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Short Communication

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

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ABSTRACT

Objectives: We aimed to evaluate the prevalence and characteristics of people living with HIV (PLWH) eligible for the long-acting injectable (LAI) regimen with cabotegravir (CAB) and rilpivirine (RPV), in comparison with ineligible individuals.

Methods: This was an observational, cross-sectional study from the ARCA cohort, including virologically suppressed PLWH with at least one genotypic resistance testing (GRT) for reverse transcriptase and integrase from plasma and/or PBMCs. Eligibility criteria for LAI CAB+RPV were: negative HBsAg, absence of previous virological failures and/or resistance-associated mutations for non-nucleoside reverse transcriptase inhibitors (NNRTIs) and/or integrase strand transfer inhibitors. Potential differences between eligible and ineligible individuals were investigated by univariable and multivariable analyses.

Results: A total of 514 individuals were included: 377 (73.3%) were male, median age was 51 (IQR: 43–58), on ART for 9 years (IQR: 4–17), virologically suppressed for 63 months (IQR: 35–105). Eligible individuals for CAB+RPV were 229 (44.5%, 95%CI: 40.8–48.8); compared with ineligible individuals, they received a lower number of previous regimens (aOR 0.76, 95% CI 0.71–0.83, $P < 0.001$) and were on current NNRTIs (aOR 2.16, 95% CI 1.38–3.37, $P = 0.001$).

Conclusions: Less than half of virologically suppressed PLWH in the ARCA cohort were potentially eligible for CAB+RPV. They seem to be "less complicated" with shorter exposure to ART and preferably already on NNRTIs.

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1. Introduction

The first innovative long-acting injectable (LAI) regimen with cabotegravir (CAB) and rilpivirine (RPV) has been recently approved for people living with HIV (PLWH) with undetectable HIV RNA under certain conditions [1,2]. While American guidelines give no restrictions in case of known or suspected resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and/or integrase strand transfer inhibitors (INSTIs) other than RPV and CAB, European organisms – in particular the European Medicine Agency- maintain the limitations to the whole drug classes [1–4]. In the present study, we aimed to evaluate the prevalence and characteristics of virologically suppressed PLWH potentially eligible for a LAI regimen with CAB+ RPV in the Italian Antiretroviral Response Cohort Analysis (ARCA) cohort.

2. Material and methods

This was a retrospective, observational, cross-sectional multicentre study conducted in the Antiviral Response Cohort Analysis ARCA database (https://www.dbarca.net/). This study included antiretroviral therapy (ART)-experienced PLWH in active follow-up and virologically suppressed (defined as at least two consecutive plasma HIV RNA <50 copies/mL six months apart after January first 2019). Individuals must have at least one genotypic resistance testing (GRT) for NNRTIs and INSTIs on plasma and/or peripheral blood mononuclear cells (PBMCs). Molecular phylogeny was used to determine HIV-1 subtype, as previously described [5].

Individuals were considered eligible for switch to CAB+RPV if they had: (i) negative HBsAg; (ii) no major and minor RAMs for NNRTIs and/or no major RAMs for INSTIs; (iii) no previous virological failure (VF) to INSTIs and/or NNRTIs. VF was defined as two consecutive viral loads >50 copies/ml or one viral load >1000 copies/ml. RAMs for NNRTIs and INSTIs considered for the analysis were those included in the International Antiviral Society-USA (IAS-USA) drug resistance mutations list updated in 2022 [6]. Eligible and ineligible individuals were compared according to eligibility criteria for CAB+RPV using univariable analysis (by means of Fisher's exact test and Mann-Whitney tests as appropriate) and multivariable logistic regression. A p-value below 0.05 was considered statistically significant. All the analyses were performed using R open-source environment for statistical computing (version. 4.1.2, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

We selected 514 PLWH following our inclusion criteria. Demographic, clinical and virological characteristics of the cohort are described in Table 1. Applying eligibility criteria for CAB+RPV, 229 (44.6%, 95% CI: 40.8–48.8) individuals were considered eligible. Considering the prevalence of exclusion criteria, 40 (8%) individuals had HBV co-infection; 136 (26.5%), 17 (3.3%) and 119 (23.2%) individuals had previous VFs for NNRTIs (excluded RPV), RPV and INSTIs, respectively. Major RAMs for INSTIs, any RAMs for NNRTIs (excluded RPV) and RAMs for RPV were found in 33 (6.4%), 168 (32.7%) and 104 (20.2%) individuals, respectively. The prevalence of the specific RAMs is described in Fig. 1. Among ineligible patients, 38 could have been considered eligible according with American guidelines since 18 had only minor RAMs, 10 had only major RAMs for NNRTIs excluding RPV, 10 had both RAMs and VFs for NNRTIs (except for RPV).

Compared with ineligible individuals for LAI CAB+RPV, those eligible were younger (median age was 48 vs. 54, $P < 0.001$), less frequently they were intravenous drug users (IDUs, 9.2% vs. 26.3%, $P < 0.001$) and with HCV co-infection (5.2% vs. 18.6%, $P < 0.001$) (Table 1). They were on ART for less time (6 vs. 13 years, $P < 0.001$), experiencing an inferior number of previous regimens (3 vs. 6, $P < 0.001$). At the time of the last viraemia, 33.8% of eligible individuals were on therapy with NNRTIs and 46.1% with INSTIs; moreover, they had a lower zenith viral load (4.5 vs. 5.1 Log_{10} copies/mL, $P < 0.001$) and higher CD4 cells count nadir (260 vs. 170 cell/mm^3, $P < 0.001$) at baseline. Concerning the distribution of HIV-1 subtype, individuals with subtype A1/A6 were 4 (1.4%) and 13 (5.7%) among those ineligible and eligible, respectively. Ad-

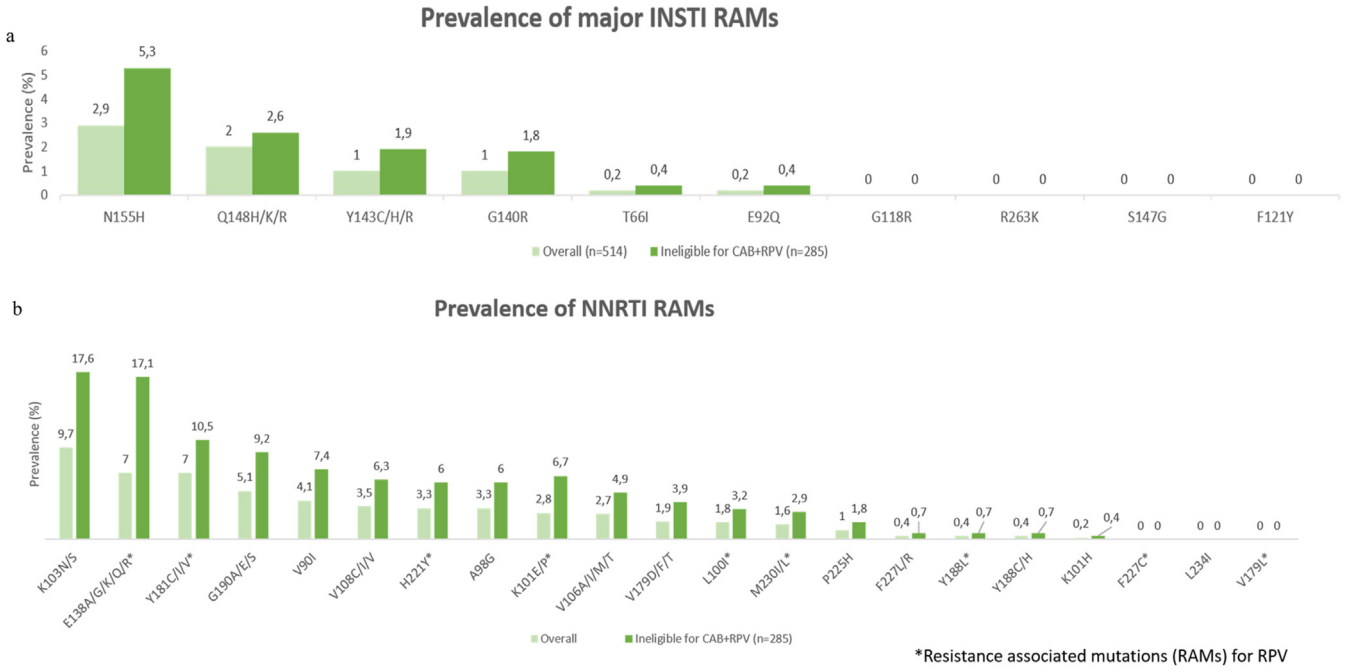

Fig. 1. Prevalence of major RAMs for INSTI (A) and NNRTI (B) in virologically suppressed HIV-positive individuals in active follow-up with available GRT in the ARCA cohort. Major resistance-associated mutations for INSTIs and any for NNRTIs according with IAS USA list 2022; specific major mutations for cabotegravir are: G118R, G140R, Q148H/K/R, N155H, R263K; specific major mutations for RPV are: L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, M230I/L.

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

Variables	Overall population (N = 514)	Eligibility for LAI CAB + RPV		
		No (N = 285)	Yes (N = 229)	P value[a]
Sex, 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/Unknown	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 (%)	498 (98.6)	276 (97.9)	222 (99.6)	0.14
NRTI	315 (62.4)	194 (68.8)	121 (54.3)	<0.001
NNRTI	349 (69.1)	227 (80.5)	122 (54.7)	<0.001
PI	388 (76.8)	244 (86.5)	144 (64.6)	<0.001
INSTI	35 (6.9)	28 (9.9)	7 (3.1)	0.005
EI (MVC)	17 (3.4)	17 (6.0)	0 (0.0)	<0.001
FI (T20)				
No. of previous drugs, median (IQR) (n = 505)	6 (4–10)	8 (6–12)	5 (4–6)	<0.001
Therapy at last viraemia, 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.
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 strand transfer inhibitor; IQR, interquartile range; LAI, long acting injectable; 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.
[a] Mann-Whitney/T-tests and χ^2 test/Fisher's tests were used for quantitative and qualitative variables, respectively.
[b] Subtype A1/A6: n = 17; subtype A7: n = 2.

justing for age, CD4 nadir and HIV risk factors, the current NNRTI use (aOR 2.16, 95% CI 1.38–3.37, $P = 0.001$) and the number of previous regimens (aOR 0.76, 95% CI 0.71–0.83, $P < 0.001$) were associated with higher probability of being eligible.

4. Discussion

This study conducted on the Italian ARCA cohort provides a picture of the clinical and virological characteristics of PLWH theoretically eligible for the injectable regimen with CAB+RPV, in comparison with those not eligible. Nearly half (44.5%) of PLWH belonging to the ARCA cohort with available GRT and in stable virological suppression could be eligible for LAI CAB+RPV. The percentage increases to 52% if considering eligible also those with RAMs for NNRTIs other than RPV and for INSTIs other than CAB. Eligible individuals were less exposed to different ART regimens, thus with a lower risk of resistance development and VF, and they were more likely on NNRTIs. Regarding HIV-1 subtypes, subtype B was the most represented, in line with other European cohorts [7,8]; also, the low prevalence of subtype A was consistent with that reported from a French cohort (3.7% and 5.1%, respectively, with a prevalence of subtype A1/A6 of 89% and 85%, respectively) [7]. The

prevalence of RAMs for NNRTIs and INSTIs was found in 54% and 6.4%, respectively. However, this prevalence decreased considering RAMs only for RPV and CAB to 20% and 5.2%, respectively.

To date HIV-1 DNA GRT is not strictly recommended as a strategy for screening patients who will receive CAB+RPV. Of 39 individuals who are ineligible only for the presence of RAMs for RPV and/or CAB, 9 (23%) had available GRT only on PBMCs. In those patients having a GRT is fundamental and it should be considered a valuable tool in absence of past GRT, even in NNRTI-naïve patients, and in case of an unclear or incomplete historical background [1,2].

In our comparative analysis, eligible individuals have a shorter duration of HIV infection, received a lower number of ART regimens, had presumably better previous adherence, and, accordingly, are already on current NNRTI treatment. In this sense, the confidence of clinicians in switching to this regimen will depend on the single patient's history, the willingness to switch and the availability of other treatment options, reinforced by the upcoming real-life data.

This study has several limitations. The ARCA cohort could not represent the overall Italian population, nevertheless it is the larger Italian cohort that provides detailed information on virological parameters such as genotypic resistance test, subtypes, and previous virological failures, fundamental to decide in favour of CAB+RPV. Furthermore, data on BMI were unavailable, however the role of higher BMI in predicting failure for CAB+RPV was lower than that of pre-existing RAMs for RPV and subtype A1/A6 [9,10]. Regarding the prevalence of A1/A6 subtype in our cohort, it is low and even lower among eligible individuals without RAMs at baseline. Another limitation is the lack of data on anti-HBc, that could underline a possible HBV occult infection. Finally, identifying individuals potentially eligible for CAB+RPV, we did not have information about other possible reasons to avoid the LAI regimen, such as history of intolerance or toxicity to RPV or INSTIs, drug-drug interactions and the desire of pregnancy in women.

Despite these limitations, one of the strengths of this analysis is to compare eligible and ineligible PLWH according to demographic, clinical and viro-immunological characteristics in a large Italian cohort with accurate data on genotypic resistance. Eligible individuals seem to be "less complicated"; however, the choice of LAI regimen with CAB+RPV must be carefully considered on the basis of individuals' characteristics and previous history, as well as the willingness to switch and the availability of other treatment options. In this context, GRT is a crucial tool in order not to compromise future treatment options.

In conclusion, our findings confirm that the choice of LAI regimen with CAB+RPV must be carefully considered on the basis of individuals' characteristics and previous history. Nowadays, GRT is confirmed to be a crucial tool in order not to compromise future treatment options.

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Conflicts of Interest: The authors have no conflicts of interest related to this manuscript.

Ethical approval: The ARCA cohort was approved by the Comitato Etico Regione Toscana Area Vasta Sud-Est (Regional Ethics Committee for Clinical Experimentation, Area Vasta South-East, Tuscany Region) with the ethic approval code ARCA/2014 of 21 July 2014. Written informed consent was obtained from all patients before participation. The study was performed following the ethical guidelines of the Declaration of Helsinki (seventh revision) and the International Conference on Harmonization Good Clinical Practice guidelines.

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