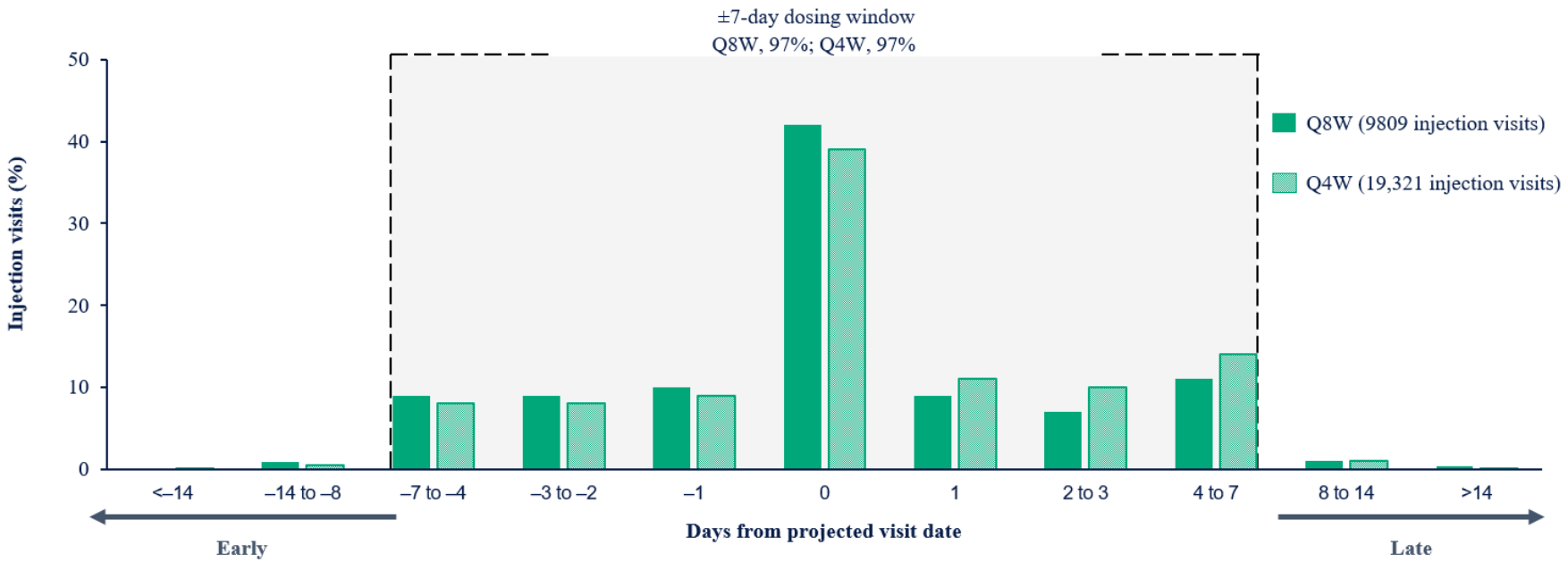
Supplementary data

Figure S1. Adherence to dosing schedule through Week 152[a]

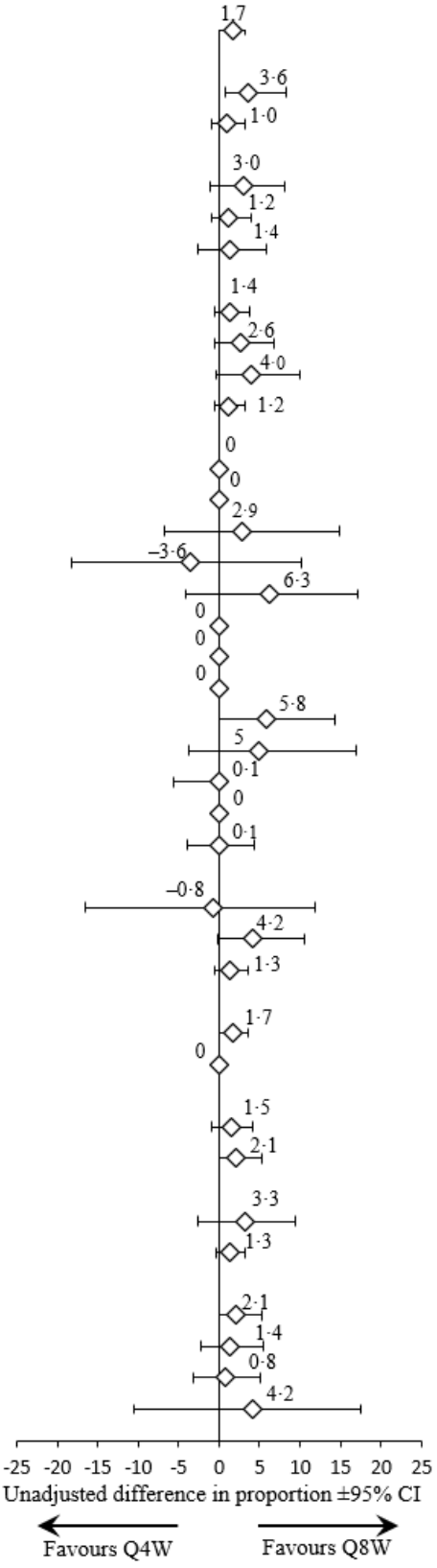


[a] In the Q8W arm, in 242 visits and 186 participants, LA was administered after a 9-week interval between injections without oral therapy. In the Q4W arm, in 310 visits and 204 participants, LA was administered after a 5-week interval between injections without oral therapy.

LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks.

Figure S2. Summary of outcomes (plasma HIV-1 RNA ≥50 copies/mL at Week 152) by subgroup, FDA Snapshot algorithm (ITT-E population)

		Q8W, n/n (%)	Q4W, n/n (%)
Overall		14/522 (3)	5/523 (1)
Sex at birth	Female	5/137 (4)	0/143 (0)
	Male	9/385 (2)	5/380 (1)
Age (years)	<35	6/137 (4)	2/145 (1)
	35-<50	4/242 (2)	1/239 (<1)
	≥50	4/143 (3)	2/139 (1)
Race	White	10/371 (3)	5/393 (1)
	Non-White	4/151 (3)	0/130 (0)
	Black/Afr Amer	4/100 (4)	0/90 (0)
	Non-Black/Afr Amer	10/422 (2)	5/433 (1)
Countries	Argentina	0/12 (0)	0/17 (0)
	Australia	0/8 (0)	0/15 (0)
	Canada	1/35 (3)	0/41 (0)
	France	0/26 (0)	1/28 (4)
	Germany	3/48 (6)	0/36 (0)
	Italy	0/26 (0)	0/22 (0)
	South Korea	0/18 (0)	0/9 (0)
	Mexico	0/10 (0)	0/6 (0)
	Russia	4/69 (6)	0/69 (0)
	South Africa	2/40 (5)	0/42 (0)
	Spain	1/77 (1)	1/81 (1)
	Sweden	0/13 (0)	0/8 (0)
	United States	3/140 (2)	3/149 (2)
Baseline CD4+ (cells/mm^3)	<350	1/35 (3)	1/27 (4)
	350 to <500	4/96 (4)	0/89 (0)
	≥500	9/391 (2)	4/407 (1)
Baseline HIV-1 RNA (copies/mL)	<50	14/519 (3)	5/513 (1)
	≥50	0/3 (0)	0/10 (0)
Prior exposure to CAB+RPV (weeks)	0	10/327 (3)	5/327 (2)
	≥1	4/195 (2)	0/196 (0)
Baseline BMI (kg/m^2)	<30	8/409 (2)	3/425 (1)
	≥30	6/113 (5)	2/98 (2)
Baseline third agent class	CAB+RPV	4/195 (2)	0/196 (0)
	NNRTI	4/151 (2)	2/156 (1)
	INSTI	3/136 (2)	2/141 (1)
	PI	3/40 (8)	1/30 (3)

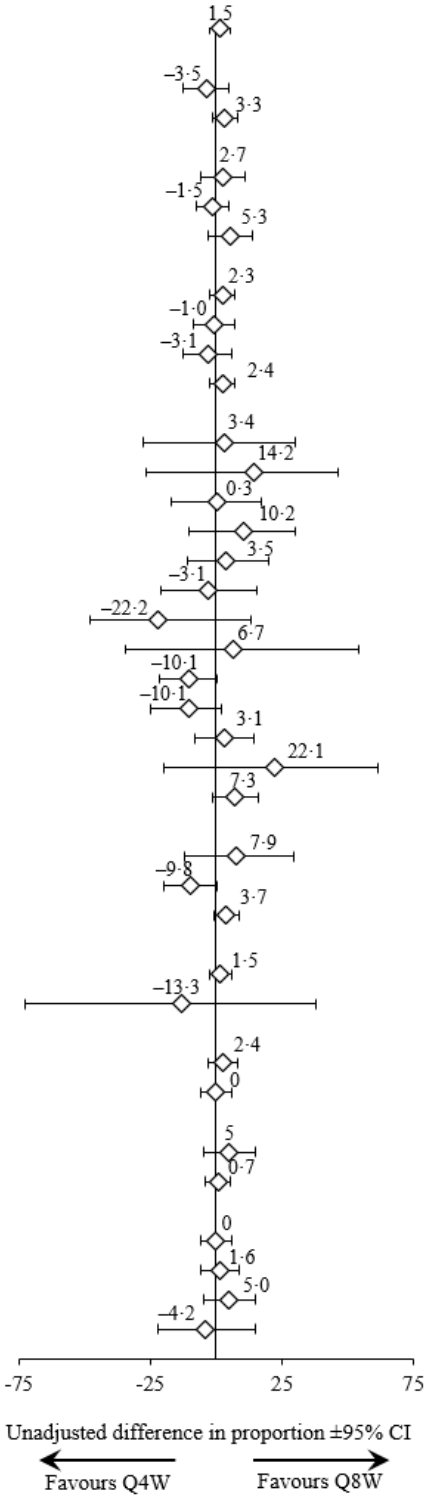


BMI, body mass index; CAB, cabotegravir; CI, confidence interval; FDA, U.S. Food and Drug Administration;

INSTI, integrase strand transfer inhibitor; ITT-E, intention-to-treat exposed; n/n, number of participant with virologic non-response/total number of people in subgroup; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Figure S3. Summary of outcomes (plasma HIV-1 RNA <50 copies/mL at Week 152) by subgroup, FDA Snapshot algorithm (ITT-E population)

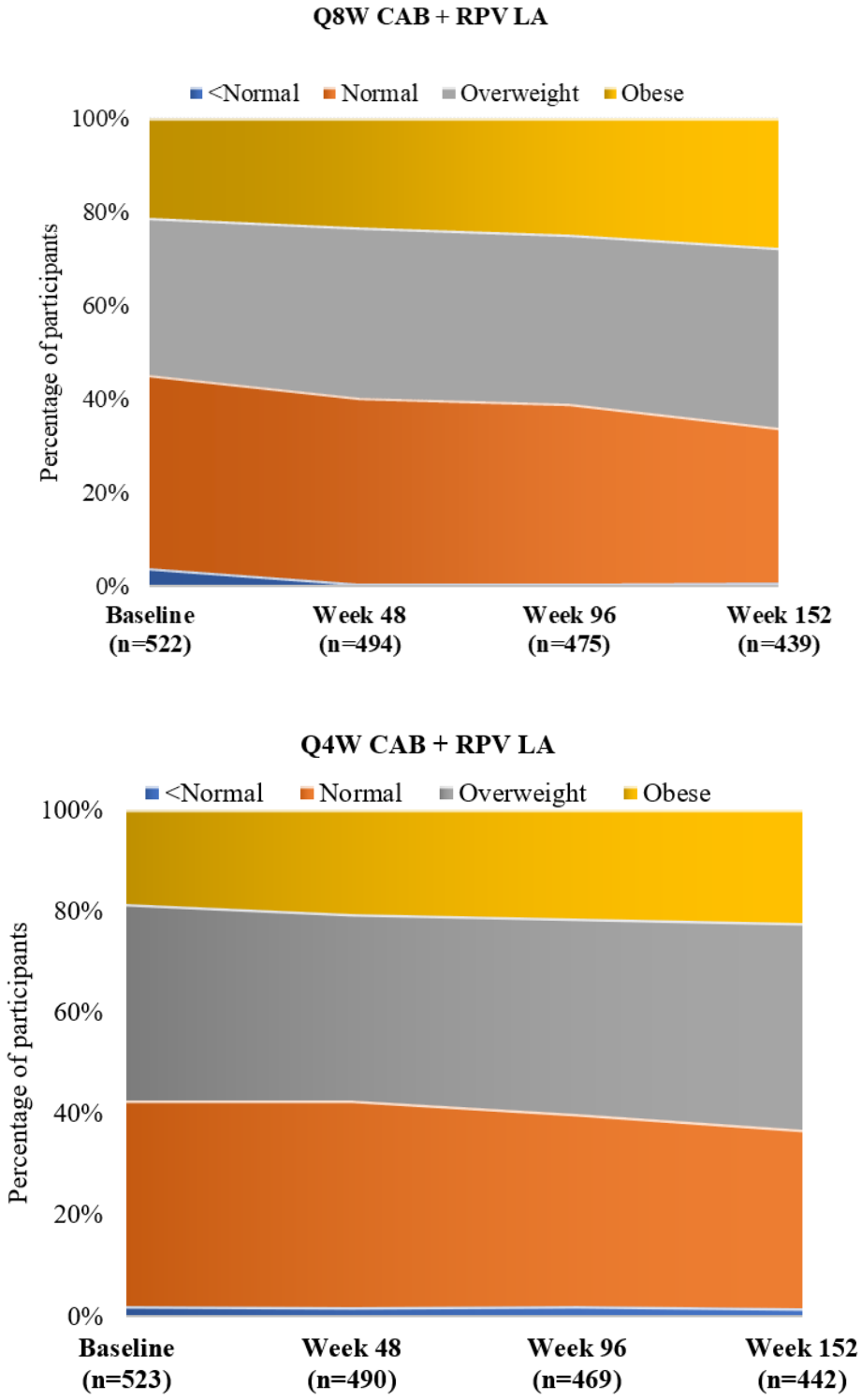
		Q8W, n/n (%)	Q4W, n/n (%)
Overall		456/522 (87)	449/523 (86)
Sex at birth	Female	114/137 (83)	124/143 (87)
	Male	342/385 (89)	325/380 (86)
Age (years)	<35	119/137 (87)	122/145 (84)
	35-<50	209/242 (86)	210/239 (88)
	≥50	128/143 (90)	117/139 (84)
Race	White	324/371 (87)	334/393 (85)
	Non-White	132/151 (87)	115/130 (88)
	Black/Afr Amer	88/100 (88)	82/90 (91)
	Non-Black/Afr Amer	368/422 (87)	367/433 (85)
Countries	Argentina	11/12 (92)	15/17 (88)
	Australia	7/8 (88)	11/15 (73)
	Canada	30/35 (86)	35/41 (85)
	France	24/26 (92)	23/28 (82)
	Germany	43/48 (90)	31/36 (86)
	Italy	24/26 (92)	21/22 (95)
	South Korea	14/18 (78)	9/9 (100)
	Mexico	9/10 (90)	5/6 (83)
	Russia	58/69 (84)	65/69 (94)
	South Africa	35/40 (88)	41/42 (98)
	Spain	68/77 (88)	69/81 (85)
	Sweden	11/13 (85)	5/8 (63)
	United States	122/140 (87)	119/149 (80)
Baseline CD4+ (cells/mm^3)	<350	30/35 (86)	21/27 (78)
	350 to <500	78/96 (81)	81/89 (91)
	≥500	348/391 (89)	347/407 (85)
Baseline HIV-1 RNA (copies/mL)	<50	454/519 (87)	441/513 (86)
	≥50	2/3 (67)	8/10 (80)
Prior exposure to CAB+RPV (weeks)	0	279/327 (85)	271/327 (83)
	≥1	177/195 (91)	178/196 (91)
Baseline BMI (kg/m^2)	<30	357/409 (87)	368/425 (87)
	≥30	99/113 (88)	81/98 (83)
Baseline third agent class	CAB+RPV	177/195 (91)	178/196 (91)
	NNRTI	136/151 (90)	138/156 (88)
	INSTI	110/136 (81)	107/141 (76)
	PI	33/40 (83)	26/30 (87)



BMI, body mass index; CAB, cabotegravir; CI, confidence interval; FDA, U.S. Food and Drug Administration; INSTI, integrase strand transfer inhibitor; ITT-E, intention-to-treat exposed; n/n, number of participant with

virologic suppression/total number of people in subgroup; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Figure S4. Summary of BMI shift from baseline at Week 152 (ITT-E population)[a]



[a] Proportion of participants with missing data: Q8W, Baseline n=0/522 (0%); Week 48, n=28/522 (5%); Week 96, n=47/522 (9%); Week 152, n=83/522 (16%); Q4W, Baseline, n=0/523 (0%); Week 48, n=33/523 (6%); Week 96, n=53/523 (10%); Week 152, n=81/523 (15%).

BMI, body mass index; CAB, cabotegravir; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Figure S5. CAB and RPV concentrations irrespective of prior exposure through Week 152[a]

[a] Median (IQR) trough concentrations.

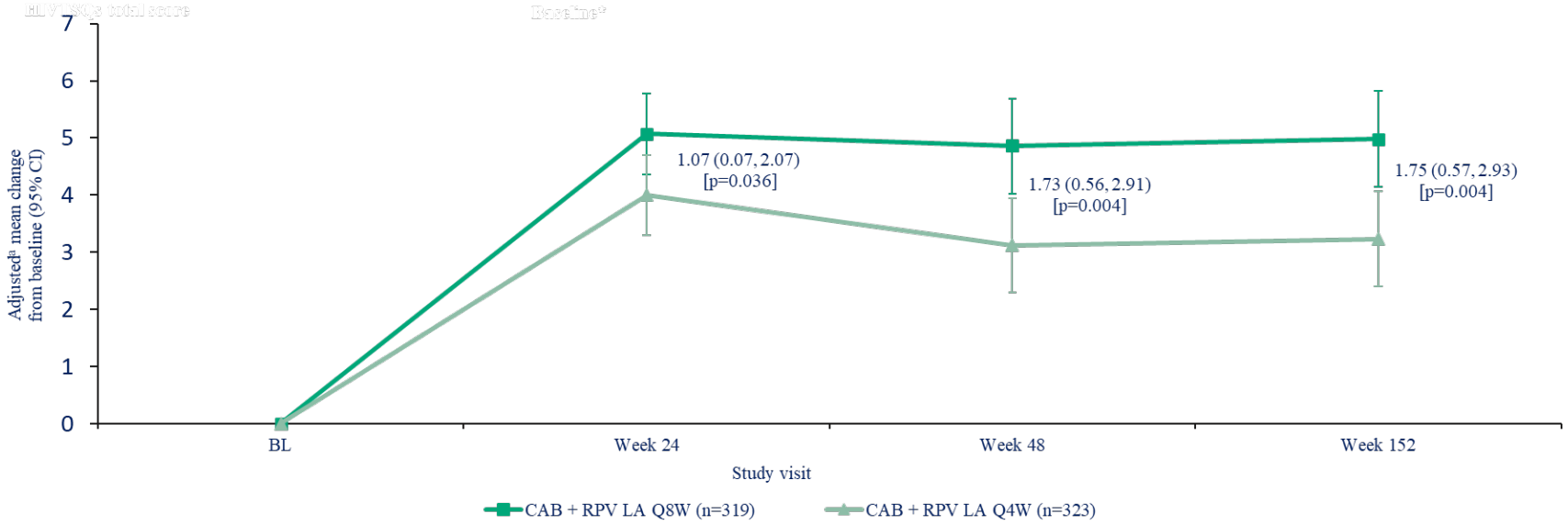
[b] Median CAB (µg/mL) (IQR) Q8W: W8, 1.92 (1.25–2.63); W48, 1.69 (1.27–2.32); W96, 1.64 (1.21–2.21); W152, 1.65 (1.26–2.29). CAB Q4W: W8, 2.11 (1.34–2.86); W48, 2.74 (2.17–3.48); W96, 2.80 (2.14–3.48); W152, 2.84 (2.21–3.70). CAB Q8W: W8 n=440, W48 n=353, W96 n=344, W152 n=290. CAB Q4W: W8 n=426, W48 n=386, W96 n=339, W152 n=303.

[c] W8 represents the first trough concentration following initial CAB+RPV LA injection at W4.

[d] Median RPV (ng/mL) (IQR) Q8W: W8, 55.5 (37.5–78.6); W48, 73.8 (54.7–98.6); W96, 93.1 (74.7–117.0); W152, 99.3 (76.9–126). RPV Q4W: W8, 57.9 (36.8–86.9); W48, 97.2 (73.9–135.0); W96, 121.0 (95.5–164.0); W152, 139 (105.0–182.0). RPV Q8W: W8 n=439, W48 n=355, W96 n=342, W152 n=289. RPV Q4W: W8 n=425, W48 n=387, W96 n=339, W152 n=303.

CAB, cabotegravir; IQR, interquartile range; LA, long-acting; PA-IC_{90}, protein-adjusted concentration required for 90% inhibition; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; W, week.

Figure S6. HIVTSQs total score in participants without prior CAB exposure



[a] Adjusted for baseline score, sex at birth, age (<50, ≥50 years), race (White, non-White), and third agent class (INSTI, PI, NNRTI). Week 152 change from baseline (95% CI): Q8W, 4.98 (4.15–5.82); Q4W, 3.23 (2.40–4.06).

BL, baseline; CAB, cabotegravir; CI, confidence interval; HIVTSQs, HIV Treatment Satisfaction Questionnaire status version; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Table S1. Participants with CVF since the Week 96 analysis[a]

#, arm	Sex at birth, BMI (kg/m^2), country	HIV-1 subtype at baseline	Viral load at CVF (copies/mL)	RPV RAMs[e] observed at SVF	INSTI RAMs[h] observed at SVF	CAB trough concentration at SVF (μg/mL)	RPV trough concentration at SVF (ng/mL)	Phenotypic resistance to CAB at SVF (fold change)	Phenotypic resistance to RPV at SVF (fold change)
Participants with protocol-defined CVF since Week 96									
1, Q8W[b]	Male, <30, Germany	B	24,221	E138A+ M230M/L	Q148R	0.837[c]	36.0[c]	3.3	16.0
2, Q8W[d]	Male, <30, Russia	A6[f]	59,467	E138A+ Y181Y/C	Q148R	2.43	57.0	9.5	3.4
Participant with non-protocol-defined virologic failure[g]									
3, Q8W	Male, <30, Spain	A1	1038	E138K	None[i]	1.87	48.5	[j]	3.5

[a] Details on participants with CVF at Week 48 and Week 96 analyses have been previously presented [10, 17]. The participants who met the protocol-defined CVF criterion since the Week 96 analysis did so at Week 112 and Week 120. Both participants had treatment-emergent RAMs to RPV (E138A+M230M/L; E138A+Y181Y/C) and INSTIs (Q148R) at SVF. The participant who met the CVF criterion at Week 112 had no RPV or INSTI RAMs from baseline PBMCs; however, integrase polymorphism L74I at baseline was retained at SVF (Week 112). This participant had 122 days of CAB+RPV LA exposure before entering the ATLAS-2M study. The participant who met the CVF criterion at Week 120 had no RPV or INSTI RAMs from baseline PBMCs and entered the ATLAS-2M study while on daily oral ART. The additional participant that had non-protocol-defined virologic failure at Week 48 (Q8W) had no RPV or INSTI RAMs present from baseline PBMCs; the RPV RAM E138K and the INSTI mutation

S230S/R were detected at retest (Week 56). This participant entered the ATLAS-2M study while on daily oral ART. None of these three participants had missed injection visits.

[b] The participant later resuppressed with darunavir/cobicistat/emtricitabine/tenofovir alafenamide.

[c] Trough concentrations for CAB and RPV at withdrawal (Week 128).

[d] This participant had the integrase polymorphism L74I at baseline. The participant was prescribed lamivudine/tenofovir disoproxil fumarate/darunavir/ritonavir and resuppressed during the long-term follow-up.

[e] Per the IAS–USA list of NNRTI mutations associated with resistance to RPV [28].

[f] This participant was originally classified as subtype A1 but, upon reanalysis, was later reclassified as subtype A6.

[g] This participant met the SVF criterion at Week 48 with an HIV-1 RNA value of 918 copies/mL; however, virologic failure was not confirmed at the Week 48 retest result (39 copies/mL). At Week 56, HIV-1 RNA was elevated again at 1038 copies/mL. Resistance analysis data in the table are from the retest at Week 56. The participant was prescribed darunavir/cobicistat/emtricitabine/tenofovir alafenamide and resuppressed during the long-term follow-up.

[h] Per the IAS–USA list of mutations associated with resistance to bictegravir, cabotegravir, dolutegravir, elvitegravir, or raltegravir for INSTI [28].

[i] The mutation S230S/R was detected but is not identified as an INSTI RAM.

[j] The INSTI phenotypic assay failed at SVF (Week 48) and withdrawal (Week 51).

ART, antiretroviral therapy; BMI, body mass index; CAB, cabotegravir; CVF, confirmed virologic failure; IAS, International Antiviral Society; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; PBMC, peripheral blood mononuclear cell; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine; SVF, suspected virologic failure.

Table S2. Summary of CAB and RPV concentration data at long-term follow-up visits by dosing regimen, following cessation of CAB and RPV injections

Long-term follow-up visit	Plasma CAB concentrations (μg/mL)[a]				Plasma RPV concentrations (ng/mL)[b]			
	Q8W n=48		Q4W n=47		Q8W n=48		Q4W n=47	
	n (n imputed)[c]	Median (range)	n (n imputed)[c]	Median (range)	n (n imputed)[c]	Median (range)	n (n imputed)[c]	Median (range)
Month 1	44 (0)	1.99 (0.462–5.38)	46 (0)	2.24 (0.398–4.80)	43 (0)	81.4 (12.4–269)	36 (0)	90.0 (47.4–270)
Month 3	41 (1)	0.987 (NQ–3.28)	44 (2)	1.04 (NQ–3.17)	39 (0)	64.6 (4.7–269)	33 (1)	65.1 (NQ–213)
Month 6	33 (4)	0.282 (NQ–1.85)	42 (7)	0.299 (NQ–2.18)	31 (0)	40.0 (4.8–182)	32 (1)	40.0 (NQ–125)
Month 9	35 (9)	0.110 (NQ–1.21)	39 (13)	0.107 (NQ–1.37)	34 (0)	32.9 (2.7–127)	28 (1)	31.9 (NQ–200)
Month 12	35 (16)	0.047 (NQ–0.794)	37 (16)	0.046 (NQ–0.841)	34 (0)	23.0 (2.8–111)	27 (1)	22.6 (NQ–67.5)

[a] CAB concentrations taken on/after the start date of oral CAB were excluded for participants who received oral CAB after their last injection.

[b] RPV concentrations taken on/after the start date of oral RPV were excluded for participants who received oral RPV after their last injection.

[c] Non-quantifiable (NQ) values were assigned a value equal to the lower limit of quantification (CAB, 0.025 μg/mL; RPV, 1 ng/mL).

CAB, cabotegravir; NQ, non-quantifiable; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.