of one hexamer and two residues (N183 and K70) from the neighbouring hexamer's C-terminal domain. At different stages of the HIV-1 replication process, this event either inhibits or stops the development of HIV-1 capsid, preventing its various activities. Consequently, LEN interferes with several stages of the HIV-1 life cycle, including capsid-facilitated nuclear entrance, viral production and release, and maturation of the capsid nucleus [9-12].

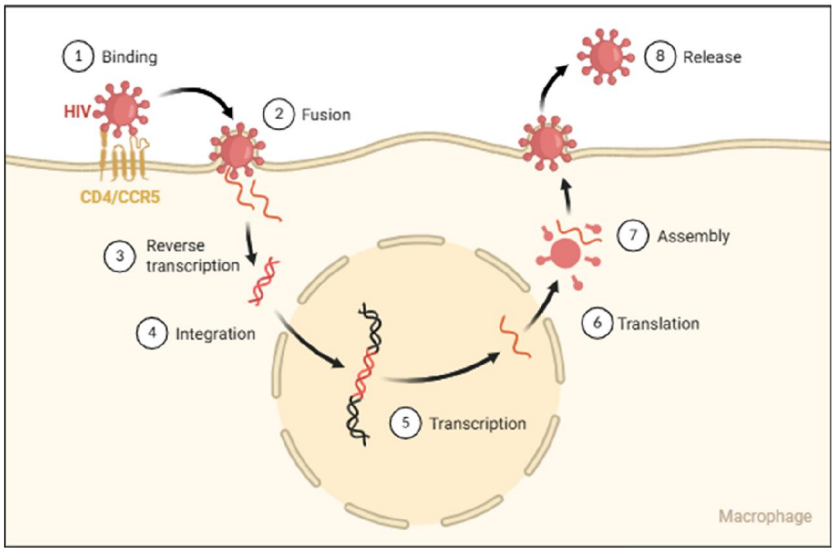

Fig 3: HIV life cycle

3.1 Pharmacodynamics

Lenacapavir primarily targets HIV-1 capsid activity and halts HIV-1 replication by binding directly to the region where capsid subunits of proteins assemble. Inhibition of capsid-binding importing co-factors to prevent viral nuclear import,

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destabilisation of Gag and/or Gag-Pol the polyproteins for the formation of virion, and interference with appropriate capsid core assembly are the three phases of the replication of the HIV lifecycle during which this inhibition takes place. Lenacapavir's EC50 in HIV-1-infected cells was measured in vitro using three distinct concentrations: 105 pmol/L for MT-4 cells, 32 pmol/L for primary human CD4+ cells, and 56 pmol/L for macrophages. A, A1, AE, AG, B, BF, C, D, E, F, G, and H are among the HIV-1 subtypes against which renapavir has demonstrated efficacy. When compared to the wild type, some HIV-1 variants with capsid alterations L56I, M66I, Q67H, K70N, Q67H+N74S, and Q67H+T107N showed reduced sensitivity to lenacapavir in vitro, exhibiting 6 to > 3200-fold resistance [13-15].

After 26 weeks of treatment, lenacapavir-related capsid mutations were seen in 8 of the 19 patients in the ongoing worldwide phase II/III CAPELLA clinical research who were evaluated for resistance and administered lenacapavir in addition to optimal background therapy (OBT). Six people with the alterations M66I (one of which also possessed the N74D mutation), an individual with the variations Q67H and K70H, and a single individual with the alteration K70H made up the patient group. In comparison to patients with wild type, those had Q67H+K70R, M66I, and K70H mutations showed a 15-fold, 234-fold, and 265-fold reduction in lenacapavir susceptibility. Patients who received only effective lenacapavir treatment experienced eight incidences of lenacapavir resistance; four of these cases were brought on by noncompliance with oral behaviour therapy (OBT), and four of these cases resulted from the absence of any other completely successful medications in the treatment regimen [16-17].

In the phase II CALIBRATE trial, two (out of 157) patients were found to have developed resistant mutations: Q67H+K70R and M184M/I in one of them (at week 10) and Q67H in one of them (at week 54). These patients were likely not following oral antiretroviral therapy (ART) while receiving lenacapavir, a study for patients who had never received treatment. When HIV-1 strains were exposed to changes that render them immune to several kinds of antiviral drugs, lenacapavir's capacity to combat viruses remained unaffected [18]. Additional in vitro research indicates that lenacapavir may have an extra antiviral effect when taken with islatravir, rilpivirine, or cabotegravir [19]. This is especially true for larger quantities. Lenacapavir had no discernible effect on the QTcF interval, and there was no correlation seen between changes in lenacapavir levels in plasma with variations in QTcF [20].

3.2 Pharmacokinetics

Whereas the pharmacokinetics of SC lenacapavir are proportionate to the dosage in the 309–927 mg range, the pharmacokinetics of oral lenacapavir exhibit nonlinear sequences and are not directly proportionate to the dosage in the 50–1800 mg range. Because of the late release at the point of injection, lenacapavir's peak plasma levels following subcutaneous administration occur 84 days later than those following oral administration, which occurs approximately 4 hours after the dose [16-21].

Lenacapavir's absolute bioavailability ranges from 6 to 10% when taken orally. Meals had no effect on the oral pharmacokinetics of lenacapavir. Lenacapavir's AUCtau, Cmax, and Ctrough increased by 29–84% in HIV-1-positive patients with a long history of treatment, according to a population pharmacokinetic analysis. Since none of lenacapavir's bloodstream metabolites accounted for over 10% of the total amount of plasma exposure, there is no indication that the drug is extensively metabolised. The primary enzymes that break down drugs are CYP3A4 and UGT1A1. One iv doses of radiolabeled lenacapavir resulted in less than 1% of radioactivity being found in the urine and 76% in the faeces of healthy people [17].

Lenacapavir had an average half-life of 8–12 weeks when administered sublingually and 10–12 days when taken orally. Lenacapavir was found to be more prevalent in the systems of patients with minor liver difficulties and severe kidney disease (estimated CrCl 15–29 mL/min) as compared to healthy individuals. Nevertheless, these elevated levels were not considered clinically significant. Because lenacapavir binds to proteins around 99.8% of the time, haemodialysis is unlikely to affect the drug's exposure. Because lenacapavir is metabolised by CYP3A, UGT1A1, and P-glycoprotein (P-gp), it is not recommended to use it with strong inducers of these enzymes because this could lower blood levels of lenacapavir, which would affect its effectiveness and possibly cause resistance to the drug. Given the possibility of a large rise in plasma lenacapavir levels, it is not advised to give strong medications that inhibit of all three enzymatic routes at the same time (e.g., atazanavir/cobicistat) [22-23].

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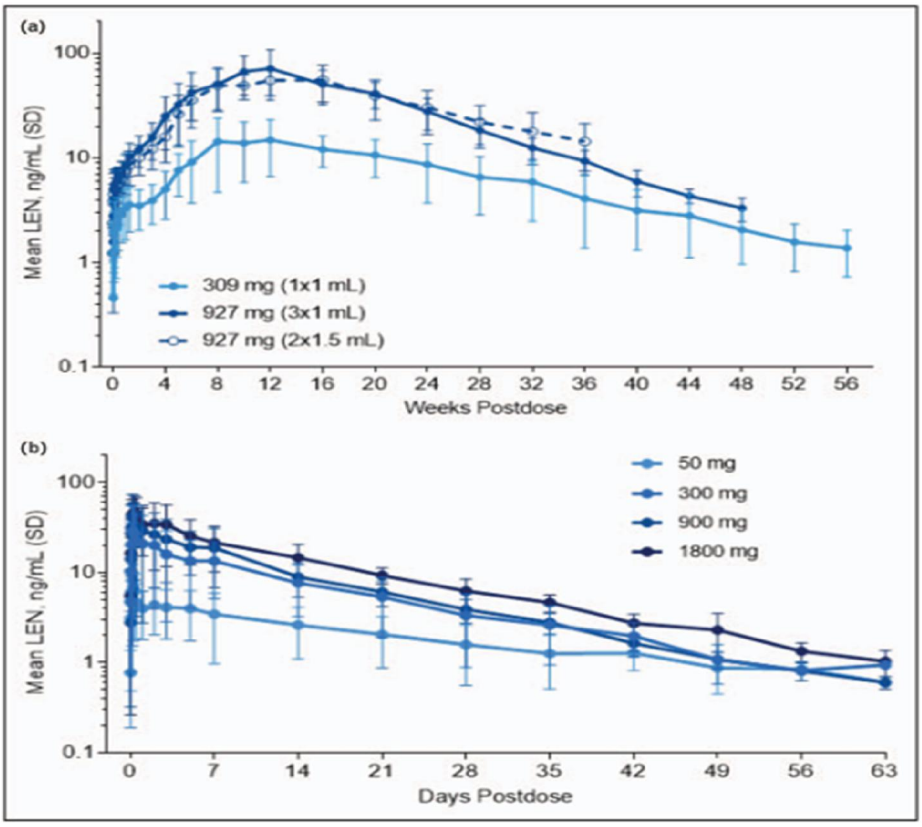

Fig 4: Observed lenacapavir plasma concentrations following oral (a) and subcutaneous (b) administration. Adopted [24-25]

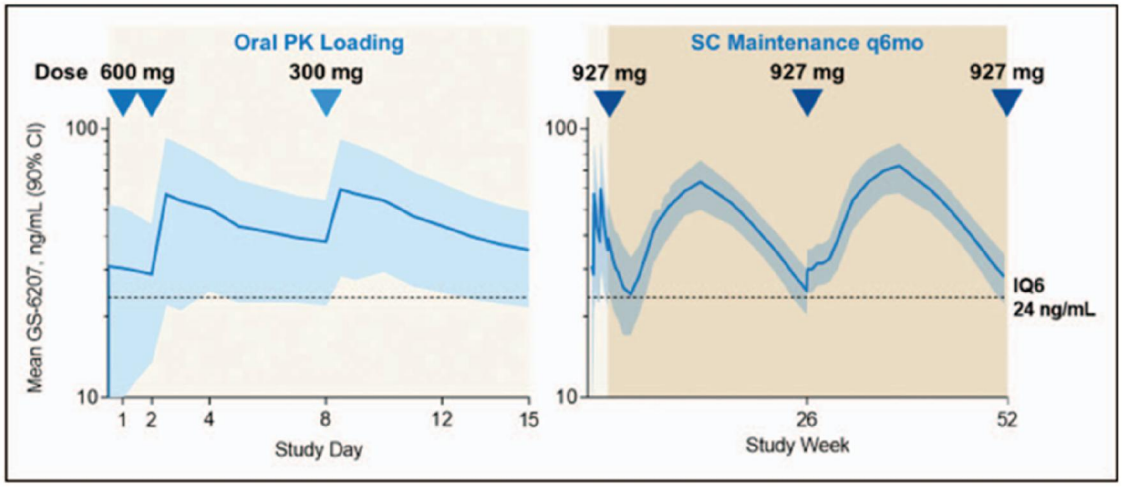

Fig 5: Predicted lenacapavir pharmacokinetics for phase 2/3 oral and subcutaneous combination regimens in healthy volunteers [23]

IV. METABOLISM

The cytochrome P450 system's isoenzyme CYP3A metabolises lenacapavir, and uridin diphosphate glucu ronosyltransferase 1A1 (UGT1A1) glurcuronidates it.

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It may function as a mild antagonist on the same enzyme unit and does not induce CYP3A. With no modifying impact on Pgp, BCRP (breast cancer resistant protein), or OAT (organic anion transporter), the medication is an intermediate of the P-glycoprotein (Pgp) membrane transporter. As demonstrated by a single injection of radiolabelled medication, lenacapavir is primarily eliminated by the biliary system; less than 1% of radioactive lenacapavir was detected in the urine and 76% in the faeces. The major molecule in plasma (69%) and faeces (33%), respectively, was unchanged lenacapavir.

4.1 Drug – drug interactions

It may function as a mild antagonist on the same enzyme unit and does not induce CYP3A. With no modifying impact on Pgp, BCRP (breast cancer resistant protein), or OAT (organic anion transporter), the medication is an intermediate of the P-glycoprotein (Pgp) membrane transporter. As demonstrated by a single administration of radiolabelled medication, lenacapavir is primarily eliminated by the biliary system; less than 1% of radioactive lenacapavir was detected in the urine and 76% in the faeces. The major molecule in plasma (69%) and faeces (33%), respectively, was unchanged lenacapavir. Lenacapavir should also be introduced cautiously after stopping such potent inducers because their effects last for weeks after stopping them, and it is advised to wait at least four weeks between doses. Antiretrovirals such as Efa virenz, Nevirapine, Etravirine, and Tipranavir/Ritonavir are not advised since moderate CYP3A inducers may also result in decreases of Lenacapavir Pk exposure [26]. Atazanavir/Cobicistat-induced concurrent inhibition of CYP3A, Pgp, and UG T1A1 may considerably increase Lenacapavir Pk exposure and should not be used (not recommended). In contrast, CYP3A-only inhibition, as in the case of Voriconazole, is linked to clinically insignificant increases in Lenacapavir Pk exposure (AUC and Cmax rise by 41% and 9%, respectively). The PK alterations are not thought to be clinically significant, even in the instance of Darunavir/Cobicistat, whose inhibition activity includes both CYP3A and Pgp (AUC and Cmax raised by 94% and 130%, respectively). The moderate suppression of CYP3A and the modest blocking of Pgp by Lenacapavir are the relevant pathways in metabolism of interest when considering Lenacapavir as a potential cause of drug-drug interactions. When it comes to medications having a limited therapeutic index, caution should be used. Dihydroergotamine, ergotamine, sildenafil, vardenafil, systemic dexamethasone or hydrocortisone/cortisone, lovastatin, sim vastatin, digoxin, midazolam, triazolam, rivarox aban, dabigatran, and edoxaban are some of the substrates that are of some concern in this case. Because Lenacapavir concentrations endure for extended periods of time, the drug's inhibitory effects may still affect these substrata's Pk exposure nine months after the last Lenacapavir injection. No restrictions occurred for Lenacapavir co-administration with medications that are inhibitors of BCRP, Pgp alone, OATP and the same thing applies for acid-reducing agents.

Comparing lenacapavir to the top 20 medications given in Italy as of December 2022 gives a broader picture of its low metabolic interaction potential [26-27]. Out of the twenty medications listed, only four exhibited any potential clinically significant interactions, all of which were caused by lenacapavir's inhibition of CYP3A. When used with Lenacapavir, two statins—Rosuvastatin (AUC and Cmax raised by 31% and 57%, respectively), Atorvastatin, and the b-blocker Bisoprol—are thought to have a low risk of overexposure. Amlodipine, an antihypertensive medication, is categorised as a potential interaction victim. In all of these situations, only clinical surveillance is advised rather than any preventative dose modifications [27].

V. ADVERSE EVENTS

In CAPELLA, lenacapavir was typically well tolerated when given orally and topically. During the 15-week effective monotherapy phase, 75% of patients receiving oral lenacapavir experienced not less than 1 adverse event (AE); neither of these occurrences was assessed as severe or graded III. Additionally, 25% of patients receiving a placebo experienced at least one AE. Nausea was the most common adverse effect of lenacapavir during this time, occurring in 13% of participants as opposed to 0% of those receiving a placebo. Injection site reactions, including pain (31%), swelling (31%), redness (25%), nodules (24%), and tissue stiffening (15%), were the most common side effects after 26 weeks of lenacapavir treatment; 62% of patients experienced lenacapavir-related injection site reactions. As the days went by, most injection site reactions were less severe [16-17].

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Abdominal bloating (10%), queasiness (12%), constipation (11%), and diarrhoea (11%), which were all common side effects (affecting at least 10% of patients), were mostly mild and not thought to be related to lenacapavir. In the seven individuals who took lenacapavir, there were no significant adverse events linked to the drug. One patient who established lenacapavir resistance unexpectedly passed away before the eleventh week. Of the patients, 28% had abnormal lab results of grade ≥ 3. This included high levels of blood sugar (fasting; 6%), AST (3%), bilirubin level directly (3%) and albumin in the urine (3%), as well as elevated creatinine levels (10%) and creatinine clearance (13%) [21].

After 52 weeks of treatment, lenacapavir was usually well tolerated in the CAPELLA research. A grade 1 spot of injection nodule caused one patient to stop taking lenacapavir 10 weeks after taking a dose at 52 weeks. Lenacapavir generally shown good tolerability when administered with any of the CALIBRATE combinations of medications that were investigated. The majority of injection site responses observed in patients treated with SC lenacapavir after 54 weeks were low to moderate in intensity. Erythema accounted for 27% of the reactions, edoema for 23%, and pain for 19%. Headache and nausea were the most frequent adverse events that were not related to the injection site, occurring in 13% of cases. There were no significant side effects linked to lenacapavir that were documented [21, 28].

The current article reviewed data from ongoing clinical trials that have demonstrated the safety and efficacy of LEN in HTE-PLWH, despite the small sample size. In the CAPELLA trial, virologic effectiveness of 78% was achieved at 52 weeks, with a small percentage of patients experiencing grade 3–4 adverse events.10,11 Moreover, ISRs, although frequent, were primarily mild to moderate in intensity. The long-acting, subcutaneous LEN composition, which can be administered every 6 months, is an important modification to the HIV treatment arsenal due to its distinct features. However, despite data showing the effectiveness of treatments containing LEN as a single successful drug, LEN should not be misused in the HTE population. For HTE individuals who have failed ART, it might be challenging to create regimens with the minimum of two active medications; nevertheless, the add-on technique, in which an active medication is added to a poor regimen, should be highly discouraged for LEN. The good news is that new treatments from novel medication classes have recently become available (like fostemsavir and ibalizumab) or might be accessible soon (like islatravir and broadly neutralising antibodies). Therefore, LEN should be paired with an OBR that incorporates minimum a second active compound that considers new as well as previous classes, whenever possible [29-30].

In order to identify the optimum course of treatment for HTE-PLWH on a failing ART, it is advised that the entire medication history, cumulative viral genotypes, and, if available, the use of phenotype resistance testing be reassessed. 1,6,40 The potential application of long-acting LEN administration in simplification strategies for HTE-PLWH with regulated HIV viraemia makes it especially appealing. 30 Treatment regimens with a high number of medications are frequently used for multi-experienced PLWH, which leads to a significant pill burden and a significant percentage of adverse events. But before this approach can be applied to HTE-PLWH in clinical practice, more research is required [31-33].

VI. CYCLE OF LEN DEVELOPMENT

The significant event (patent filing, clinical studies, and drug regulatory affairs) of LEN illustrates Figure 6.

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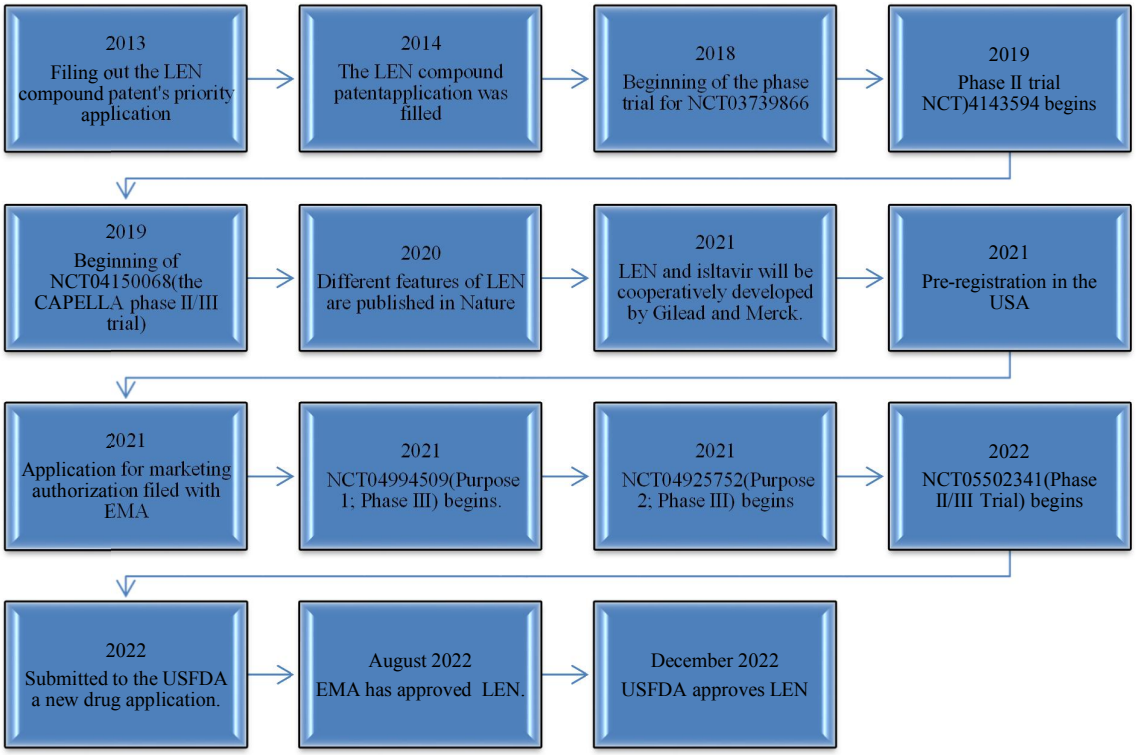

Fig 6: Important Events

VII. PRE-CLINICAL STUDIES

The literature provides a thorough description of the preclinical research on LEN [17, 34-37]. LEN has received approval from the USFDA, Health Canada, and EMA to disclose all of its pharmacological data. As a result, this section only offers an overview of pre-clinical research. 105 pM (MT-4 cells infection with HIV-1), 32 pM (human CD4+ T cells), 20–160 pM (23 clinical isolates of HIV-1), 56 pM (macrophages), and 885 pM (HIV-2 isolates) were the half-maximum effective concentrations (EC50) that LEN showed. Additionally, according to these findings, LEN is roughly 8 to 10 times more inactive for HIV-2 isolates than HIV-1 isolates [7, 35]. LEN's half-maximal cytotoxic concentration (CC50 in M) ranged from 24.7 M to >50 M in the cytotoxicity assay conducted on cell lines from humans (MT4, Huh-7, Gal-HepG2, Gal-PC-3, and MRC-5) and 1º human cells (hepatocytes, quiescent PBMCs, stimulated PBMCs, CD4+T-lymphocytes, and monocyte-derived macrophages). The corresponding selectivity index (CC50/EC50 for HIV-1) was found to be between 140,000 and 1,670,000. There was no discernible reaction to the off-target experiment of LEN (10 M) among 87 distinct receptors, also enzymes, and ion channels [35]. These data signified the potency of LEN against HIV-1 and the low potential of LEN to provide off-target effects. The effect of LEN against drug-resistant isolates of HIV-1 was also promising Table 1 [7].

Table 1: LEN's ability to combat drug-resistant HIV-1 isolates

ART Class	HIV-1 Mutant	Fold Resistance (LEN)	Fold Resistance (Control)	Fold Resistance (ART Agent)
Nucleoside reverse transcriptase inhibitor	K65R	0.6 ± 0.2	Emtricitabine	Emtricitabine 14.1 ± 2.6
	M184V	0.3 ± 0.3	Emtricitabine	Emtricitabine >23.0
	6TAMs	0.2 ± 0.1	Emtricitabine	Emtricitabine 4.0 ± 2.8

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Non-nucleoside reverse transcriptase inhibitor	Y188L	0.5 ± 0.1	Efavirenz	Efavirenz >22.5
	L100I + K103N	0.5 ± 0.2	Efavirenz	Efavirenz >22.5
	K103N + Y181C	0.6 ± 0.2	Efavirenz	Efavirenz >22.5
Integrase inhibitor	E138K + Q148K	0.6 ± 0.3	Elvitegravir	Elvitegravir >53.8
	G140S + Q148R	0.8 ± 0.3	Elvitegravir	Elvitegravir >53.8
	E92Q + N155H	0.8 ± 0.3	Elvitegravir	Elvitegravir >53.8
	N155H + Q148R	1.2 ± 0.7	Elvitegravir	Elvitegravir >52.9
Maturation inhibitor	V230I in Capsid	0.7 ± 0.2	Bevirimat	Bevirimat >67.5
	V7A in 14-amino acid spacer peptide 1 (SP1)	0.8 ± 0.2	Bevirimat	Bevirimat >67.5
Protease inhibitor	M46I + I50V	0.7 ± 0.2	Darunavir	Darunavir 27.1 ± 23.1
	I84V + L90M	0.3 ± 0.1	Atazanavir	Atazanavir 32.7 ± 7.8
	G48V + V82A + L90M	0.3 ± 0.1	Atazanavir	Atazanavir 31.0 ± 11.9
	G48V + V82S	0.4 ± 0.2	Atazanavir	Atazanavir 15.2 ± 3.2

The USFDA, EMA, and Health Canada documents, as well as Gilead's patent/patent application file, reveal the pharmacokinetics data of LEN in the animal models (Sprague-Dawley rats, Beagle dogs, and Cynomolgous monkeys). LEN was examined in rats (100 mg/kg and 10 mg/kg) to evaluate its impact on the central nervous system and respiratory system, and in dogs (100 mg/kg) to evaluate its impact on the heart (blood pressure, heart rate, ECG, QT, and QTc) (36–39). There was no discernible risk to the lungs, central nervous system, or heart in these animal-based investigations. LEN was non-carcinogenic and non-mutagenic, and it showed no effects on animal fertility [7].

7.1 Clinical Studies

Eight clinical studies centred on lenacapavir (LEN) were found by using the above keywords to search Gilead's website and the clinical trial database. These studies, which cover a range of populations and phases pertinent to LEN research, which includes its function in HIV prevention and treatment, are described in detail in Table 3 of the referenced material. All finished and continuing LEN clinical trials in these sources were identified and summarised thanks to this thorough study [40-41].

Table 2: An overview of interventional clinical trials sponsored by Gilead evaluating LEN for the treatment of HIV infection

NCT Number (Other IDs; Start Date; Completion Date; Last Update)	Objective/Interventions (Number Enrolled; Allocation; Primary Purpose)	Phase (Status; Location; Results)
NCT05502341 (GS-US-621-6289 and 2022-509029-33-00; 16 August 2022; January 2026; 18 January 2023)	Safety and efficacy of Bictegravir/LEN versus ART (671; Randomized; Treatment)	2/3 (Recruiting; United States; Not available)
NCT05052996 (GS-US-563-6041; 5 October 2021; August 2023; 21 December 2022)	Safety and efficacy of the combination of LEN and islatravir (136; Randomized; Treatment)	2 (Active; United States; Not available)

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NCT04949590 (GS-US-412-5624 and DOH-27-072021-6125; 30 August 2021; March 2024; 18 January 2023)	Safety and efficacy of LEN and emtricitabine/tenofovir alafenamide (F/TAF) for PrEP—PURPOSE 1 (5010; Randomized; Prevention)	3 (Recruiting; South Africa; Not available)
NCT04925752 (GS-US-528-2023 and DOH-27-102021-6681; 28 June 2021; January 2024; 31 January 2023)	Safety and efficacy of LEN in preventing HIV-1 infection—PURPOSE 2 (3000; Randomized; Treatment)	3 (Recruiting; United States; Not available)
NCT05181040 (GS-US-536-5816; 8 April 2021; 9 June 2022; 8 November 2022)	Safety and tolerability of the combination of LEN with tenofovir and zlnirlvudine (32; Randomized; Treatment)	1 (Active; United States; Not available)
NCT04150068 (GS-US-200-4625 and 2019-003814-16; 21 November 2019; 5 October 2020; 19 October 2022)	Safety and efficacy of LEN as an add-on to a failing HIV-1 therapy due to drug resistance—CAPELLA (72; Randomized; Treatment)	2/3 (Active; United States; Results posted on 20 October 2021)
NCT04143594 (GS-US-200-4334; 22 November 2019; 30 September 2021; 19 December 2022)	Safety and efficacy of regimens (LEN + ARTs) against HIV-1—CALIBRATE (183; Randomized; Treatment)	2 (Active; United States; Results posted on 19 December 2022)
NCT03739866 (GS-US-200-4072; 26 November 2018; 15 June 2020; 9 April 2021)	Safety, antiviral activity and pharmacokinetic study of LEN in HIV-1 infected patients (53; Randomized; Treatment)	1 (Completed; United States; Results posted on 9 December 2020)

The clinical trial database contains the findings of three clinical investigations (NCT03739866, NCT04143594, and NCT04150068) [41]. A few clinical studies pertaining to LEN were found by our PubMed search. Below is a summary of these studies. The clinical trial's website and the literature both provide the results from the clinical phase 1 research (NCT03739866) [35]. The safety, effectiveness, and notable pharmacokinetic properties of LEN were demonstrated in this study. The combination of LEN and other ART has been shown in clinical phase 2 data (NCT04143594)(42,43). After 54 weeks, the combination of LEN with several ARTs (emtricitabine, tenofovir, and bictegravir) showed a virological suppression of 85–92%. The study found that while erythema, swelling, and suffering were linked to SC administration of LEN, headache and nausea were the most common problems associated with oral treatment. NCT04150068's clinical phase 3 data was just released. MDR HIV-1 individuals were the subjects of this investigation [44]. More than 81% of patients in the LEN-treated group showed a higher reduction in viral load than those in the placebo group [45]. A commentary has been released regarding the current clinical phase 3 data of LEN (NCT04925752, Purpose 2 study). Nevertheless, this study makes no mention of its complete and definitive findings [46]. The activity of LEN against LEN-associated mutations in resistance was also examined in a proof-of-concept clinical trial. This study found a positive inverse relationship between medication resistance and HIV-1 replicating capacity. Additionally, two people in the research developed a capsid mutation (Q67H) after receiving LEN monotherapy.

7.2 Pharmacological Properties

LEN's important pharmacological parameters (dosing, pharmacokinetics, adverse effects, warning, toxicity, and drug interactions) are summarized:

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Table 3: Pharmacological parameters

Parameters	Summary
Dose/Regimen	Option1 Day 1: Abdominal SC injection (2 injections of 463.5 mg/1.5 mL) and Tablet (2 × 300 mg); Day 2: Tablet (2 × 300 mg); Maintenance dose every six months: Abdominal SC injection (2 injections of 463.5 mg/1.5 mL).(47) Option2 Day 1: Tablet (2 × 300 mg); Day 2: Tablet (2 × 300 mg); Day 8: Tablet (2 × 300 mg); Day 15: Abdominal SC injection (2 injections of 463.5 mg/1.5 mL); Maintenance dose every six months: Abdominal SC injection (2 injections of 463.5 mg/1.5 mL)(47) Option3
Absorption	Absolute bioavailability: 6–10% (oral) and 100% (SC); Tmax: 4 h (oral) and 77 to 84 days (SC)(17,35,47,48)
Volume of distribution	19240 (oral); 9500-11700 (SC); 976 Litres(17,47,49)
Protein binding	>98.5%(35,47,49)
Metabolism	CYP3AandUGT1A1metabolize LEN. LEN does not induce CYP3A4. LEN is neither a substrate nor induces/inhibits CYP2D6, CYP2C19, CYP2C9, CYP2C8, CYP2B6, and CYP1A2. LEN does not inhibit UGT1A1andanion transporters(35,47,49)
Renal Excretion	Excretion of the unchanged drug into feces;(35,47,49)
Half-life	Oral: 10–12 days; Subcutaneous: 8–12 weeks(35,47,49)
Clearance	Fifty-five days (oral) and 4.2 weeks (SC) (35,47,49)
Adverse Effects	It is common to experience nausea and injection site responses, such as oedema, discomfort, erythema, nodule, induration, pruritus, extravasation, or mass. Immune reconstitution syndrome, proteinuria, hyperglycemia, glycosuria, and elevated liver and creatinine enzymes are among the rare but potential side effects. (35,47,49)
Drug interactions	The development of drug resistance may result from the coadministration of certain medications (such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, efavirenz, nevirapine, rifabutin, rifampin, and rifapentine) and potent CYP3A inducers. Some medications (darunavir + cobicistat, cobicistat, famotidine, pitavastatin, rosuvastatin, tenofovir, alafenamide, and voriconazole) have not been shown to interact significantly.(35,47,49)
Food Interactions	The tablet may be taken with or without food (35,47,49)
Contraindications	It is not advised to take Sunlenca concurrently with potent CYP3A inducers/inhibitors, atazanavir/cobicistat, and certain herbal products (St. John's wort).(35,47,49)
Warning/Precautions	hepatitis, and polymyositis. Non-adherence to the recommended dose can cause drug resistance (35,47,49)
Toxicity/Overdose	There is little information on LEN's toxicity. In addition to supportive care, toxicity therapy is based on symptoms and indicators. Since LEN is a strong bound by protein medication, dialysis might not be beneficial. There are no reports of cardiotoxicity with LEN. (35,47,49)
Special population	The impact of LEN on the elderly, children, and pregnant/breastfeeding women has not been investigated. (35,47,49)

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VIII. CLINICAL TRIAL

Lenacapavir was authorised by the FDA based on data from a phase 2/3 research. The CAPELLA trial assessed the safety and efficacy of lenacapavir in conjunction with an appropriate background regimen for individuals with HIV-1 infection who were resistant to multiple medications. Seventy-two participants, all twelve years of age or older, from eleven different nations participated in this double-blind, randomised trial. Patients had to be resistant to at least two antiretroviral medications in three separate classes and have two or fewer antiretroviral medications that were completely effective when taken jointly in order to qualify. Depending on their amount of HIV-1 RNA, individuals were divided into each of the two cohorts during the screening phase. The viremia levels of 36 participants in Cohort 1 were constant, declining by 50 copies/mL at weeks 26 and 52 to exceed 200 copies/mL. The sample group's overall age of 52 years and 75% male sex preponderance were its main features. Over 99 percent of participants reported having documented resistance to at least two NRTI treatments, while 97 percent of participants reported having documented resistance to NNRTI medications. The lenacapavir group exhibited lesser median HIV-1 RNA levels (4.2 log10 copies/mL versus 4.9 log10 copies/mL) than the placebo group, but there were no discernible differences in baseline demographics between the groups in cohort 1. At the end of Cohort 1's functional monotherapy phase, 88% of the lenacapavir group achieved the primary goal, compared to just 17% of the placebo group (95% CI, 35% to 90%; $P < 0.001$). Regardless of the number of fully active agents in the optimised background therapy, 81% of patients in cohort 1 had a viral load of less than 50 copies/mL and 86% had less than 200 copies/mL at week 26 of the maintenance phase. Four of the eight individuals had HIV-1 RNA levels below 50 copies/mL, and they all demonstrated resistance to all 25 capsid inhibitors. Four of the eight people in the study had background therapy that was optimised and free of fully active medications, while one of the four did not adhere to background therapy to the required level. Lenacapavir's antiviral efficacy was unaffected by patients' resistance to any of the five types of antiretroviral medications or to any particular medication. Additionally, when lenacapavir was approved by the FDA, a fresh phase 2 studies was published. Lenacapavir's safety and effectiveness in treatment-naive individuals were examined in the CALIBRATE study, rather than those with a history of multidrug resistance [50-51].

Since the company is anticipated to file an application to expand the applications of lenacapavir before the end of this year, this review includes a summary of the CALIBRATE trial. In order to generate first clinical data for the development of future lenacapavir-containing regimens, the CALIBRATE trial is presently carrying out a phase 2 randomised, open-label, active-controlled investigation. Four intervention groups were randomly assigned to a total of 183 individuals from the Dominican Republic and the United States. In addition to daily oral emtricitabine/tenofovir alafenamide, participants in both groups 1 and 2 administered subcutaneous lenacapavir 927 mg every 26 weeks. The emtricitabine/tenofovir alafenamide combination was discontinued. Before starting injections, individuals in groups 1 and 2 received oral loading doses of lenacapavir. Group 3 was administered oral lenacapavir and oral emtricitabine/tenofovir alafenamide on a daily basis [52]. Lenacapavir was not administered to the fourth group of participants; instead, they were given bictegravir/emtricitabine/tenofovir alafenamide. All trial participants had a CD4+ T cell count of ≥200 cells/μL, an HIV-1 RNA viral load of ≥200 copies/mL, and no history of antiretroviral medication at the time of screening. Participation was prohibited for those with active hepatitis B or C infections. The primary objective was to count the total amount of patients who had a viral load below 50 copies/mL by week 54. Changes in log10HIV-1 RNA and CD4+T cell counts at weeks 28, 38, 54, and 80 were among the secondary outcomes that were evaluated, as was the proportion of participants who had a non-detectable viral load by those dates. Additionally, the rates of resistance, rebound, and virological failure were evaluated. The results from week 80 of the 2023 Conference on Retroviruses and Opportunistic Infections were comparable to those from week 58. The primary objective was accomplished in 85% to 92% of cases, and by week 54, there were no discernible differences between the therapy groups. 94% of individuals who received lenacapavir by injection or oral treatment showed a rapid decrease in virus levels by week 28 [53-54].

8.1 Role of Lenacapavir in treating HIV patients who have received multiple rounds of therapy

Despite the small sample size, the study examined data from ongoing clinical trials that demonstrate LEN is safe and beneficial in HTE-PLWH. Only a small percentage of patients in the CAPELLA research experienced significant adverse effects, and 78% of subjects had achieved viral suppression at 52 weeks. Furthermore, the majority of ISRs were mild to

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moderately severe, even though they were common. The extended-release LEN injection, which is given subcutaneously every six months, is a noteworthy addition to the HIV therapy toolbox because of its special qualities. Despite the effectiveness of regimens in which LEN is the only active medicine, it is recommended that the HTE population avoid overusing LEN [55-56].

For HIV patients who do not react to antiretroviral therapy, creating treatment plans including several efficacious drugs may be challenging. However, patients with few treatment alternatives should not be advised to add another medicine to a failing regimen. Thankfully, novel drugs like islatravir and broadly neutralising antibodies, which come from uncharted pharmacological classes like fostemsavir and ibalizumab, are now or will soon be accessible. As a result, if feasible, LEN should be paired with an OBR that includes at least one additional active agent from other classes, including both new and old ones. A review of their entire medication history, accumulated viral genotypes, and, if relevant, phenotype-resistant testing should be carried out in order to decide on the most effective mode of action for HTE-PLWH who are not responding to ART. The use of long-acting LEN administrations is very appealing for HTE-PLWH with controlled HIV viremia because it can be incorporated into more straightforward treatment regimens. Complex pharmaceutical regimens are frequently recommended to HIV patients who have tried several treatments, which lead to a high pill burden and a high incidence of side effects [57-59].

IX. FUTURE ASPECTS

Lenacapavir, a first-in-class capsid inhibitor, showed strong antiviral activity in HIV-1 patients, prophylactic activity in macaques, and high efficacy when combined with other antiretrovirals for patients at both ends of the treatment spectrum: heavily treated patients with multidrug resistance and those starting therapy for the first time. Future studies will investigate ways to translate the unique properties of lenacapavir, such as its novel mechanism of action with no pre-existing resistance, flexible route of administration (oral or injectable) and dosing interval (daily, weekly or up to every 6 months), into clinical benefit. Lenacapavir has the potential to address the diverse needs of individuals with HIV1, who have varied treatment histories, prior resistance, status of viremia and preferences for daily or long-acting therapy, as well as those at risk for HIV-1.

Treatment tiredness and difficulties adhering to oral daily therapy may be addressed by long-acting regimens involving infrequent doses, such as injectable up to every six months or oral weekly. For many PWH, subcutaneous lenacapavir, which is given by healthcare professionals every six months, does not add to the burden of treatment and aligns with the minimal clinical visit schedule. People who want an oral regimen that can be taken less frequently than daily may benefit from an oral weekly regimen. The development of a long-acting partner drug to be used in conjunction with lenacapavir for a comprehensive long-acting weekly oral or injectable regimen is still under progress. In virologically suppressed PWH, lenacapavir is now being tested as part of a weekly oral regimen in conjunction with islatravir, a nucleoside reverse transcriptase translocation inhibitor (NRTTI) (ClinicalTrials.gov Identifier: NCT05052996). Additionally, a longer dose interval injectable regimen of lenacapavir and islatravir is being developed.

Subcutaneous lenacapavir administered every 6 months is being evaluated as PrEP in two Phase 3 studies: PURPOSE-1 (ClinicalTrials.gov Identifier: NCT04994509) in adolescent girls and young women at risk of HIV-1 infection and PURPOSE-2 (ClinicalTrials.gov Identifier: NCT04925752) in cisgender men, transgender women, transgender men and sex nonbinary people at least 16 years of age at risk for HIV-1 infection. Lenacapavir is a first-in-class capsid inhibitor with long-acting properties. It has the potential to be developed as part of an injectable regimen with an up to 6-month dosing interval or an oral regimen with an up to weekly dosing interval, providing additional treatment options to address the diverse needs of persons with HIV-1 and for those who would benefit from PrEP.

X. CONCLUSION

Lenacapavir is a new medication that has been approved by the FDA, and it is administered subcutaneously every six months following a two to eight-day oral induction period. It has a distinct mechanism of action as the first capsid inhibitor authorized by the FDA for HIV-1 treatment. Clinical studies have shown that lenacapavir is safe and effective for treating individuals with multidrug resistance who have previous treatment experience. Due to limited treatment options for patients with multidrug resistance, cost may be considered a potential barrier, but healthcare providers should not

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underestimate its significance in treatment. Lenacapavir is currently under study for additional applications. The approval of LEN is a major achievement for patients who are HIV-1 positive. Observing the progress of several advantageous LEN-based drugs for combating drug-resistant HIV-1 infection would be fascinating. LEN is the initial CA inhibitor approved to treat HTE-PLWH on failing ART regimens who are resistant, intolerant, or have safety concerns with other drugs. Clinical studies have demonstrated that LEN is highly efficient and typically safe for people in this specific group who are infected with a virus resistant to various medications. In the years to come, LEN's qualities could play a major role in treating HTE-PLWH.

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