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Beyond Viral Suppression: Immunologic Evolution After Switching to Long-Acting Cabotegravir Plus Rilpivirine in Real-World Practice

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Background

Immune and virological trajectories after switching to long-acting cabotegravir plus rilpivirine (CAB+RPV LA) remain incompletely characterized in routine care settings.

Objective

To characterize longitudinal immune and virological trajectories after switching to CAB+RPV LA in virologically suppressed adults in routine clinical care.

Methods

Design:

Multicenter retro-prospective observational study (RELATIVITY cohort, Spain).

Population:

3,349 PWH with suppressed HIV-1 RNA who switched to CAB+RPV LA; 2,929 had an available last paired CD4/CD8 ratio assessment.

Definition of virological failure:

Two consecutive HIV-1 RNA measurements ≥200 copies/mL, or one measurement ≥500 copies/mL leading to CAB+RPV LA discontinuation.

Analysis:

Paired longitudinal changes in CD4+, CD8+, and CD4/CD8 ratio were assessed using Wilcoxon signed-rank tests. Multivariable linear regression evaluated predictors of CD4/CD8 ratio change, with sensitivity analyses restricted to sustained virological suppression and excluding virological failure.

Results

A total of 3349 participants were included in the study. CD4/CD8 ratio was available for 2995 participants: 1549 had a CD4/CD8 ratio <1.0, and 1446 had a ratio ≥1.0. The median baseline CD4+ T-cell count was 797 cells/mm³ (IQR, 602–1026), CD8+ T-cell count was 826 cells/mm³ (IQR, 607–1104), and CD4/CD8 ratio was 0.98 (IQR, 0.70–1.31). The median duration of pre-switch virological suppression was 81 months (IQR, 34-132). Baseline CD8+ counts did not differ significantly by recorded geographic origin (Spain, 831 [IQR, 603-1117]; Latin America, 818 [618-1059]; Africa, 745 [597-1031]; global P=0.237). Main characteristics are described in Table 1.

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Overall paired immunological changes

Median clinical follow-up was 25.1 months (IQR, 19.3–30.8). At the last immune assessment (median, 22 months), CD4+ T-cell counts showed no meaningful change (median change, −7 cells/mm³), while CD8+ T-cell counts decreased by 60 cells/mm³ and the CD4/CD8 ratio increased by +0.07. Among participants with available HIV-1 RNA data, 2570/2921 (88.0%) had all recorded post-switch values <50 copies/mL through the immune assessment, while 2666/2761 (96.6%) were suppressed at the selected immune visit. Protocol-defined virological failure occurred in 28/3,349 participants (0.8%).

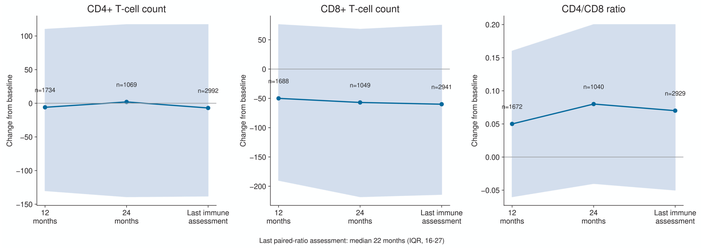


***Figure 1**. Paired immunological changes after switching to CAB+RPV LA*
Points represent different paired-data subsets; shading denotes IQR, not confidence intervals. The last assessment is not a fixed later visit (median 22 months for CD4/CD8).

Variable	Overall	Baseline CD4/CD8 <1.0	Baseline CD4/CD8 ≥1.0	P value
Participants, n	2995	1549	1446	
Age, years	45 [37 to 54]	45 [37 to 55]	45 [38 to 54]	0.873
Age ≥60 years	371/2995 (12.4)	207/1549 (13.4)	164/1446 (11.3)	0.093
Female sex	450/2964 (15.2)	185/1534 (12.1)	265/1430 (18.5)	<0.001
Recorded geographic origin: Spain	2121/2974 (71.3)	1075/1538 (69.9)	1046/1436 (72.8)	0.107
Recorded geographic origin: Latin America	662/2974 (22.3)	367/1538 (23.9)	295/1436 (20.5)	
Recorded geographic origin: Africa	66/2974 (2.2)	37/1538 (2.4)	29/1436 (2.0)	
Recorded geographic origin: Other regions	125/2974 (4.2)	59/1538 (3.8)	66/1436 (4.6)	
Body mass index, kg/m²	25.4 [23.3 to 28.1]	25.4 [23.3 to 28.0]	25.4 [23.2 to 28.3]	0.906
Number of comorbidities	0 [0 to 1]	0 [0 to 1]	0 [0 to 1]	0.226
≥2 comorbidities	537/2995 (17.9)	287/1549 (18.5)	250/1446 (17.3)	0.377
CD4+ T-cell nadir, cells/mm³	338 [191 to 496]	270 [134 to 422]	403 [266 to 559]	<0.001
CD4+ nadir <200 cells/mm³	625/2393 (26.1)	453/1247 (36.3)	172/1146 (15.0)	<0.001
Prior AIDS	376/2720 (13.8)	262/1414 (18.5)	114/1306 (8.7)	<0.001
Previous virological failure	103/2412 (4.3)	66/1245 (5.3)	37/1167 (3.2)	0.010
Baseline CD4+ T-cell count, cells/mm³	797 [602 to 1026]	683 [514 to 870]	919 [718 to 1162]	<0.001
Baseline CD4+ T-cell count <500 cells/mm³	438/2995 (14.6)	364/1549 (23.5)	74/1446 (5.1)	<0.001
Baseline CD4+ T-cell count ≥500 cells/mm³	2557/2995 (85.4)	1185/1549 (76.5)	1372/1446 (94.9)	<0.001
Baseline CD8+ T-cell count, cells/mm³	826 [607 to 1104]	1010 [780 to 1308]	662 [506 to 851]	<0.001
Baseline CD4/CD8 ratio	0.98 [0.70 to 1.31]	0.71 [0.55 to 0.85]	1.32 [1.14 to 1.65]	<0.001
Virological suppression before switch, months	81 [34 to 132]	69 [24 to 122]	93 [48 to 140]	<0.001
Years on ART before CAB+RPV LA	9.2 [5.0 to 15.0]	9.0 [4.0 to 15.0]	10.0 [6.0 to 15.0]	<0.001
Pre-switch INSTI-containing regimen	2398/2995 (80.1)	1233/1549 (79.6)	1165/1446 (80.6)	0.508
Pre-switch NNRTI-containing regimen	966/2995 (32.3)	500/1549 (32.3)	466/1446 (32.2)	0.976
Pre-switch PI-containing regimen	183/2995 (6.1)	103/1549 (6.6)	80/1446 (5.5)	0.202

***Table 1**. Baseline characteristics according to baseline CD4/CD8 ratio category*

Subgroup analysis

The largest difference was by baseline immune profile: participants with baseline CD4/CD8 <1.0 had a median ratio increase of +0.09 (IQR, -0.01 to +0.20), compared with +0.05 (IQR, -0.12 to +0.21) among those with baseline CD4/CD8 ≥1.0. Changes by recorded geographic origin were small; median increases were +0.06 for Spain and +0.10 for Latin America, Africa, and other regions.

Participants with all recorded post-switch HIV-1 RNA <50 copies/mL had a median ratio increase of +0.07 (IQR, -0.05 to +0.20), as did those with any recorded HIV-1 RNA ≥50 copies/mL (+0.07 [IQR, -0.08 to+0.21]); the adjusted analysis accounted for baseline and follow-up factors (Table 2).

Subgroup	Category	n CD4	Delta CD4 median [IQR]	n CD8	Delta CD8 median [IQR]	n ratio	Delta CD4/CD8 median [IQR]
Age group	<60 years	2625	-7 [-140 to 120]	2576	-63 [-218 to 75]	2566	0.08 [-0.05 to 0.21]
	≥60 years	367	-5 [-132 to 100]	365	-30 [-198 to 74]	363	0.06 [-0.07 to 0.17]
Sex	Male	2521	-8 [-137 to 115]	2474	-60 [-220 to 78]	2464	0.07 [-0.06 to 0.20]
	Female	439	-3 [-143 to 118]	435	-60 [-200 to 50]	434	0.10 [-0.05 to 0.25]
Recorded geographic origin	Spain	2124	-8 [-136 to 112]	2091	-54 [-210 to 78]	2084	0.06 [-0.06 to 0.19]
	Latin America	661	-4 [-147 to 124]	644	-82 [-240 to 59]	640	0.10 [-0.03 to 0.23]
	Africa	65	-15 [-191 to 134]	65	-80 [-211 to 35]	65	0.10 [-0.05 to 0.22]
	Other regions	122	16 [-124 to 136]	121	-54 [-217 to 82]	120	0.10 [-0.03 to 0.22]
Comorbidity burden	0-1	2467	-8 [-134 to 120]	2423	-63 [-218 to 75]	2412	0.07 [-0.05 to 0.21]
	2-3	453	-7 [-158 to 96]	446	-52 [-201 to 71]	445	0.06 [-0.06 to 0.19]
	≥4	72	20 [-108 to 131]	72	-40 [-240 to 64]	72	0.07 [0.01 to 0.14]
Baseline CD4/CD8 ratio	<1.0	1515	12 [-112 to 124]	1513	-99 [-290 to 70]	1509	0.09 [-0.01 to 0.20]
	≥1.0	1419	-27 [-176 to 110]	1417	-35 [-147 to 75]	1420	0.05 [-0.12 to 0.21]
Baseline CD4+ count	<500 cells/mm³	440	75 [0 to 156]	432	19 [-141 to 140]	429	0.08 [0.00 to 0.20]
	≥500 cells/mm³	2552	-30 [-164 to 105]	2509	-72 [-225 to 55]	2500	0.07 [-0.06 to 0.20]
CD4+ nadir	<200 cells/mm³	620	17 [-82 to 109]	610	-49 [-204 to 85]	610	0.07 [-0.02 to 0.18]
	≥200 cells/mm³	1787	-20 [-156 to 120]	1751	-68 [-224 to 68]	1740	0.08 [-0.07 to 0.21]
Pre-switch ART class	INSTI	2390	-11 [-144 to 116]	2353	-66 [-224 to 66]	2344	0.08 [-0.05 to 0.21]
	NNRTI	966	3 [-126 to 130]	950	-30 [-196 to 92]	946	0.05 [-0.08 to 0.18]
	PI	186	12 [-123 to 110]	182	-78 [-204 to 88]	181	0.10 [-0.03 to 0.19]
Post-switch virological status	All recorded HIV-1 RNA <50 copies/mL	2605	-4 [-132 to 115]	2581	-59 [-211 to 75]	2570	0.07 [-0.05 to 0.20]
	Any recorded HIV-1 RNA ≥50 copies/mL	354	-22 [-167 to 133]	351	-76 [-246 to 70]	351	0.07 [-0.08 to 0.21]

Table 2. Immunological changes at the last available assessment by subgroup
Changes in CD4+ and CD8+ T-cell counts are expressed in cells/mm³. Pre-switch ART classes are not mutually exclusive.

CD4/CD8 ratio categories and predictors of ratio change

Among 2929 participants with paired ratios at baseline and the last available assessment, 323/1509 (21.4%) with a baseline ratio <1.0 reached ≥1.0, whereas 146/1420 (10.3%) with a baseline ratio ≥1.0 moved to <1.0. Consequently, the proportion with a ratio ≥1.0 increased from 1420/2929 (48.5%) to 1597/2929 (54.5%).

The primary complete-case model included 1727 participants (Figure 2). Baseline CD4/CD8 <1.0 was associated with a greater ratio increase (adjusted beta, +0.060; 95% CI, +0.030 to +0.090; P<0.001). Longer pre-switch suppression per 5 years (adjusted beta, -0.028; 95% CI, -0.045 to -0.012; P<0.001) and any post-switch HIV-1 RNA ≥50 copies/mL (adjusted beta, -0.054; 95% CI, -0.098 to -0.010; P=0.017) were associated with smaller increases.

Female sex had a positive association, whereas African origin did not differ independently from Spanish origin. None of the ART classes in the regimen immediately preceding CAB+RPV LA was independently associated with ratio change.

The association for baseline CD4/CD8 <1.0 persisted among participants with all recorded post-switch HIV-1 RNA <50 copies/mL (n=1519; adjusted beta, +0.057; 95% CI, +0.026 to +0.089; P<0.001) and after excluding 28 protocol-defined virological failures (n=1712; adjusted beta, +0.061; 95% CI, +0.031 to +0.092; P<0.001)

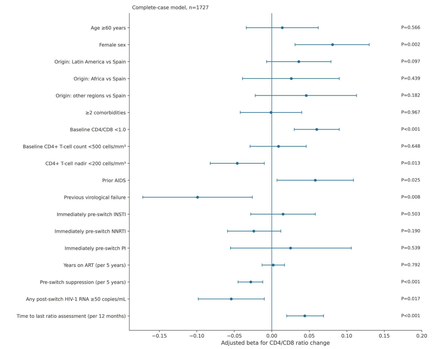


***Figure 2**, Multivariable correlates of CD4/CD8 ratio change at the last available assessment*

Conclusions

Among virologically suppressed PWH receiving CAB+RPV LA, CD4+ T-cell counts showed no meaningful change, CD8+ T-cell counts declined modestly, and the CD4/CD8 ratio increased slightly.

In this selected cohort, these findings are consistent with overall immunological stability.

The small ratio increase primarily reflected CD8+ decline and should not be interpreted as a CAB+RPV LA-specific effect.

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