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Review Article

A Comprehensive Review of the Safety and Efficacy of Lenacapavir in the Treatment of Human Immunodeficiency Virus

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ABSTRACT

Acquired Immunodeficiency Syndrome (AIDS) is a sexually transmitted disease that can be passed from partner to partner, mother to child, or through blood exchange using infected syringes. AIDS symptoms might vary depending on characteristics such as age, gender, and physical activity. Headaches, muscle and joint discomfort, rashes, diarrhoea, weight loss, coughing, night sweats, sore throat, stomatitis, swollen lymph nodes, malaise, oral yeast infections, shingles (herpes zoster), and lung infections are all common symptoms. The Food and medication Administration (FDA) of the United States authorised Lenacapavir, a novel AIDS therapy medication, in 2022. Lenacapavir is a capsid inhibitor available in tablet and injection form that directly targets the Human Immunodeficiency Virus Type 1 (HIV-1) Capsid Protein. Various research and papers, like the Capella study, which assessed the safety and efficacy of subcutaneous Lenacapavir, were used to assess the safety and efficacy of Lenacapavir. The Calibrate study shed light on the absence of phenotypic resistance to Lenacapavir in HIV Gag cleavage site mutants and isolates resistant to existing medication classes. These studies also included data from a proof-of-concept clinical research on HIV patients examining phenotypic resistance to Lenacapavir and its efficacy as a monotherapy. The approval of Lenacapavir represents a viable new therapy option for those living with HIV. Its method of action, as well as promising safety and efficacy results from numerous studies, offer hope for better outcomes in the treatment of this severe disease.

Keywords: Lenacapavir, HIV treatment, AIDS therapy, Capsid inhibitor, Human Immunodeficiency Virus Type 1 (HIV-1), Capella study.

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INTRODUCTION

Acquired Immune Deficiency Syndrome (AIDS) is a disease caused by the Human Immunodeficiency Virus (HIV) that weakens the immune system, making the body susceptible to serious infections and illnesses. It is primarily transmitted through heterosexual intercourse. The impact of AIDS in many regions, including sub-Saharan Africa and Thailand, is similar, with the virus affecting individuals in these areas in various ways.[1] The first occurrence of AIDS in a demented person was reported in the United States in 1981. Doctors and scientists were astounded at the fast start of Kaposi's sarcoma, a rare malignancy in apparently healthy young gay men, at the time. The AIDS virus, now known as HIV (Human Immunodeficiency Virus), was discovered in 1983 and has been linked to this illness ever since. It spread not only among American men, but also among those who inject narcotics or undergo blood transfusions. Data from the Global Burden of Disease Report 2019 and United Nations Programme on HIV/AIDS (UNAIDS) 2019. From 1990 through 2019, the dataset comprises annual HIV/AIDS figures for 204 nations and all areas of the world.[2-5] Prevalence The researchers looked at rates, incidence, mortality, disability-adjusted life expectancy, and trends. Demographic changes were assessed using an analysis of age and gender distributions in various locations. The illness load was estimated using projections until 2040. Although incidence rates in many countries have decreased, Russia, Ukraine, Portugal, Brazil, Spain, and the United States have seen a rise in the number of new cases since 2010 due to population expansion. More than 0.5% of the global population is afflicted.[6,7] Every day, over 5,000 people become infected, including 500 children. Global mortality rates are decreasing. There are currently 11 deaths per 100,000 people; however, this figure is anticipated to fall to 8.5 by 2040. Prevalence is increasing, with South Africa, Nigeria, Mozambique, India, Kenya, and the United States suffering the most. And the percentage is rising year after

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year. Despite effective preventive measures, the risk of mother-to-child transmission remains high. There is an urgent need to create programmes to combat the rising prevalence of HIV.[8,9] In 1986, he became India's first known AIDS patient. Since then, the number of people living with HIV in India has risen to over 1.5 million, making it one of the countries with the highest HIV prevalence. The primary modes of HIV transmission in India are through prostitution and the high prevalence of genital ulcers. Wasting is a common symptom among HIV-positive individuals in India, but Pneumocystis carinii, a type of pneumonia, appears to be rare. Tuberculosis is the most common opportunistic infection among people with HIV in India. The misuse and overuse of antibiotics have led to an increase in multidrug-resistant strains of tuberculosis. The severity of the HIV epidemic in India is attributed to a lack of commitment to public health and education. There is no standardized national case reporting system, and homosexuality and prostitution are illegal. Reliable data on risk factors are difficult to obtain, and HIV education is limited. A survey found that a significant percentage of physicians were unaware that HIV causes AIDS or believed that AIDS can be transmitted through casual contact. The HIV epidemic in India extends beyond the initially affected groups, such as gay men and injection drug users. High HIV prevalence rates have been observed among various populations, including female Job Corps participants, young gay men, recovering alcoholics, and patients in psychiatric facilities. Accurate data on the epidemic are limited due to the lack of universal HIV testing and reporting.[10] Despite significant efforts to develop effective medications and a vaccine, a complete treatment, cure, or vaccine for AIDS is still years away. It is crucial to continue expanding efforts to prevent the spread of HIV by addressing behaviors that contribute to transmission. Understanding and influencing human behavior is essential in this endeavor. The institutions responsible for AIDS research (National Institute on Alcohol Abuse and Alcoholism-NIAAA, National Institute on Drug Abuse-NIDA, and National Institute of Mental Health-NIMH) primarily focus on designing, completing, and evaluating HIV prevention programs for different populations. These interventions should be based on foundational behavioral and social scientific research that investigates the factors influencing behavior and behavior change. However, much of this basic research is still in its early stages. In the early years of the epidemic, political obstacles hindered the study of relevant behaviors such as drug use and sex. Federal and legislative restrictions prevented the implementation of scientific and policy initiatives that advocated for a comprehensive national study on sexual behavior to assess the risk of HIV transmission in the general population.[11] According to the World health Organization (WHO) global health sector HIV plan, the number of HIV infections worldwide is predicted to fall from 1.5 million in 2020 to 335,000 by 2030. Similarly, the number of AIDS-related deaths is expected to fall from 680,000 in 2020 to under 240,000 by 2030. According to the National AIDS Control Organisation (NACO), around 2.14 million people in India were living with AIDS in 2017. Despite having a lower AIDS prevalence rate than many other nations, India has the world's third-largest population of persons living with AIDS. South Africa and Nigeria had higher incidence rates in 2018. In 2016, India's predicted HIV prevalence rate was 0.30%, placing the country 80th in the world.[12-14]

Lenacapavir is a new type of HIV medication that belongs to the capsid inhibitor class. It works by targeting the capsid protein, which is essential for the replication and spread of the HIV-1 virus. By interfering with the assembly of the virus, lenacapavir prevents it from reproducing in the body. The drug is available in both tablet and injectable forms. Initially, it is taken orally in divided doses over a two-week period. After that, patients can switch to the injectable formulation, which is given as a subcutaneous injection just under the skin. The injectable form has a long half-life of up to six months, which means it only needs to be administered a few times a year. Lenacapavir has shown potent antiviral activity and a favourable safety profile in clinical trials, with no significant adverse events reported. It is currently undergoing regulatory review by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of HIV-1 infection in adults with multidrug-resistant HIV-1. If approved, lenacapavir could offer a convenient and effective treatment option for people living with HIV-1.[15] Lenacapavir is a novel antiviral medication that targets the HIV-1 capsid protein. The capsid protein is required for the HIV life cycle and is involved in viral infectivity and maturation. Lenacapavir works by attaching to the HIV-1 capsid and prevents it from properly multimerizing into hexamers and pentamers, which are required for viral core production and replication. This interruption in capsid assembly prevents nuclear import and particle production, ultimately blocking the viral cycle's early stages. As a result, by interfering with key phases in the HIV infection process, lenacapavir shows promise as a potential treatment for AIDS.[16-18] Recently, a new small drug called Gilead Sciences 6207 (GS-6207) has shown promising results in suppressing the function of the HIV capsid in both laboratory and animal experiments (*in vitro* and *in vivo*). When lenacapavir (LEN; GS-6207) was injected subcutaneously at a dose of 450 mg, it resulted in a significant reduction in Human Immunodeficiency Virus Type 1 Ribonucleic Acid (HIV-1 RNA) viral load (2.3 log10) after 9 days. LEN demonstrated a multistage mode of action and exhibited potent antiviral activity in picomolar concentrations. Its characteristics, such as high antiviral efficacy, expected slow clearance from the body, and low water solubility, make it suitable for use as a long-acting drug with infrequent dosing. To assess the potential development of resistance against LEN, researchers conducted experiments where they exposed the virus to the drug in a controlled environment. They identified several variants in the Capsid (CA) portion of the Gag protein (L56I, M66I, Q67H, K70N, N74D/S, and T107N) that were associated with decreased susceptibility to LEN. However, these mutations were also found to be linked to reduced viral

fitness, meaning that the virus became weaker and less able to replicate. Notably, a recent study examined samples from 1,500 people living with HIV, representing various HIV-1 subtypes, and found none of these mutations, regardless of whether the individuals had previously taken Protease Inhibitors (PI) or not. This suggests that LEN may have a lower likelihood of resistance development compared to other drugs in its class.[19] The presence of various mutations in the HIV Gag protein has been associated with different levels of resistance to Maturation Inhibitors (MIs) and Protease Inhibitors (PIs). Mutations around specific cleavage sites within the Gag protein have been linked to resistance against Antiretroviral Therapy (ART) and the selection of PI-resistant mutants. Certain Gag substitutions, such as Q430R, A431V, K436E, I437V/T, L449F, and P453L, have been identified as conferring PI resistance and enhancing the fitness of PI-resistant mutants. Additional Gag mutations at non-cleavage locations, including L75R, H219Q, V390D/A, R409K, and E468K, have also been observed during resistance selection trials with PIs.

Regarding Maturation Inhibitors (Mis), naturally occurring Gag polymorphisms have been found to confer resistance to specific inhibitors like Bevirimat (BVM), which targets the last cleavage site of Gag. The V3620I mutation and polymorphisms at residues 369 to 371 in Signal Peptide 1 (SP1) have been associated with resistance to BVM. Resistance mutations at the CA/SP1 cleavage site (L363F/M, A364V, and A366T/V), where the V362I substitution naturally occurs, have emerged due to resistance selection against BVM. The study aimed to assess the sensitivity of HIV isolates carrying Gag mutations, including cleavage site mutations and naturally occurring substitutions, to a drug called LEN, which targets the capsid component of the Gag polyprotein. Additionally, the researchers examined LEN mutants with resistance mutations to the four major drug classes (Protease Inhibitors-PIs, Nucleoside Reverse Transcriptase Inhibitors-NRTIs, Non-Nucleoside Reverse Transcriptase Inhibitors-NNRTIs, and Integrase Strand Transfer Inhibitors-INSTIs) to better understand their resistance profiles.[20,21]

FDA Approval of lenacapavir

The Human Immunodeficiency Virus Type 1 (HIV-1) long-acting capsid inhibitor lenacapavir (Sunlenca) is being created by Gilead Sciences Inc. It is offered as an oral tablet and an injectable solution, the latter of which has a slow-release formulation to enable subcutaneous treatment every two years.[22] Lenacapavir gained its initial authorization in the EU in August 2022 for use in people with multi-drug resistant HIV infection for whom it is otherwise not viable to design a suppressive anti-viral regimen in combination with other antiretrovirals. Lenacapavir development milestones that led to its initial approval for the treatment of HIV-1 infection are outlined in this article.[23] Lenacapavir received FDA approval as the first long-acting capsid inhibitor for the treatment of individuals with Multidrug-Resistant Human Immunodeficiency Virus Type 1 (MDR HIV-1) in December 2022.This development would have a significant effect on Highly Treatment-Experienced People With HIV (HTE PWH) with few treatment options, which further motivated me to research the effectiveness of lenacapavir in HIV Pre-Exposure Prophylaxis (PrEP) clinical trials. To comprehend the safety, effectiveness, and resistance profiles of innovative Antiretroviral Therapy (ART) for the prevention and treatment of HIV, rigorous, long-term trials will undoubtedly need to be expanded upon. Lenacapavir, a first-in-class, long-acting capsid inhibitor that can be administered through biennial injection, received historic FDA approval for MDR HIV-1 treatment on December 22, 2022. This was a milestone for HTE PWH with few treatment choices. Based on results from the CAPELLA research (NCT04150068), this medication can be taken in combination with other antiretroviral medications. In upcoming clinical studies, potential lenacapavir companion drugs are being researched further for the treatment of HIV. Also in January 2021, the FDA approved a combination of the long-acting injectable medications cabotegravir and rilpivirine given every 4 or 8 weeks to adults with HIV-1 who have virologic suppression on a daily oral ART regimen.[24-26]

Lenacapavir acts by disrupting the mode of action of HIV-1, the virus that causes AIDS. During the replication cycle of HIV-1, the virus utilizes various components of the host cell to enter, integrate into the nucleus, replicate, and assemble new viral particles. One crucial component involved in this process is the viral capsid. After fusing with the host cell membrane, the viral capsid is released into the cytoplasm. The capsid is composed of monomeric Capsid proteins (CA) that assemble into hexamers and pentamers to form the capsid structure. The N-Terminal and C-Terminal Domains (NTD/CTD) on each CA monomer play a role in interacting with the host cell machinery. Lenacapavir targets the interaction between the CA monomers in the assembled capsid structure. It disrupts the binding of host proteins, such as Cleavage and Polyadenylation Specificity Factor subunit 6 (CPSF6) and Nucleoporin 153 (Nup153), to the capsid. These host proteins are essential for the capsid to cross the nuclear envelope and facilitate the integration of HIV-1's genetic material into the host cell genome. Specifically, lenacapavir binds to a phenylalanine-glycine binding pocket located between the NTD and CTD of adjacent CA monomers in the assembled capsid. By interfering with the binding of host proteins, lenacapavir prevents the capsid from efficiently entering the nucleus and inhibits the process of HIV-1 genomic integration. Overall, lenacapavir mode of action disrupts critical steps in the HIV-1 replication cycle, offering a potential therapeutic strategy to combat the virus.[27-29]

Lenacapavir has a difluorobenzyl ring that, in the overlayed structures, overlaps with the benzyl group of F321 in CPSF6 and F1417 in Nucleoporin 153 (Nup153) to occupy the same binding pocket as CPSF6/Nup153. Six lenacapavir molecules connect to each CA hexamer, forming extensive hydrophobic contacts, two

cation-interactions, and seven hydrogen bonds while making contact with over 2,000 square meters of buried protein surface area, according to the crystal structures of lenacapavir coupled to CA hexamers. Lenacapavir potent binding interferes with CPSF6 and Nup153 capsid interactions in a competitive manner. The EC_{50} values for *in vitro* HIV-1 replication inhibition trials in a few cell lines range from 12 to 314 pM., with early steps being more effectively inhibited than later ones. Lenacapavir prevents viral nuclear entrance at very low concentrations (0.5 nM), and at higher values (5–50 nM), it also prevents viral DNA synthesis and reverse transcription. Lenacapavir binding is anticipated to impede these interactions and prevent capsid nuclear entry because CPSF6 and Nup153 are necessary for nuclear entry.[30]

Lenacapavir is very newly approved drug which is used in AIDS. It is used as capsid inhibitor there are very few studies because it is approved in 2022 by FDA. We review lenacapavir to review the safety and efficacy of LEN to identify side effect and effectiveness of LEN. Due to which we review some safety and efficacy data.

METHODOLOGY

Search Strategy

We conducted a comprehensive literature search to gather information on the safety and efficacy of lenacapavir in HIV patients. We utilized databases such as Google Scholar to search for relevant articles published between 2019 and 2022. We focused on including the latest data available on the safety and efficacy of lenacapavir in HIV patients. Studies conducted prior to 2019 were excluded since lenacapavir was approved in 2022 and there was limited data available on its safety and efficacy before that time. We used commonly utilized terminology related to the safety and efficacy of lenacapavir in HIV patients while conducting the database search.

Selection Criteria

Initially, we screened the titles and abstracts of all articles to identify those that discussed the safety and efficacy of lenacapavir in AIDS patients. After carefully reviewing the full-text articles, we included data on safety and efficacy based on predefined inclusion criteria. Any minor wording changes were carefully reviewed during this process. We considered observational studies such as cohorts, randomized trials, and non-randomized trials that focused on individuals with HIV and explored the safety and efficacy of lenacapavir. We only included data that were freely available and not behind paywalls.

Data Extraction

We extracted relevant data from the included studies to gather information on the safety and efficacy of lenacapavir in HIV patients. The extracted data were based on the studies' findings regarding the safety and efficacy of lenacapavir in patients with HIV. To ensure accuracy during data extraction, we used an Excel sheet and followed a checklist for strengthening the reporting of observational studies.

Data Assessment

We analyzed the overall incidence of safety and efficacy based on the available data from all the studies. We also identified the incidence of safety and efficacy specifically in patients with HIV. The safety and efficacy studies were conducted in various countries, including Canada, Japan, Germany, Italy, Thailand, USA, Spain, South Africa, and France. We added the values based on the information provided in the studies.

RESULTS

The analysis was conducted based on a total of 13 citations retrieved from electronic database searches and reference lists of relevant articles. After removing duplicates, there were 5 unique articles that provided information on the safety and efficacy of lenacapavir in patients with HIV. One of the articles did not contain data on the efficacy and safety of lenacapavir, so a final review was performed using the remaining 4 articles. One of the studies reviewed was the Capella study, which focused on the safety and efficacy of long-acting subcutaneous lenacapavir in heavily treatment-experienced individuals with HIV. The study reported various adverse events, including injection site reactions and laboratory abnormalities. However, these problems were generally non-serious and temporary. The efficacy study conducted in two cohorts showed that viremia suppression, defined as a decrease of at least 0.5 log10 copies per mL in plasma HIV-1 RNA, was achieved by day 15. Another study reviewed was the Calibrate study, which examined the safety and efficacy of lenacapavir in combination with antiretroviral agents in people with HIV. The study reported mild to moderate responses, and the efficacy analysis was conducted in four groups using different combinations of antiretroviral agents with lenacapavir. By week 28, 94% of the participants receiving lenacapavir achieved viral suppression (HIV-1 RNA<50 copies per mL). The next study focused on the absence of lenacapavir phenotypic resistance in HIV gag cleavage site mutants and isolates with resistance to existing drug classes. The study evaluated several criteria, including the antiviral activity of lenacapavir against viruses with resistance to the four main drug classes. The results showed little change in phenotypic susceptibility to lenacapavir, with an average fold change of 0.65 across all participants (range 0.25 to 1.1). The study also assessed the susceptibility of lenacapavir in Treatment-Naïve (TN) and Treatment-Experienced (TE) HIV isolates. The TN isolates demonstrated unaltered susceptibility to lenacapavir, while TE isolates showed similar sensitivity to the wild type virus. The study further evaluated the phenotypic susceptibility of lenacapavir in the presence of gag cleavage site mutants, indicating that lenacapavir maintained its potency with little variation among the mutants. The final study reviewed was a proof-of-concept clinical study involving 29 participants,

which examined phenotypic resistance to lenacapavir and its monotherapy efficacy. The study investigated different doses of lenacapavir and identified the maximum change in HIV-1 RNA from baseline for each dose. The mean maximum change ranged from 1.4 to 2.3 log10 copies/mL. One participant in each dose group developed emerging CA resistance at day 10. In summary, the review of these four articles provided insights into the safety (Table 1) and efficacy (Table 2) of lenacapavir in patients with HIV. The studies demonstrated that lenacapavir exhibited favourable safety profiles with temporary and non-serious adverse events. Additionally, lenacapavir showed promising efficacy in achieving viral suppression in heavily treatment-experienced individuals and in combination with other antiretroviral agents. Furthermore, lenacapavir demonstrated little susceptibility changes against viruses with resistance to existing drug classes and maintained potency even in the presence of gag cleavage site mutants. The proof-of-concept study highlighted the dose-dependent effect of lenacapavir on HIV-1 RNA suppression, although emerging resistance was observed in some participants at higher doses.

DISCUSSION

The safety and efficacy of lenacapavir in patients with HIV have been explored through various articles. Four articles were reviewed, out of which two contained both safety and efficacy data, while the other two only had efficacy data. The first study reviewed was titled "Safety of Long Acting Subcutaneous Lenacapavir in Phase 2/3 in Heavily Treatment Experienced People with HIV." This study was conducted in multiple countries, including Canada, Japan, Germany, Italy, Thailand, USA, Spain, France, and South Africa. It involved 72 participants and focused on genotypic and phenotypic analysis. Several adverse events were observed during the study, including diarrhea, nausea, cough, headache, pyrexia, urinary tract infection, arthralgia, back pain, constipation, rash, oral candidiasis, and injection site reactions such as swelling, erythema, pain, nodule, and induration. Some participants also experienced grade 3 laboratory abnormalities, including low creatinine clearance in 11% of participants, glycosuria in 6%, and nonfasting/fasting hyperglycaemia in 6%. However, it's important to note that none of these adverse events led to the discontinuation of the study, and there were no Serious Adverse Events (SAEs) reported.

Table 1: Safety and efficacy data of lenacapavir .

Study	Study type	Country	Author	Participants	Result	Conclusion
Safety of Long Acting Subcutaneous Lenacapavir in Phase 2/3 in Heavily Treatment Experienced People with HIV.[31]	Genotypic and phenotypic resistance testing study.	Canada, Japan, Germany, Italy, Thailand, USA, Spain, South Africa, France).	Jean-micheal, sorana segal-maurer, M rhee (2019-2021).	72	Adverse events: Diarrhea, nausea, cough, headache, pyrexia, urinary tract infection, abdominal distension, Arthralgia, back pain, constipation, oral candidiasis, Rash. Injection site reaction Swelling, erythema, pain, nodule, induration, Grade 3 or 4 laboratory abnormalities, grade 3 or 4 lab abnormalities in 26%, low creatinine clearance 11%, glycosuria in 6%, nonfasting/fasting hyperglycemia 6%.	There were no AEs due to which study to be discontinued and there were no SAEs. Pain resolve in 1 day, swelling and erythema resolve in 4 and 8 days. Low creatinine clearance was temporary. Hyperglycemia and glycosuria were brief, unsubstantiated. Grade 3 or 4 lab abnormalities were clinically important.
Safety data of lenacapavir in combination with other antiretroviral agents in people with HIV.[32]	Genotypic study.	USA	Martin rhee, ross martin, Nicolas margot, laurie vanderveen (2021).	182	The most frequent adverse non-injection site response events were headache and nausea. Mild or moderate injection site response associated with lenacapavir were most frequently described as erythema (27%, 28 of 105), edema (23%, 24 of 105), and discomfort (19%, 20 of 105).	There were no significant adverse events connected to trial therapy. These adverse events are very Mild due to which no discontinuation of combination treatment occurs.

Pain resolved within one day, while swelling and erythema resolved within 4 and 8 days, respectively. The low creatinine clearance was temporary, and hyperglycaemia and glycosuria were brief and not confirmed. Grade 3 or 4 lab abnormalities were clinically significant. This study provides insights into the safety profile of long-acting subcutaneous lenacapavir in heavily treatment-experienced people with HIV. In addition to the safety study mentioned earlier, another study focused on evaluating the safety of lenacapavir in combination with other antiretroviral agents in people with HIV. This genotypic study took place in the USA and involved 182 participants. The study identified the most common non-injection site adverse events as headache and nausea. Mild or moderate injection site responses associated with lenacapavir were primarily described as erythema (27% of participants), edema (23% of participants), and discomfort (19% of participants). However, there were no significant adverse events linked to these responses, and they were considered to be mild. As a result, no discontinuation of the combination treatment was required. On the other hand, the efficacy of lenacapavir was also examined in the reviewed articles. One of the studies focused on the efficacy of long-acting subcutaneous lenacapavir in heavily treatment-experienced individuals with HIV. This genotypic and phenotypic study involved 72 participants from various countries, including Canada, Japan, Germany, Italy, USA, Thailand, Spain, France, and South Africa. The participants were divided into two groups, with 36 patients in each group.[31,32]

The study found that the majority of patients in both groups achieved viremia suppression, which was defined as a decrease of at least 0.5 log10 copies per mL in plasma HIV-1 RNA by day 15, resulting in a viral load between 50 and 200 copies per mL. After 26 weeks, the mean change in viral load from baseline was 2.49 log10 copies per mL for the patients in cohort 1, and comparable viral suppression was observed in patients in cohort 2. These findings suggest that lenacapavir has demonstrated efficacy in suppressing

Table 2: Efficacy data of lenacapavir.

Study	Study type	Country	Author	Participants	Result	Conclusion
Efficacy of Long Acting Subcutaneous Lenacapavir in Phase 2/3 in Heavily Treatment Experienced People with HIV.[31]	Genotypic and phenotypic study.	Canada, Japan, Germany, Italy, USA, Thailand, Spain, France, South Africa.	Jean-Michel Molina, Sorana Segal-maurer, Martin Rhee (2019-2021).	Cohort 1 randomized n=36 With ratio 2:1 cohort 2 non-randomized *n*=36.	The majority of patients in both groups had viremia suppression, which was defined as decrease of at least 0.5 log 10 copies per mL in plasma HIV1 RNA by day 15 and viral load of between 50 and 200 copies per mL. With mean change in viral load from baseline of 2.49 log10 copies per mL after 26 weeks, the patients in cohorts 2 similarly showed comparable viral suppression lenacapavir treatment boosted the CD4+ count by 104 cells per cubic mm in cohort 2 and 75 cells per cubic mm in cohort 1.	Despite the limited number of participants, the CAPELLA study provide evidence in favour of HIV- 1 treatment with long-acting drug that have mode of action that may limit the emergence of resistance mutation. the prospect for using medications like lenacapavir, which is now being tested for HIV-1 preexposure prophylaxis, is equally enticing.
Efficacy data of lenacapavir in combination with other antiretroviral agents in people with HIV.[32]	Genotypic study	USA	Martin rhee, ross martin, Nicolas margot, laurie vanderveen (2021).	182 Group 1=52 Group 2=53 Group 3=52 Group 4=25.	By week 28, 94% of lenacapavir group 1,2,3(157) was virally suppressed (HIV-1 RNA 50 copies per mL). At week 54, 47 out of 52 patients in group 1, 45 out of 53 in group 2, 44 out of 52 in group 3 and 23 out of 25 had viral suppression.	The efficacy of lenacapavir in combination with other antiretroviral agents in people with HIV having high percentage of suppression of HIV as compare to the single Lenacapavir. In group 1 tenofovir alafenamide is used, in group 2 bictegravir, in group 3 emtricitabine and tenofovir alafenamide, in group 4 bictegravir, emtricitabine and tenofovir alafenamide is used orally in combination with lenacapavir.

Study	Study type	Country	Author	Participants	Result	Conclusion
Absence of lenacapavir (GS-6207) phenotypic Resistance in HIV Gag cleavage site mutants and in isolates with resistance to existing drug classes.[30]	Phenotypic susceptibility study.	USA	Nicolas margot, Renee ram, Martin rhee, Christian callebauta (2022).	40 51 (15 from TN and 36 from TE). 19	Antiviral activity of LEN against viruses with resistance to the 4 main drug classes (NRTIs, NNRTIs, PIs, INSTIs). This panel of mutants showed little change in phenotypic susceptibility to LEN, with an average fold change of 0.65 across all 40 mutants (range from 0.25 to 1.1) in contrast to the wild type. Phenotypic susceptibility to LEN in HIV isolates from treatment-naïve and treatment experienced PWH With a median fold change of 0.8 in contrast to that of the wild type (FC ranging from 0.6 to 1.6). the susceptibility to LEN across the 15 TN isolate was unaltered from that of the wild type. TE isolates sensitivity to LEN was basically unchanged from the wild type, with a median FC of 0.8 and little variation among the 36 isolates. Phenotypic susceptibility of LEN in the presence of GCSMs LEN had potency that was close to that of wild type, with little variation among 19 mutant and FCs from WT ranging from 0.7 to 1.9. Gag sequence analysis of patients isolate from TE and TN diseased revealed that 24 of the 36 TE isolates had GCSMs, but none of the TN isolates did.	We have demonstrated that the presence of PI-associated Gag cleavage site mutation (GCSMs) selected as a result of prior PI treatment did not affect the picomolar potency of LEN (fold changes 1.5), indicating that there was no interaction between the presence of PI-associated GCSMs and capsid function inhibition by LEN.
Phenotypic resistance to LEN and monotherapy efficacy in a proof-of-concept clinical study.[33]	Phenotypic and genotypic study.	USA	Nicolas margot, Laurie vanderveen, Vidula naik, PC parvangada, Ross martin, Martin rhee, Christian callenbaut. (2021) (USA).	29 Divided on the Basis of dose 20 mg (n=6) 50 mg (n=6) 150mg (n=6) 450mg (n=6) 750mg (n=5).	Mean maximum change in HIV1 RNA from baseline is 1.4°. with one participant with emerging CA resistance at day 10 for 20 mg dose. Mean maximum change in HIV1 RNA from baseline is 1.8°. with one participant with emerging CA resistance at day 10 for 50 mg dose. Mean maximum change in HIV1 RNA from baseline is 1.8°. with one participant with emerging CA resistance at day 10 for 150 mg dose. Mean maximum change in HIV1 RNA from baseline is 2.2°. with one participant with emerging CA resistance at day 10 for 450mg dose. Mean maximum change in HIV1 RNA from baseline is 2.3°. with one participant with emerging CA resistance at day 10 for 750 mg dose. Baseline is (log10 copies/mL) same for all dose.	The resistance seen in study 4072 is evidence that the negative association between resistance and a mutant virus capacity for replication *in vitro* may also be at work *in vivo*. Lenacapavir resistance developed in two of the subjects who took part in this dose-ranging research after receiving lenacapavir smallest doses (20 and 50 mg).

viral load in heavily treatment-experienced individuals with HIV. In this broader explanation, we will discuss the findings of several studies related to the efficacy and resistance of lenacapavir, a drug used in combination with other antiretroviral agents for the treatment of HIV. The second study reviewed the efficacy data of lenacapavir in combination with different antiretroviral agents in people with HIV. The study was conducted in the USA and involved 182 participants divided into four groups. Group 1 had 52 participants, group 2 had 53 participants, group 3 had 52 participants, and group 4 had 25 participants. Each group received a specific combination of lenacapavir with other antiretroviral agents. The combinations included tenofovir alafenamide in group 1, bictegravir in group 2, emtricitabine and tenofovir alafenamide in group 3, and bictegravir, emtricitabine, and tenofovir alafenamide in group 4. The results showed that by week 28, 94% of participants in groups 1, 2, and 3 (157 individuals) achieved viral suppression (HIV-1 RNA <50 copies per mL). At week 54, viral suppression was observed in 47 out of 52 patients in group 1, 45 out of 53 in group 2, 44 out of 52 in group 3, and 23 out of 25 in group 4. These findings suggest that lenacapavir, when used in combination with other antiretroviral agents, can effectively suppress the HIV virus in a high percentage of individuals compared to using lenacapavir alone. The third study reviewed the absence of phenotypic resistance to lenacapavir in HIV Gag cleavage site mutants and in isolates with resistance to existing drug classes. This study, conducted in the USA, evaluated the antiviral activity of lenacapavir against viruses with resistance to the four main drug classes used for HIV treatment: NRTIs, NNRTIs, PIs, and INSTIs. The study included 40 participants, and the results showed that the panel of mutants tested demonstrated little change in susceptibility to lenacapavir, with an average fold change of 0.65 across all 40 mutants. This indicates that lenacapavir remains effective even against HIV strains that have developed resistance to other drug classes. Additionally, the study included 51 participants (15 treatment-naive and 36 treatment-experienced), and the results showed that lenacapavir maintained its efficacy in both groups, with a median fold change of 0.8 compared to the wild type. These findings suggest that lenacapavir can be effective in individuals who have not received previous treatment as well as those who have developed resistance to other HIV drugs. The fourth study reviewed the phenotypic resistance to lenacapavir and the efficacy of monotherapy in a proof-of-concept clinical study. This study, which included 29 participants, aimed to evaluate the impact of different doses of lenacapavir on HIV viral load. The participants were divided into groups based on the dose administered (20 mg, 50 mg, 150 mg, 450 mg, and 750 mg). The results showed that the mean maximum change in HIV-1 RNA from baseline ranged from 1.4 to 2.3º across the different dose groups. Resistance to lenacapavir was observed in two participants who received the lowest doses (20 mg and 50 mg). These findings suggest that there may be a negative association between resistance to lenacapavir and the ability of mutant.[33]

CONCLUSION

In conclusion, the Capella study evaluated the safety and efficacy of subcutaneous lenacapavir in HIV patients. The study found that lenacapavir was effective in treating HIV with minimal adverse effects. The adverse effects observed did not have a significant impact on the patients' health, and discontinuation of the study was not necessary. The Calibrate study examined the safety and efficacy of lenacapavir in combination with antiretroviral agents. It observed very few mild adverse effects, and the combination therapy demonstrated higher efficacy compared to lenacapavir alone. Another study investigated the resistance of lenacapavir in HIV Gag cleavage site mutants and isolates with resistance to existing drug classes. It showed that lenacapavir remained potent even in the presence of Gag cleavage site mutations resulting from prior Protease Inhibitor (PI) treatment. Furthermore, a proof-of-concept clinical study assessed phenotypic resistance to lenacapavir and its monotherapy efficacy. It revealed that lenacapavir resistance developed in two subjects who received the smallest doses of lenacapavir (20 and 50 mg). Overall, lenacapavir is a relatively new drug approved by the FDA in 2022. It has shown low incidence of mild adverse effects and demonstrated efficacy in treating patients with HIV.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AIDS: Acquired Immunodeficiency Syndrome; **FDA:** Food and Drug Administration; **HIV:** Human Immunodeficiency Virus; **UNAIDS:** United Nations Programme on HIV/AIDS; **EU:** European Union; **EMA:** European Medicines Agency; **MDR HIV-1:** Multidrug-Resistant Human Immunodeficiency Virus Type 1; **PrEP:** Pre-Exposure Prophylaxis; **ART:** Antiretroviral Therapy; **NIAAA:** National Institute on Alcohol Abuse and Alcoholism; **NIDA:** National Institute on Drug Abuse; **NIMH:** National Institute of Mental Health; **PI:** Protease Inhibitors; **NRTIs:** Nucleoside Reverse Transcriptase Inhibitors; **NNRTIs:**

Non-Nucleoside Reverse Transcriptase Inhibitors; I**NSTIs:** Integrase Strand Transfer Inhibitors; **CPSF6:** Cleavage and Polyadenylation Specificity Factor Subunit 6; **Nup153:** Nucleoporin 153; **CA:** Capsid; **NTD:** N-Terminal Domain; **CTD:** C-Terminal Domain; **EC_{50}:** Half-maximal Effective Concentration; **USA:** United States of America; **Excel:** Spreadsheet software; **Capella study:** Study focusing on the safety and efficacy of long-acting subcutaneous lenacapavir; **RNA:** Ribonucleic Acid; **TN:** Treatment-Naïve; **TE:** Treatment-Experienced; **mL:** Milliliter; **SAEs:** Serious Adverse Events.

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