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Long acting cabotegravir plus lenacapavir as a fully injectable maintenance antiretroviral regimen in people with HIV with adherence issues

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Background

- Long-acting injectable (LAI) antiretroviral therapy (ART) represents a breakthrough in managing HIV, providing an alternative to daily oral ART, especially for people with HIV (PWH) with adherence challenges. Intramuscular cabotegravir (CAB) and rilpivirine (RPV) have shown efficacy in maintaining viral suppression.[1–3]
- However, many PWH who experienced virological failures selected RPV-associated resistance mutations, avoiding this LAI regimen.
- Lenacapavir (LEN) is a novel capsid inhibitor, administered as subcutaneous injections, that has been shown to achieve viral suppression in combination with oral ART in PWH with multidrug-resistant HIV-1 strains.[4]

Study rationale and methods

- **A combination of LAI-CAB with LAI-LEN may help address barriers to oral treatment adherence among PWH with RPV-resistant viruses.**[5]
- In this series, we report on 8 pretreated virally suppressed (plasma viral load [pVL] <50 copies/mL) adult PWH with RPV-resistant viruses, who started LAI-CAB plus LAI-LEN between January 2021 and August 2023, after approval by a multidisciplinary committee in two French hospitals.
- LAI-CAB and LAI-LEN were started on the same day: oral loading dose of LEN 600mg on D1 and D2, and subcutaneous LEN 927mg on D1 and then every 6 months, in combination with intramuscular CAB 600mg on D1, W4, and then every 8 weeks.

Results

- Patients were 4 women and 4 men. The median (IQR) age was 56 years (44-58), the duration from ART initiation was 25 years (18-32), the duration of viral suppression was 32 months (7-59).
- Four had CD4 counts below 200/mm^3 at time of LAI-CAB plus LAI-LEN.
- All had difficulty accepting their illness and adherence problems.
- All patients were monitored for at least 6 months, and 3 for 12 months, with a median of 3 pVL measurements per patient (range: 1-4).
- No virologic failures were observed during follow-up, as all pVL remained below 50 copies/mL.
- No serious adverse events or discontinuations were reported.
- Antiretroviral plasma concentrations (C_{pl}) were routinely determined by UPLC-MS/MS at each visit. All LEN trough C_{pl} were >15.5ng/mL (4xPA-IC95 in MT-4 cells) and median (IQR) CAB C_{pl} was 1829 ng/mL (1483-2166) approximately 58 days after the last intramuscular injection.

Patient	#1	#2	#3	#4	#5	#6	#7	#8
Gender	Female	Female	Female	Male	Male	Male	Male	Female
Age	39 years	41 years	66 years	36 years	58 years	57 years	63 years	54 years
Body mass index (kg/m²)	24	23	22	18	23	30	28	29
Transmission mode	Mother to child	Mother to child	Intravenous drug use	Sex with men	Intravenous drug use	Sex with men	Sex with women	Sex with men
CD4 T-cell nadir	1 cell/µL	1 cell/µL	5 cells/µL	537 cells/µL	25 cells/µL	109 cells/µL	5 cells/µL	128 cells/µL
Time from ART initiation	35 years	33 years	31 years	5 years	28 years	21 years	20 years	13 years
Cumulated duration of HIV plasma viral load ≥200 copies/mL from ART initiation	144 months	32 months	76 months	2 months	18 months	43 months	204 months	29 months
HIV subtype	B	A1	B	B	B	B	CRF02AG	CRF02-AG
Archived genotypic resistance to NRTIs	TDF/TAF: S 3TC/FTC: S ABC: S AZT: S	TDF/TAF: S 3TC/FTC: S ABC: S AZT: S	TDF/TAF: S 3TC/FTC: R ABC: S AZT: S	TDF/TAF: S 3TC/FTC: S ABC: S AZT: S	TDF/TAF: S 3TC/FTC: R ABC: S AZT: S	TDF/TAF: S 3TC/FTC: S ABC: S AZT: S	TDF/TAF: S 3TC/FTC: R ABC: R AZT: S	TDF/TAF: S 3TC/FTC: R ABC: S AZT: S
Archived genotypic resistance to NNRTIs	EFV: R NVP: R ETV: R RPV: R[a] DOR: S	EFV: S NVP: S ETV: R RPV: R[b] DOR: S	EFV: R NVP: R ETV: S RPV: R[c] DOR: S	EFV: S NVP: S ETV: S RPV: R[d] DOR: S	EFV: R NVP: R ETV: S RPV: R[e] DOR: S	EFV: R NVP: R ETV: S RPV: R[f] DOR: R	EFV: R NVP: R ETV: R RPV: R[g] DOR: S	EFV: R NVP: R ETV: R RPV: R[h] DOR: R
Archived genotypic resistance to PIs	bDRV qd: S bDRV bid: S	bDRV qd: S bDRV bid: S	bDRV qd: S bDRV bid: S	bDRV qd: S bDRV bid: S	bDRV qd: S bDRV bid: S	bDRV qd: S bDRV bid: S	bDRV qd: S bDRV bid: S	bDRV qd: S bDRV bid: S
Archived genotypic resistance to INSTIs	RAL: S bEVG: S DTG qd: S DTG bid: S CAB: S BIC: S	RAL: S bEVG: S DTG qd: S DTG bid: S CAB: S BIC: S	RAL: S bEVG: S DTG qd: S DTG bid: S CAB: S BIC: S	RAL: R bEVG: R DTG qd: S DTG bid: S CAB: S BIC: S	RAL: S bEVG: S DTG qd: S DTG bid: S CAB: S BIC: S	RAL: S bEVG: S DTG qd: S DTG bid: S CAB: S BIC: S	RAL: S bEVG: S DTG qd: S DTG bid: S CAB: S BIC: S	RAL: S bEVG: S DTG qd: S DTG bid: S CAB: S BIC: S
Prior ART before switch	BIC/FTC/TAF	BIC/FTC/TAF+DTG	bDRV+RPV	RPV/FTC/TAF	bEVG/FTC/TAF	bDRV+RPV	BIC/FTC/TAF	DTG/3TC
HIV plasma viral load at time to switch	<20 copies/mL	<20 copies/mL	<20 copies/mL	51 copies/mL	<20 copies/mL	<20 copies/mL	54 copies/mL	<20 copies/mL
Duration of viral suppression (HIV plasma viral load <50 copies/mL) prior switch	60 months	8 months	58 months	3 months	182 months	20 months	1 month	44 months
CD4 T-cell count	88 cells/µL	54 cells/µL	383 cells/µL	886 cells/µL	406 cells/µL	714 cells/µL	124 cells/µL	128 cells/ µL
Reasons for adherence difficulties with oral ART	Feeling of injustice about having been infected with HIV at birth; disgust and nausea when taking ART	Non-acceptance of illness; fear of stigmatisation; dysphagia and difficulty swallowing pills	Major depressive disorders, social loneliness (and drug interactions with breast cancer therapy)	Non-acceptance of illness; fear of stigmatisation	Unweaned IV drug addiction	Major depressive disorders	Non-acceptance of illness; stigmatisation; socio-economic precarity	Non-acceptance of illness; stigmatisation; socio-economic precarity

a. E138K. **b.** L100I; K103N; V179I; G190E; P225H; P236L. **c.** A98S; K103N; V106A; V179I; Y181C; G190A. **d.** M230I. **e.** K101E; G190A. **f.** K101E; G190A. **g.** E138A; E138G. **h.** A98S, K101E, G190A, M230I.

Conclusions

- **LAI-CAB plus LAI-LEN maintained effective viral suppression with good tolerability.**
- Despite the expected moderate injection site reactions, all patients expressed a preference for this treatment over oral ART.
- To improve the administration of this full injectable strategy, it would be interesting to administer LAI-CAB at months 0, 1 and 2, and then every 2 months to coincide with LEN injections every 6 months.
- **It holds great promise for vulnerable PLWH struggling with oral ART adherence, particularly when RPV is not an option anymore, and merits prospective evaluation in a large, randomised trial.**

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