GILEAD | Medical Information

Sunlenca® (lenacapavir) Efficacy Against HIV-2

This document is in response to your request for information regarding the efficacy of Sunlenca® (lenacapavir [LEN]) as treatment for HIV-2.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.

Product Labeling[1]

Indications and Usage

LEN, an HIV-1 capsid inhibitor, in combination with other ARV(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 whose current ARV regimen is failing due to resistance, intolerance, or safety considerations.

Microbiology

Antiviral activity in cell culture

LEN has antiviral activity that is specific to HIV (HIV-1 and HIV-2). LEN was 15- to 25-fold less active against HIV-2 isolates relative to HIV-1.

Clinical Data on the Efficacy of LEN Against HIV-2

ANRS MIE CO5 HIV-2 Cohort (France)[2]

Study design and demographics

Efficacy of LEN against HIV-2 was evaluated in people with HIV-2 (N=8) who received treatment with LEN and an OBR in the French ANRS MIE CO5 HIV-2 Cohort. Outcomes included virologic response and changes in CD4 cell counts. Genotypic resistance testing was performed, and capsid sequences were compared to viral sequences obtained prior to LEN treatment to identify any mutations associated with treatment resistance. Phenotypic assays were also performed to assess drug susceptibility. OBR selection was determined using genotypic data; most participants received a backbone containing BIC, FTC, TAF, DTG, and DRV/R.

Table 1. Baseline Demographics and Disease Characteristics (Le Hingrat et al)[2]

Key Demographics and Characteristics	LEN + OBR (N=8)
Age, median (range), years	57 (36–66)
Male, n	4
CD4, median (range), cells/mm^3	135 (0–360)
Resistance to all NRTIs, n	3
Resistance to all NRTIs except zidovudine, n	5
Resistance to all PIs, n	7
Resistance to all INSTIs, n	5
GSS of OBR, median (range)	1.25 (0–2.5)
≤1 fully active drug in OBR, n	5

Abbreviations: INSTI=integrase strand transfer inhibitor.

Results

Most participants (6/8) had detectable HIV-2 VLs at initiation, with a median (range) of 3830 (665–60,400) c/mL. Two participants achieved virologic suppression (HIV-2 RNA <50 c/mL) after the OBR was initiated, which was a few weeks before LEN was initiated. Within 3 months of initiating LEN + OBR, 6 participants had ≥1 undetectable plasma VL. Of the 6 participants who had data available at Month 6, 3 participants had HIV-2 RNA <200 c/mL. Of these 3 participants, 1 had HIV-2 RNA <50 c/mL.

Data was available for 6 participants at Month 6; 1 participant achieved virologic suppression, and 3/6 participants had HIV-2 RNA <200 c/mL. The median (range) plasma VL among participants with HIV-2 RNA >50 c/mL was 757 (117–3000) c/mL. Within 1 year, HIV-2 RNA levels were near baseline levels.

From baseline to Month 6, the median (range) CD4 cell count for the 6 participants who had available data increased from 135 to 185 (90–290) cells/mm^3, with a median gain of 3 (-110 to +130) cells/mm^3.

Capsid mutations were detected in 5 participants, with 1 virus selecting Q66H + R69 and 4 viruses presenting a N73D mutation, 2 of which were N73D + A76V. Three of these 4 participants had OBR GSS ≤1.5. Persistently high plasma VLs with no capsid mutations were observed in the remaining 3 participants. Phenotypic assay results found that the N73D mutation was associated with a 30-fold reduction in susceptibility to LEN (IC_{50} of N73D virus was 30-fold higher than IC_{50} of wild type).

No safety results were reported.

Case Report

There are limitations in the interpretation of case reports. Case reports cannot be generalized. Unlike controlled clinical trials, causality cannot be inferred based on uncontrolled observational data. In addition, incidence or prevalence cannot be estimated due to the lack of a representative population sample. Other limitations of case reports include the retrospective design and publication bias.[3]

An adult female patient presented with pneumonia and cytomegalovirus retinitis and tested positive for HIV-2 with a plasma VL of 1.2×10^4 c/mL in 2002. The patient was started on a combined ARV regimen of 3 NRTIs (3TC, TDF, and didanosine) but was unable to achieve virologic suppression. She was switched to an RTV-boosted PI + 2 NRTI regimen and achieved virologic suppression temporarily before experiencing virologic failure. After

5.6 years, the patient was switched to DRV/r + RAL + ABC/3TC, and virologic suppression was briefly achieved before virologic failure occurred. Two years later, RAL was discontinued, and the patient remained on DRV/r +ABC/3TC for approximately 4 years. The patient was then switched to DRV/c + DTG (initially 50 mg once daily and increased to 50 mg twice daily a couple years later) + ABC/3TC, which over the course of approximately 5 years was unable to lower HIV-2 plasma VL (2.2×10^4 c/mL) or improve CD4 T-cell counts (90 cells/mcL), and T66I and G118R integrase substitutions emerged. LEN was then added on a compassionate use basis, with an oral lead-in followed by SUBQ LEN administration. The patient developed bursitis in her left hip in the months following the first injection, which was deemed unrelated to the administration of SUBQ LEN. The patient's HIV-2 plasma VL decreased to 115 c/mL, and CD4 counts increased to 260 cells/mcL; however, the N73D substitution in capsid emerged 41 days after LEN initiation. The patient was then switched to BIC/FTC/TAF + weekly oral LEN, resulting in modest decrease in her HIV-2 VL from 8.23×10^3 c/mL to 4.78×10^2 c/mL at the most recent VL assessment. CD4 T-cell counts maintained but did not improve significantly.[4]

In Vitro Data on Efficacy of LEN Against HIV-2

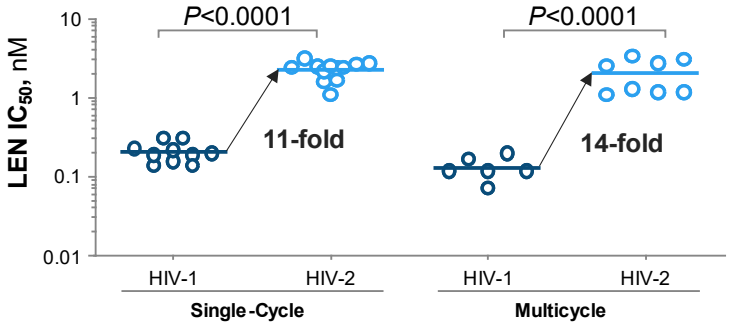
Kiarie et al[5]

Pseudovirion inhibition assays were used to assess the inhibition profile of LEN against HIV-2 in cell culture. LEN inhibited HIV-2 (IC_{50} [SE]=206.2 [0.2] pM) and HIV-1 (IC_{50} [SE]=399.3 [±0.2]).

Smith et al[6]

The in vitro activity of LEN against HIV-2 was evaluated using HIV-1 and HIV-2 isolates from treatment-naive individuals. LEN activity against HIV-2 was significantly lower than HIV-1 (Figure 1), with the single-cycle and multicycle assays showing an 11- to 14-fold decrease, respectively. In single-cycle assay, LEN susceptibility was not affected by the presence of drug resistance mutations in HIV-2 reverse transcriptase, protease, or integrase (fold change in LEN [IC_{50}]: 0.67–1 relative to wildtype HIV_{ROD9}), with the exception of a 1.9-fold increase in the IC_{50} for the protease mutation 154M + I84V + L90M ($P \leq 0.01$). In multicycle assay, protease mutation 154M + I84V + L90M was fully susceptible to LEN.

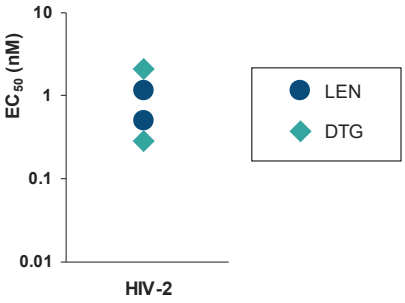
Figure 1. Activity of LEN in HIV-1 vs HIV-2 Isolates (Smith et al)[6]



Link et al[7]

To determine susceptibility to LEN, 2 HIV-2 isolates (CBL20 and CDC310319) were analyzed in vitro by means of an antiviral assay using fresh human PBMCs. LEN demonstrated broad activity against these two HIV-2 clinical isolates (EC_{50}: 885 pM; Figure 2).

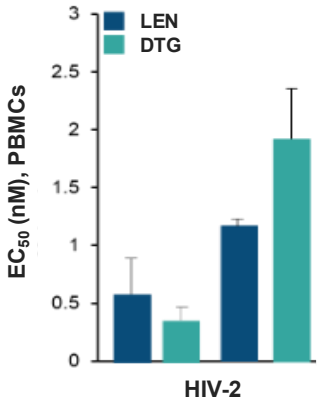
Figure 2. Antiviral Activity of LEN Against HIV-2 (Link et al)[7]



Yant et al[8]

When human PBMCs were activated with PHA/IL-2 and infected with HIV-2 clinical isolates, LEN was found to be a suppressor of HIV-2 replication. High-resolution dose-response curves were used to determine EC_{50} and Hill slope values (Figure 3).

Figure 3. Antiviral Activity of LEN Against HIV-2 (Yant et al)[8]



References

1. SUNLENCA, Gilead Sciences Inc. SUNLENCA® (lenacapavir) tablets, for oral use. SUNLENCA® (lenacapavir) injection, for subcutaneous use. US Prescribing Information. Foster City, CA.
2. Le Hingrat Q, Bertine M, Peytavin G, et al. Rapid Selection of HIV-2 Capsid Mutations After Failure of a Lenacapavir-Containing Regimen. [Poster 00682]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); March 3-6, 2024; Denver, Colorado.
3. Nissen T, Wynn R. The Clinical Case Report: A Review of Its Merits and Limitations. *BMC Res Notes.* 2014;7:264. https://www.ncbi.nlm.nih.gov/pubmed/24758689
4. van Kampen JJA, van Nood E, Mahmud R, et al. Novel Dolutegravir and Lenacapavir Resistance Patterns in Human Immunodeficiency Virus Type 2 Infection: A Case Report. *Open Forum Infect Dis.* 2024;12(1):1-8.

5. Kiarie IW, Hoffka G, Laporte M, et al. Efficacy of Integrase Strand Transfer Inhibitors and the Capsid Inhibitor Lenacapavir against HIV-2, and Exploring the Effect of Raltegravir on the Activity of SARS-CoV-2. *Viruses.* 2024;16(10):1607.
6. Smith RA, Raugi DN, Nixon RS, et al. Antiviral Activity of Lenacapavir Against Human Immunodeficiency Virus Type 2 (HIV-2) Isolates and Drug-Resistant HIV-2 Mutants. *J Infect Dis.* 2024;229(5):1290-1294.
7. Link JO, Rhee MS, Tse WC, et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. *Nature.* 2020.
8. Yant SR, Mulato A, Stepan GJ, et al. GS-6207, A Potent and Selective First-in-Class Long-Acting HIV-1 Capsid Inhibitor [Poster 1504]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 04-07 March, 2019; Seattle, WA.

Abbreviations

3TC=lamivudine
ABC=abacavir
ANRS MIE=National Agency for Research on AIDS and Viral Hepatitis
ARV=antiretroviral
BIC=bictegravir
CD4=cluster of differentiation-4
DRV=darunavir
DRV/c=darunavir/cobicistat
DRV/r=darunavir/ritonavir
DTG=dolutegravir
EC_{50}=half maximal effective concentration
FTC=emtricitabine
GSS=genotypic susceptibility score
IC_{50}=half maximal inhibitory concentration
IL-2=interleukin-2
LEN=lenacapavir
NRTI=nucleos(t)ide reverse transcriptase inhibitor
OBR=optimized background regimen
PBMC=peripheral blood mononuclear cell
PHA=phytohemagglutinin
PI=protease inhibitor
RAL=raltegravir
RTV=ritonavir
SUBQ=subcutaneous(ly)
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
VL=viral load

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Sunlenca US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.

Follow-Up

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☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

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