Capsid Inhibition with Lenacapavir in HIV-1 Infection: Real-life Results from the French Compassionate Use Program

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BACKGROUND

Lenacapavir is a first-in-class capsid inhibitor that showed substantial antiviral activity in a phase 3 study among participants with multidrug-resistant HIV-1.
We aimed to evaluate the efficacy and safety of lenacapavir with an optimised background regimen (OBR) received through the compassionate access in France.

METHODS

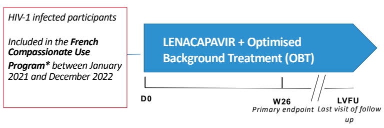
Between January 2021 and December 2022, lenacapavir has been made available in France through an early access process (**French Compassionate Use Program**) for viremic patients who have a serious or immediately life-threatening disease or no satisfactory alternative therapy.

We retrospectively enrolled HIV-1–infected participants who received lenacapavir through the early access program and described their follow-up through December 31, 2023

Following a 2-week oral lenacapavir, participants received subcutaneous lenacapavir every W26 with an OBT.

A retrospective efficacy analysis was performed with the primary end point as the percentage of participants with HIV-1 viral load (VL) < 50copies/ml at W26.

Secondary endpoints were virological outcomes at end of follow up, emergence of lenacapavir resistance in case of virological failure (confirmed VL > 50 copies/ml at W26 or in case of discontinuation at the last time point before W26, and in case of confirmed virological rebound after a VL<50 copies/ml) and tolerance.



RESULTS

TABLE 1 describes the baseline characteristics of the 33 HIV-1 infected participants.
Thirty-three participants (11/33 females) were analysed with a median (IQR) age of 56 (41-59) years.

At lenacapavir initiation, median CD4 cells count was 330 (106-500) cells/µL with 11/27 (41%) participants having less than 200 cells per µL.

VL was 2.54 (1.48-4.27) $\log_{10}$ copies/ml with 14/33 (42%) having VL below 50 copies/ml.

OBR included mainly darunavir/r (n=12), dolutegravir (n=11), cabotegravir (n=10), fostemsavir (n=12), maraviroc (n=8), ibalizumab (n=7) and enfuvirtide (n=4).

The median GSS was 2 (1-2) with 2 patients who had no fully active drugs.

24 individuals (73%) of the 33 received 3 injections of lenacapavir

TABLE 1: Participant baseline characteristics

	Total (N=33)	Baseline VL <50copies/ml (N=14)	Baseline VL ≥50copies/ml (N=19)
Age, years	56 (41-59)	57 (48-60)	55 (35-58)
Sex at birth			
Male	22 (67%)	12 (86%)	10 (53%)
Female	11 (33%)	2 (14%)	9 (47%)
Transmission group			
Homo-bisexual	11 (33%)	7 (50%)	4 (21%)
Heterosexual	13 (39%)	5 (36%)	8 (42%)
Other	9 (27%)	2 (14%)	5 (37%)
Geographic origin			
France	21 (64%)	9 (65%)	12 (63%)
Sub-Sahara Africa	7 (21%)	3 (21%)	4 (21%)
Other	5 (15%)	2 (14%)	3 (16%)
Duration from HIV diagnosis, years	28 (19-34)	31 (23-34)	27 (14-34)
Duration under ART, years	25 (17-27)	26 (21-27)	24 (13-28)
HIV viral load, $\log_{10}$ copies/mL			
≥50 copies/mL	19 (58%)		19 (100%)
Median (IQR)	2.6 (1.5-4.3)	-	4.0 (2.6-5.1)
CD4 count, cells/µl			
Median (IQR)	330 (106-500)	464 (129-714)	278 (72-444)
< 200 cells/µl	11/27 (41%)	4/11 (36%)	7/16 (44%)
Clinical stade C	18 (55%)	8 (57%)	10 (53%)
Viral subtype			
B	23 (70%)	11 (79%)	12 (63%)
Non B	10 (30%)	3 (21%)	7 (27%)
Resistance to two or more drugs in major class			
Nucleoside reverse transcriptase	27 (82%)	10 (71%)	17 (89%)
Non-nucleoside reverse transcriptase	30 (91%)	12 (86%)	18 (95%)
Protease inhibitor	16 (49%)	8 (57%)	8 (42%)
Integrase strand transfer inhibitor	20 (61%)	9 (64%)	11 (58%)
All four major classes	13 (39%)	7 (50%)	6 (32%)
Composition of optimised background regimen#			
NRTI	14 (45%)	7 (50%)	7 (37%)
NNRTI	9 (27%)	5 (36%)	4 (21%)
PI	12 (36%)	4 (29%)	8 (42%)
INSTI	21 (64%)	11 (79%)	10 (53%)
Enfuvirtide	4 (12%)	1 (7%)	3 (16%)
Fostemsavir	12 (36%)	4 (29%)	8 (42%)
Ibalizumab	7 (21%)	2 (14%)	5 (26%)
Maraviroc	8 (24%)	3 (21%)	5 (42%)
Foscarnet	2 (6%)	1 (7%)	1 (5%)
Overall susceptibility score of optimized background treatment, median£	2 (1 – 2,5)	1.75 (1 – 2)	2 (1 – 3)
Number of fully active agents in the optimised background regimen			
0 - 0,5	2 (6%)	0 (0%)	2 (11%)
≥1-1,5	11 (33%)	7 (50%)	4 (21%)
≥2	20 (61%)	7 (50%)	13 (68%)

Of the 33 HIV-1 infected participants, 7 (21%) received dolutegravir twice a day and 9 (27%) received boosted darunavir twice a day.

£ Genotypic susceptibility scores (1 for full, 0·5 for partial, or 0 for no susceptibility) were determined using the ANRS French algorithm V35 to interpret cumulated historical resistance reports. The overall susceptibility score of the optimised background treatment was the sum of the individual scores.

CONCLUSION

In this real-life cohort of highly treatment-experienced HIV-1 participants, lenacapavir in combination with an OBR resulted in a high level of virological suppression up to 26 weeks, even increasing throughout the end of follow-up.

FIGURE 1
Percentage of participants who achieved HIV-1 RNA <50 copies/mL at Week 26 according to the US FDA snapshot algorithm

At W26 (W22 to W30), a VL < 50 copies/ml was reported in 66.7% (CI95% 48.2-82.0) of the participants. Virological failure was observed for 8 among 33 (24%) participants and 3 had no virological data.

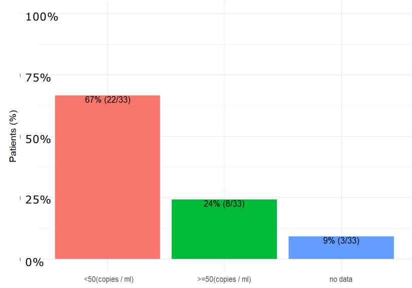


TABLE 2 Virological responses at W26 and at last week of follow up according to the baseline VL

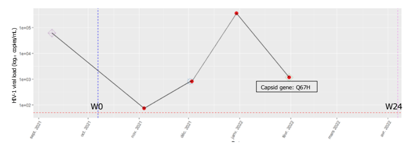
	Baseline VL<50 copies/mL N=14	Baseline VL≥50 copies/mL N=19
HIV-1-RNA at week 26 window (W22 to W30)		
<50 copies/mL	12/14 (86%)	10/19 (53%)
≥50 copies/mL or virological failure definition	1/14 (7%)	7/19 (37%)
No data	1/14 (7%)	2/19 (10%)
HIV-1-RNA at last follow-up visit (12,2 (IQR11,5-15,7) months)		
<50 copies/mL	13/14 (93%)	14/19(74%)
≥50 copies/mL	1/14 (7%)	5/19 (26%)

Immunological responses

Among the 33 HIV-1 participants with CD4 cell count results, the mean increase from baseline to W26 was +86 cells/µL (IQR 10-197) and the proportion with CD4 cell count above 200 cells/µL increased from 60% to 68%. At the LVFU, the mean increase from baseline was 51 cells/µL with 81% above 200 cells/µL.

Resistance mutation at virological failure

HIV-1 capsid sequencing was performed for 6 participants with virological failure from baseline to W26. The Q67H mutation conferring resistance to lenacapavir was evidenced in one case.



Adverse events

There were no grade 3 or 4 treatment-related adverse events (included two deaths, one at W15 due to septic shock and one at W4 due to acute hepatitis with hepatocellular insufficiency leading to multivisceral failure). Injection site reactions were reported for 11/33 (33%) participants without treatment discontinuation.

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