Case Series Examining the Long-Acting Combination of Lenacapavir and Cabotegravir: Call for a Trial

Monica Gandhi;[1] Lucas Hill;[2] Janet Grochowski;[1] Alexander Nelson;[3] Katerina Christopoulos;[1] Diane Havlir;[1] Catherine A. Koss;[1] Francis Mayorga-Munoz;[1] Jon Oskarsson;[1] John Szumowski;[1] Ann Avery;[3] Laura Bamford;[2] Jillian Baron;[4] William R. Short;[4] Corrilynn O. Hileman[3]

[1]University of California, San Francisco (UCSF), SF, CA; [2]University of California, San Diego (UCSD), San Diego, CA; [3]Metrohealth Medical Center and Case Western University, Cleveland, OH; [4]University of Pennsylvania (UPenn), Philadelphia, PA

629

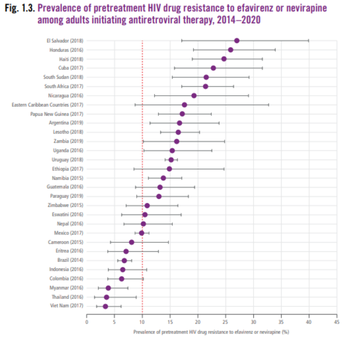
Background

- Injectable cabotegravir (CAB)/rilpivirine (RPV) is the only combination long-acting (LA) antiretroviral treatment (ART) regimen approved for HIV
- RPV is not effective among individuals with nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance (when the mutations are RPV resistance associated mutations, RAMs), which has >10% prevalence in many countries (Figure)
- Lenacapavir (LEN) is a LA capsid inhibitor given every six months but has not been studied in combination with other LA agents

Methods

- Four clinics where providers are using either LA CAB/RPV or LA CAB paired with LA LEN for selected patients with adherence challenges off-label were identified (UCSF Ward 86, UCSD Owen Clinic, MetroHealth's HIV Clinic, UPenn Clinic) and a case series assembled
- All patients in this series experienced challenges to taking oral ART which is why LA ART was prescribed
- Variables, including sex; gender; age; race; ethnicity; current housing status; substance use; viral load (VL) prior to starting LEN/CAB; duration between CAB doses (every 4 or 8 weeks); whether injectable RPV was also given; viral mutations in the NNRTI or INSTI class; BMI; time on the regimen; and LEN injection site reaction garnered from medical record
- IRB approval in clinics to present data if no patient identifiers

Figure: Rates of NNRTI resistance across countries as of WHO report 2021 (RPV 2.7-18.7%)



HIV DRUG RESISTANCE REPORT 2021

World Health Organization

In this case series of 34 patients on LEN/CAB from four U.S. academic medical centers, high rates of virologic suppression (94%) were seen (up from 47% at baseline). Clinicians used LEN/CAB for adherence challenges and NNRTI resistance. These data support a clinical trial of LEN/CAB as CAB/RPV cannot be used in LMICs with high rates of NNRTI resistance

Table: Details of patients (n=34) of LEN/CAB in this case series

Reason for LEN	Patient number	Age/Sex/ Gender/ Race-ethnicity/ substance use and/or housing insecurity/BMI (kg/m²)/ viral subtype	VL prior to LEN/CAB, copies/mL	NNRTI or minor INSTI mutations for patients 28-32	Regimen prior to LEN/CAB	Weeks between CAB doses/ RPV included/ ISR*	VS <75 after LEN/CAB start/ time to VS
NNRTI mutations-virologically suppressed when started LEN	1	55/M/M/Latino/yes/29.1	UD	A98G, K103N, V179E, G190A	DRV/c/FTC/TAF	4 weeks/ no/ no	Yes/ NA
	2	32/M/M/Latino/no/33.8	UD	K103N, G190A	DRV/c/FTC/TAF + DTG	8 weeks/ yes/ no	Yes/ NA
	3	28/M/M/Latino/no	UD	K103R, V179D	DRV/c + DTG	4 weeks/ yes/ grade 1	Yes/ NA
	4	47/F/F/Latina/no/28.1	UD	L100I, K103N	DRV/c + DTG	8 weeks/ no/ no	Yes/ NA
	5	75/F/F/Black/no/23.1/B	UD	L100I, K103N, V179I, Y181C	DTG + 3TC + DRV/r	8 weeks/ no/ no	Yes/ NA
	6	41/M/M/Black/yes/23.57/B	UD	V108I, V179D	EVG/c/FTC/TAF + DRV	8 weeks/ no/ grade 1	Yes/ NA
	7	55/M/M/White/no/21.7/B	UD	V90I, E138G	BIC/TAF/FTC	8 weeks/ yes/ no	Yes/ NA
	8	29/F/F/Black/no/30.9/AG	UD	Y181C	DTG/ABC/3TC	8 weeks/ yes/ grade 1	Yes/ NA
NNRTI mutations - viremic when started LEN	9	58/F/F/Latina/yes/29.2/B	329	K101K/Q, K103R, V179I	BIC/TAF/FTC+ DOR	4 weeks/ yes/ grade 2	Yes/ 4 wks
	10	48/M/F/Black/yes/26.7/B	815	V90I, V106I, Y181C, H221Y	DTG + TAF/FTC	4 weeks/ no/ grade 1	Yes/ 12 wks
	11	41/M/M/Black/no/46.22/B	5,280	Y181C, Y188L K103V	DRV/c/FTC/TAF + DTG	8 weeks/ yes/ grade 1	Yes/ 4 wks
	12	54/M/M/Black/yes/22.1/B	9,760	L100I, K103N, Y181Y/C, H221H/Y	EVG/c/FTC/TAF + DRV	8 weeks/ yes/ grade 1	Yes/ 16 wks
	13	50/M/M/Latino/yes/23/B	36,342	L100I, V179I, Y181I	DRV/c/FTC/TAF	4 weeks/ no/ grade 2	Yes/ 4 wks
	14	51/M/M/White/yes/28.2/B	239,000	L100I, K103N	DRV/c/FTC/TAF+DTG	4 weeks/ no/ grade 1	Yes/ 4 wks
	15	59/M/M/Latino/no/19.9/B	1,271,051	V106I, G190S, V179T, F227L	DRV/c/FTC/TAF + DTG	4 weeks/ no/ no	Yes/ 8 wks
Suspected archived NNRTI mutations	16	31/M/M/Black/no/25.18/B	7,740	None	BIC/TAF/FTC + DRV/c	8 weeks/ yes/ no	Yes/ 8 wks
	17	54/M/M/Black/yes/21.8/B	229,000	None	DRV/r/TAF/FTC	8 weeks/ yes/ no	Yes/ 16 wks
High VL within 3 months prior to starting LA ART (+/- NNRTI mutations)	18	57/M/M/Black/yes/22.0	UD	K103N, V108I, P225H	LA CAB/RPV	8 weeks/ yes/ no	Yes/ NA
	19	43/M/M/Black/no/24.9/B	UD	K103N, V108I, P225H	DRV/c/FTC/ TAF+DTG	8 weeks/ yes/ no	Yes/ NA
	20	42/M/M/White/yes/19.4/B	UD	None	LA CAB/RPV	8 weeks/ no/ grade 2	Yes/ NA
	21	28/M/M/Latino/no/30.5	UD	None	LA CAB/RPV	8 weeks/ no/ no	Yes/ NA
	22	60/M/M/White/yes/28.2/B	190	None	BIC/TAF/FTC	8 weeks/ yes/ no	Yes/ 12 wks
	23	39/M/M/Latino/yes/21.2/B	194,000	None	BIC/TAF/FTC	8 weeks/ yes/ no	Yes/ 5 wks
Low level viremia on CAB/RPV (+/- NNRTI mutations)	24	39/M/M/Latino/no/36.0/B	UD	K103R	LA CAB/RPV	8 weeks/ yes/ no	Yes/ NA
	25	35/M/M/Black/yes/34.7/B	95	None	LA CAB/RPV	8 weeks/ yes/ no	Yes/ 3 wks
	26	38/M/M/Latino/yes/23/B	145	None	LA CAB/RPV	4 weeks/ yes/ grade 2	No/ no VS
	27	42/M/M/White/yes/26.5/B	165	K103N, V106I	LA CAB/RPV	8 weeks/ yes/ no	Yes/ 16 wks
INSTI mutations	28	34/M/M/Latino/yes/22/B	UD	V90I, T66T/I	BIC/TAF/FTC	4 weeks/ yes/ grade 1	Yes/ NA
	29	52/M/M/White/yes/22.2/B	105	E92Q	DTG/RPV + DRV/c	8 weeks/ yes/ no	Yes/ 16 wks
	30	44/F/F/Black/no/25.5/B	228	T97A	BIC/TAF/FTC	8 weeks/ yes/ no	No/ no VS
	31	40/F/F/Latina/no/24.8/B	290	E92Q	DRV/c/FTC/TAF + DOR	8 weeks/ yes/ grade 1	Yes/ 9 wks
	32	72/M/M/Black/yes/17.7/B	50,900	T97A	BIC/TAF/FTC + DRV/c	8 weeks/ yes/ no	Yes/5 wks
Other	33[1]	47/F/F/Black/no/41.2/B	UD	None	BIC/TAF/FTC	8 weeks/ yes/ grade 1	Yes/ NA
	34[2]	57/M/M/White/yes/22.7/B	UD	None	LA CAB/RPV	4 weeks/ no/ grade 1	Yes/ NA

M-male; F-female; UD-undetectable; DRV/c-darunavir/cobicistat; BIC-bictegravir; TAF-tenofovir alafenamide; FTC-emtricitabine; DTG-dolutegravir; 3TC-lamivudine; EVG-elvitegravir; DOR-doravirine; [1]High BMI > 40 kg/m²; [2]Intolerance to LA-RPV; *ISR injection site reaction; K103(X) mutations not counted as RPV associated mutations

Results

- All patients (n=34: 76% male; 24% cis/trans female; 41% Black; 38% Latino/a; median age 47 [range 28-75] years; 29% and 71% on CAB every 4 or 8 weeks) reported challenges adhering to oral ART (**Table**)
- Reason(s) for using LEN/CAB with or without RPV were: either documented or suspected NNRTI mutations (n= 21, 59%), integrase mutations (n=5, 15%), high VL (n=6, 18%), or continued viremia on CAB/RPV alone (n=4, 12%)
- Injection site reactions on LA-LEN were reported in 44% (32% grade I, 12% grade 2).
- All patients but two (32/34; 94%) suppressed (VL< 75 copies/mL) after starting LEN at a median of 8 (4-16) weeks, with 16/34 (47%) suppressed at baseline.

Conclusion

- First case series of patients on a novel combination of long-acting ART with LEN (subcutaneous every 6 months) and CAB (intramuscular every 4-8 weeks) with or without RPV
- All experienced adherence challenges with oral ART
- Most common reason for use of this off-label combination was NNRTI mutations
- Overall, viral suppression doubled from 47% at baseline to 94% on LEN/CAB
- Patients with documented or suspected NNRTI mutations all achieved suppression on LEN/CAB
- Due to prevalence of NNRTI mutations worldwide (**Figure**), CAB/RPV not approved as LA ART by WHO in low-and-middle-income countries (LMICs)
- Therefore, in 2024, disparities exist in availability of LA ART between high and LMICs
- Trial needed to study LEN/CAB in patients with NNRTI resistance worldwide given this disparity; this case series serves as a call for this trial

Acknowledgements: Funded by NIAID/NIH 5R37AI098472

UCSF · Penn University of Pennsylvania · Case Western Reserve University · UC San Diego · MetroHealth Devoted to Hope, Health, and Humanity