Long-acting combination of cabotegravir plus rilpivirine: a picture of potential eligible HIV-positive individuals from the Italian ARCA cohort

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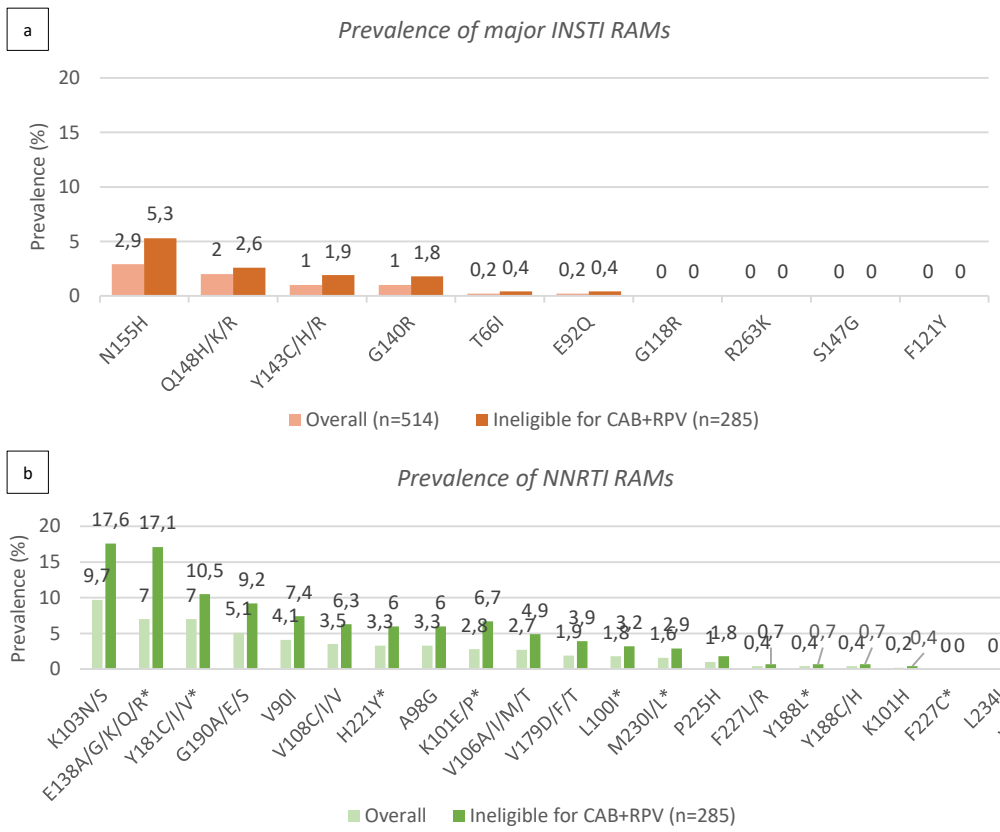
Background: The aim of this study was to compare HIV-1 positive individuals under virological control potentially eligible for the recently approved regimen with long-acting (LA) cabotegravir (CAB) and rilpivirine (RPV) with those ineligible [1,2].

Materials and methods: This was an observational, cross-sectional study from ARCA database (https://www.dbarca.net/) including HIV-positive adults with at least two consecutive viraemia <50 copies/mL after 1 January 2019 and at least one genotypic resistance testing (GRT) for RT/INT from plasma and/or PBMCs. Eligibility criteria for LA CAB+RPV were: negative HBsAg, absence of resistance-associated mutations (RAMs) for NNRTIs, of major RAMs for INSTIs (IAS-USA list 2019), and of previous virological failures (VFs) to INSTIs and/or NNRTIs [1-3]. Prevalence of eligible individuals was calculated. Univariable analysis was performed to investigate potential differences between eligible and ineligible individuals.

Results: Five hundred and fourteen individuals were included: 377 (73.3%) were male, median age was 51 (IQR 43 - 58), 41 (8%) had HBV co-infection, in ART from 9 years (IQR 4 - 17) and in virological suppression from 63 months (IQR 34.7 - 105.2) (Table 1). One hundred and nineteen (23%), 134 (26%), and 17 (3%) individuals experienced VFs to INSTIs, NNRTIs and RPV, respectively. B subtype was detected in 382 (74%) individuals. Thirty-three (6%), 123 (24%) and 104 (20%) individuals had at least one major RAM for INSTIs, for NNRTIs (excluded RPV) and for RPV, respectively. The most common major RAMs are showed in Figure 1. Among 24 ineligible individuals with GRT on both RNA and DNA, one had RAMs for NNRTI only on DNA and three had previous VFs without any RAMs. Eligible individuals for LA CAB+RPV were 229 (44.5%, 95% CI 40.8, 48.8): compared to ineligible individuals, they were younger, injected drugs less frequently, had a lower zenith viraemia (4.5 vs 5.1 log_{10} copies/mL) and higher CD4 count nadir (260 vs 170 cells/mm^3)(Table 1). They had a more recent HIV diagnosis (2012 vs 2002) as well as year of ART-start (2015 vs 2007), receiving a lower number of previous regimens (3 vs 6).

Figure 1. Prevalence of major RAMs for INSTIs (a) and of major and minor RAMs for NNRTIs (b) reported in the IAS USA 2019 list, in the overall population (n=514) and in individuals ineligible for LA CAB+RPV (n=285).



*Resistance associated mutations (RAMs) for RPV. Abbreviations: CAB, cabotegravir; INSTI, integrase stand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAM, resistance associated mutation; RPV, rilpivirine.

Conclusions: Less than half of virosuppressed HIV-positive individuals with available GRTs in ARCA cohort were potentially eligible for LA CAB+RPV. They showed a lower zenith viraemia, higher CD4 cell count, a shorter history of HIV infection and exposure to ART compared to those ineligible to LA CAB+RPV.

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3. Cutrell AG, Schapiro JM, Perno CF, Kuritzkes DR, Quercia R, Patel P, et al. Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis. AIDS. 2021 Jul 15;35(9):1333–42.

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Table 1. Demographic, clinical, therapeutic and virological characteristics of the overall population and in individuals eligible and ineligible for LA CAB+RPV.

Variables	Overall population (N=514)	Eligibility for CAB+RPV		P value[a]
		No (N=285)	Yes (N=229)	
Gender male, n (%)	377 (73.3)	198 (69.5)	179 (78.2)	0.034
Age (years), median (IQR)	51 (43-58)	54 (46-58)	48 (38-55)	<0.001
Ethnicity, n (%)				
Caucasian	314 (60.0)	169 (59.3)	145 (63.3)	0.353
Black	36 (7.0)	25 (8.7)	11 (4.8)	0.114
Other/Unkown	164 (33.0)	91 (32.0)	73 (31.9)	0.597
HIV-1 subtype, n (%)				
B	382 (74.3)	225 (78.9)	157 (68.6)	0.007
A[b]	19 (3.7)	6 (2.1)	13 (5.7)	0.058
CRF02_AG	43 (8.4)	24 (8.4)	19 (8.3)	1.000
CRFs_BC	18 (3.5)	2 (0.7)	16 (7.0)	<0.001
CRFs_BF	11 (2.1)	6 (2.1)	5 (2.2)	1.000
Others	41 (8.0)	22 (7.7)	19 (8.3)	0.939
HIV-1 risk factor, n (%)				
Heterosexual	212 (41.2)	118 (41.4)	94 (41.1)	0.935
MSM	121 (23.5)	57 (20.0)	64 (27.9)	0.035
IDU	96 (18.7)	75 (26.3)	21 (9.2)	<0.001
Other/Unknown	85 (16.5)	35 (12.3)	50 (21.8)	0.005
VL zenith (log_{10} cps/ml), median (IQR)	4.9 (4.0-5.5)	5.1 (4.4-5.7)	4.5 (3.1-5.2)	<0.001
CD4 nadir (cell/mm^3), median (IQR)	210 (80-370)	170 (50-320)	260 (120-450)	<0.001
Year of HIV-1 diagnosis, median (IQR)	2008 (1995–2014)	2002 (1991-2011)	2012 (2006-2016)	<0.001
HCV co-infection, n (%)	65 (12.6)	53 (18.6)	12 (5.2)	<0.001
HBV co-infection, n (%)	41 (8.0)	41 (14.4)	0 (0.0)	-
First therapy (calendar year), median (IQR)	2011 (2003-2016)	2007 (1997-2014)	2015 (2010-2017)	<0.001
Years from first therapy, median (IQR)	9 (4-17)	13 (6-23)	6 (3-10)	<0.001
No. of previous therapies, median (IQR) (n=505)	4 (2-7)	6 (3-11)	3 (2-4)	<0.001
Previous drug classes experienced, n (%)				
NRTI	498 (98.6)	276 (97.9)	222 (99.6)	0.14
NNRTI	315 (62.4)	194 (68.8)	121 (54.3)	<0.001
PI	349 (69.1)	227 (80.5)	122 (54.7)	<0.001
INSTI	388 (76.8)	244 (86.5)	144 (64.6)	<0.001
EI (MVC)	35 (6.9)	28 (9.9)	7 (3.1)	0.005
FI (T20)	17 (3.4)	17 (6.0)	0 (0.0)	<0.001
No. of previous drugs, median (IQR) (n=505)	6 (4-10)	8 (6-12)	5 (4-6)	<0.001
Therapy at last viremia, n (%) (n=497)				
2 NRTI + 1 INSTI	179 (36.0)	101 (36.6)	78 (35.6)	0.869
2 NRTI + 1 NNRTI	106 (21.3)	32 (11.5)	74 (33.8)	<0.001
2 NRTI + 1 PI	62 (12.5)	38 (13.7)	24 (11.0)	0.441
1 NRTI + 1 INSTI	39 (7.8)	16 (5.8)	23 (10.5)	0.074
Other	111 (22.3)	91 (32.7)	20 (9.1)	<0.001
Previous VFs, n (%)				
NNRTI	136 (26.4)	136 (47.7)	0 (0.0)	-
RPV	17 (3.3)	17 (6.0)	0 (0.0)	-
INSTI	119 (23.2)	119 (41.8)	0 (0.0)	-
Time from last VF (months), median (IQR)	63.0 (34.7–105.2)	62.1 (34.0-102.0)	64.4 (36.2-107.6)	0.583
At least one major RAM for INSTI, n (%)	33 (6.4)	33 (11.6)	0 (0)	-
At least one RAM for NNRTI, n (%)	168 (32.7)	168 (58.9)	0 (0)	-
At least one RAM for RPV, n (%)	104 (20.2)	104 (36.5)	0 (0)	-
CAB + RPV cumulative GSS, median (IQR)	2 (1.5–2)	1.5 (1-2)	2 (2-2)	<0.001

P values of variables that were significantly different (<0.05) between individuals eligible for LA CAB+RPV and those not eligible are reported in bold. [a]Mann-Whitney/T-tests and Chi-squared/Fisher's tests were used for quantitative and qualitative variables, respectively. [b]Subtype A1/A6: n=17; subtype A7: n=2.

Abbreviations: CAB, cabotegravir; EI, entry inhibitor; FI, fusion inhibitor; GSS, genotypic susceptibility score (according to Stanford algorithm; HIVdb version 9.0, https://hivdb.stanford.edu/); HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, intravenous drug users; INSTI, integrase stand transfer inhibitor; IQR, interquartile range; LA, long acting; MSM, men who have sex with men; MVC, maraviroc; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance associated mutation; RPV, rilpivirine; VF, virological failure; VL viral load.