



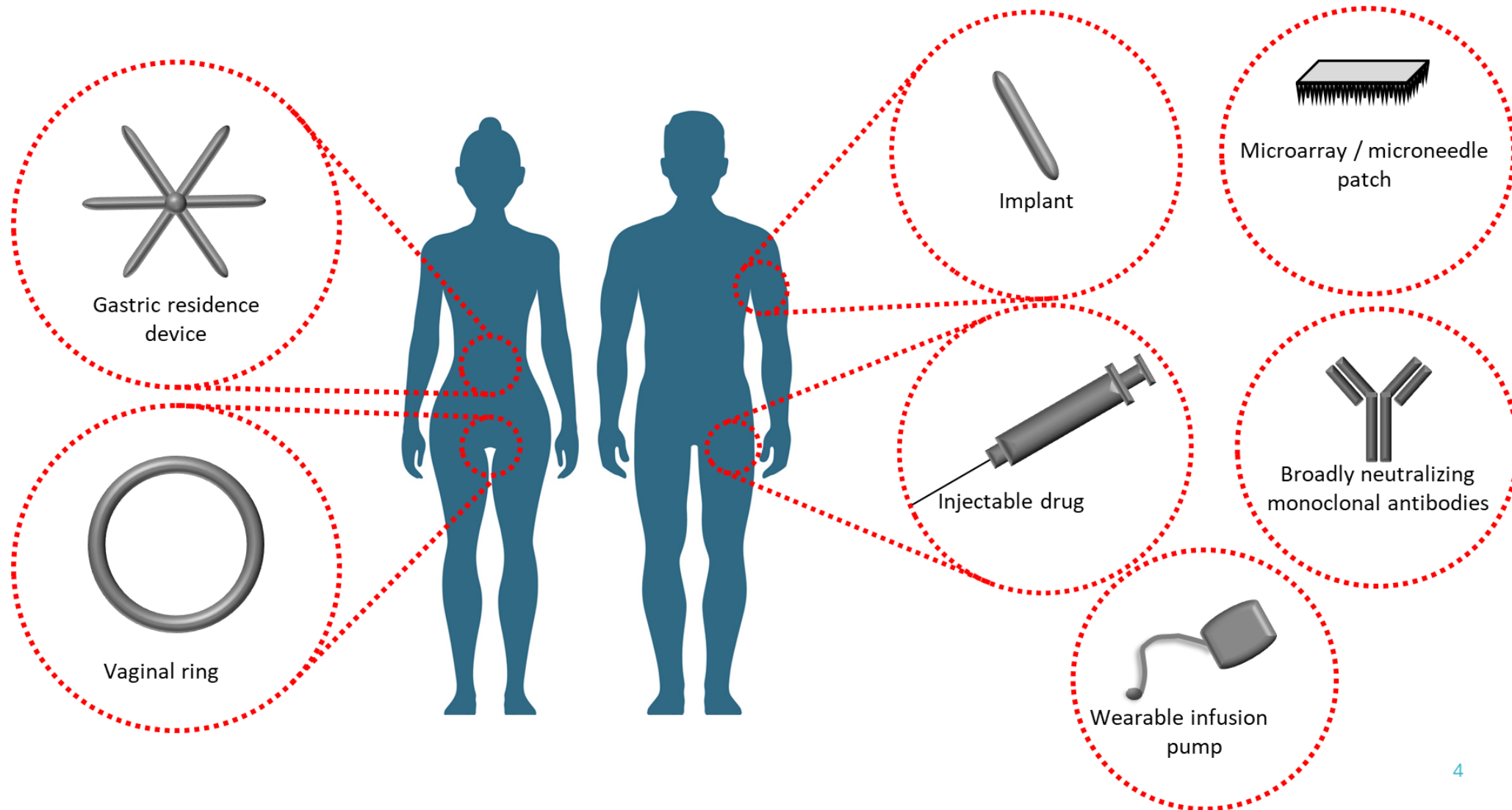
Cabotegravir e rilpivirina: evidenze da studi non sperimentali

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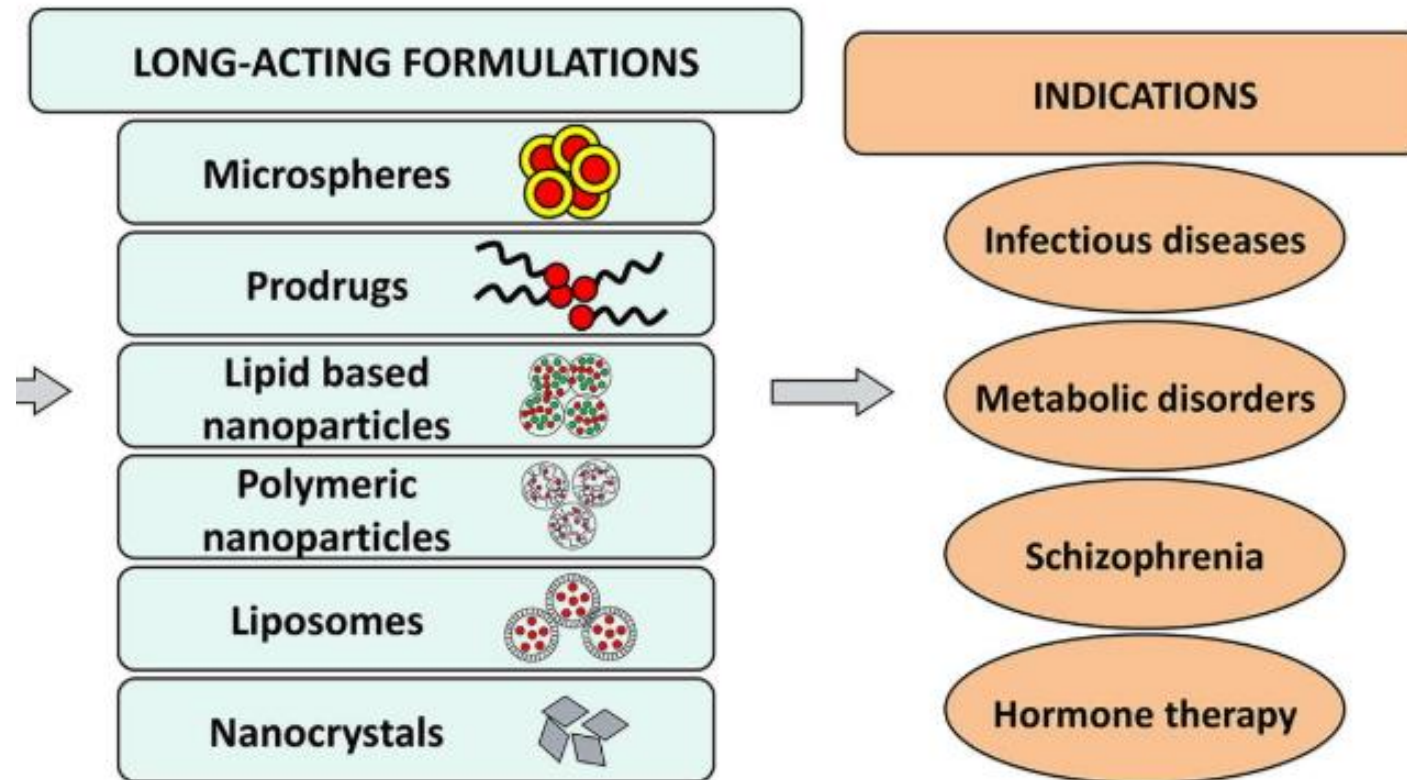
Disclosure

- I received speaking fees from ViiV Healthcare and Gilead

Drug Delivery Systems and Long-acting Technologies



Long-acting Formulations and Indications



Long-acting Drugs Approved for HIV

LA- Cabotegravir + Rilpivirine

IM, every 4 or 8 weeks
with/with out OLI

FDA/EMA Approved

Jan 2021; ART /4 weeks

Feb 1, 2022: ART /8 weeks

Switch with undetectable VL

Lenacapavir

SC every 6 months
Combined with oral ARV

FDA/EMA Approved

Dec 2022: Twice-yearly treatment
for PLH multi-drug resistant HIV

What's Happening in Clinical Practice?

RCT vs. **RWE**



**Randomized
Controlled Trial**



**Real World
Evidence**

US Cohorts

CAB/RPV Effectiveness in the OPERA Cohort

Demographic and Clinical Characteristics at CAB+RPV LA Initiation (n= 2858)

	Individuals with ≥ 1 injection
Age, median years (IQR)	39 (31, 51)
Female, n (%)	448 (16%)
Black race, n (%) ^a	1,199 (42%)
Hispanic ethnicity, n (%) ^a	853 (30%)
Married or domestic partner, n (%) ^a	486 (17%)
Injection drug use, n (%)	86 (3%)
MSM, n (%)	1,619 (57%)
Care in Southern US, n (%)	1,577 (55%)
Payer, n (%) ^b	
Medicare	342 (12%)
Medicaid	945 (33%)
Commercial Insurance	1,954 (68%)
Ryan White/ADAP	900 (31%)
Cash	85 (3%)
Other Payer	

	Individuals with ≥ 1 injection
Years since HIV diagnosis, median (IQR)	6 (2, 13)
History of AIDS-defining illnesses, n (%)	680 (24%)
BMI, median kg/m ² (IQR) ^a	27 (24, 31)
VACS Index, median (IQR) ^a	10 (0, 18)
≥ 1 comorbidity, n (%) ^c	2,208 (77%)
Co-infections (ever), n (%)	
Hepatitis B	74 (3%)
Hepatitis C	193 (7%)
Syphilis	1,337 (47%)
CD4 cell count, median cells/μL (IQR) ^a	698 (519, 912)
Prior core agent class, n (%) ^a	
INSTI	2,227 (78%)
PI	109 (4%)
NNRTI	197 (7%)
≥ 2 core agents	207 (7%)
Other	≤ 5 ^b

CAB/RPV Effectiveness in the OPERA Cohort

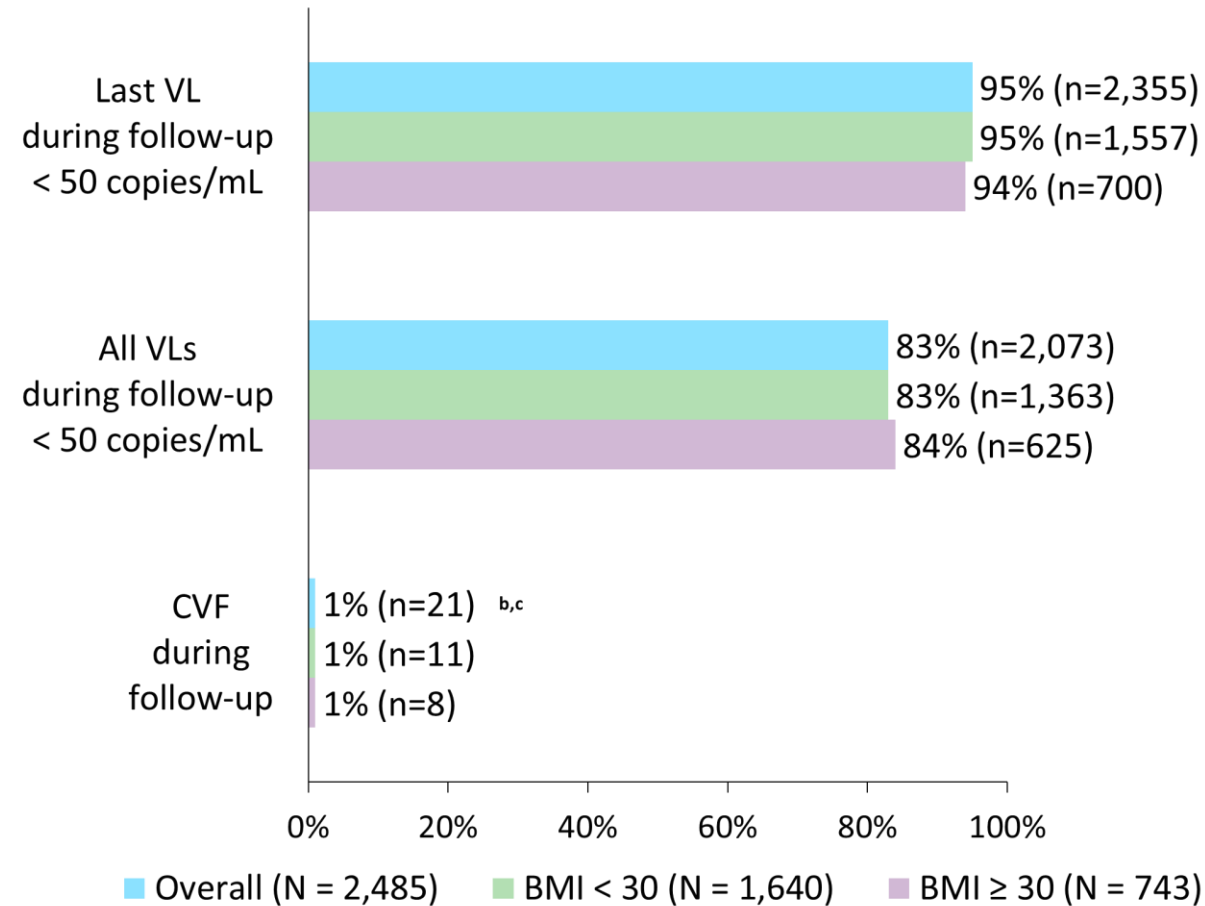
Persistence and Adherence

	Complete initiators
Months of follow-up, median (IQR)	11 (6, 18)
Receiving CAB+RPV LA at time of analysis, n (%) ^a	2,179 (83%)
Received 2 nd initiation injection on-time	2,188 (84%)
Individuals with ≥ 1 maintenance injection, n (%)	2,360
Received all maintenance injections on-time	1,475 (62%)
≥ 1 delayed maintenance injections, n (%)	711 (30%)
≥ 1 missed maintenance injections, n (%)	279 (12%)

- ✓ 2618 individuals (92%) were followed for a median of 11 months
- ✓ Most individuals received their 2nd initiation injection on-time and over half received all maintenance injections on-time
- ✓ While 38% of individuals did not receive all maintenance injections on time , ART coverage between injections with oral bridging could not be assessed

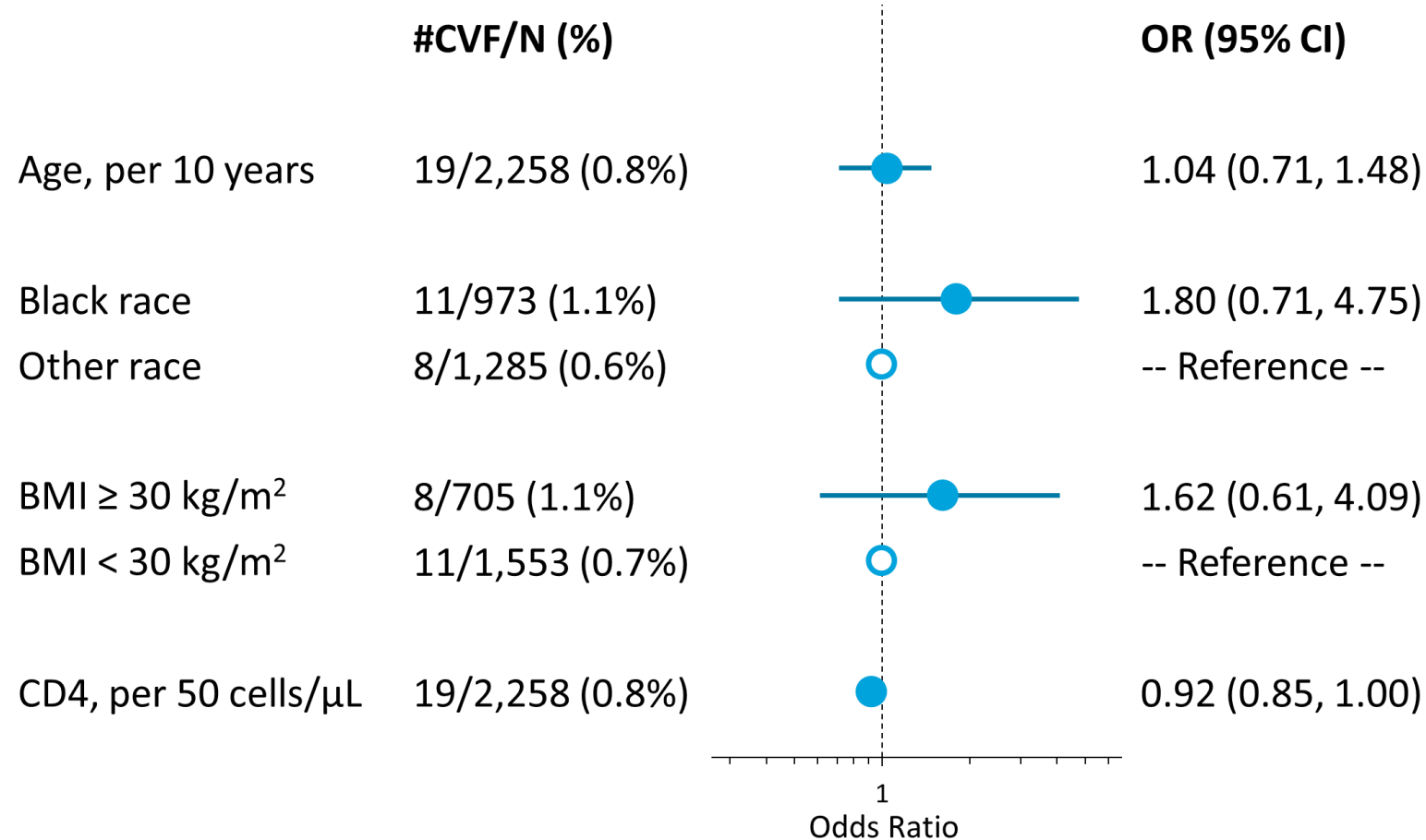
CAB/RPV Effectiveness in the OPERA Cohort

Virologic outcomes overall and stratified by BMI at initiation



CAB/RPV Effectiveness in the OPERA Cohort

Factors associated with CVF



CAB/RPV Effectiveness in the TRIO Health US Cohort

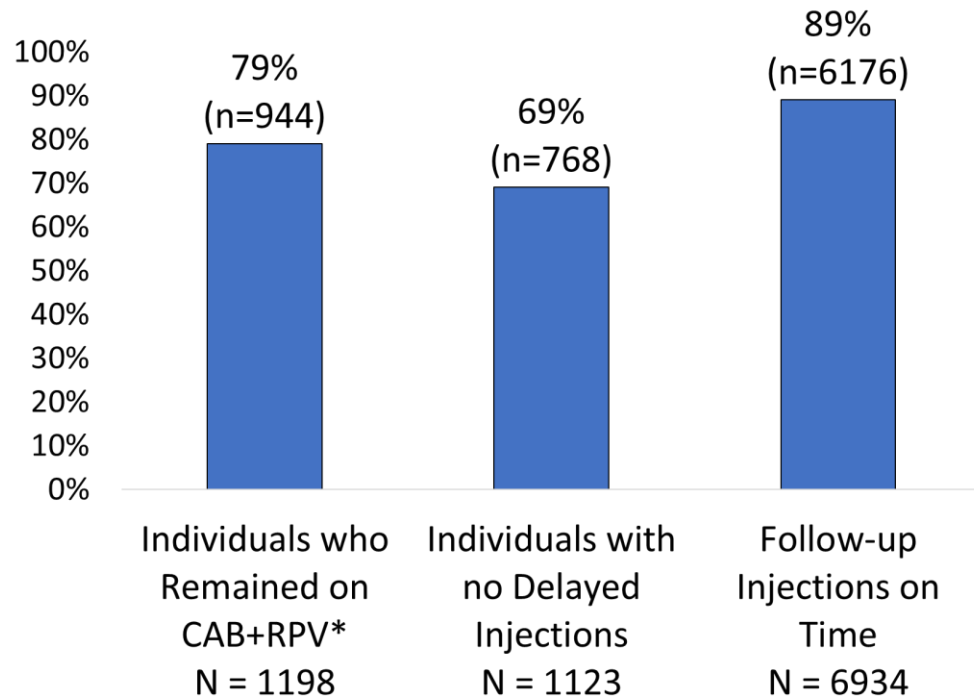
Baseline characteristics

	N (%) or Median (IQR)	All Initiators n=1198	With Viral Failure N=15
Follow-up	Months Follow-up in EMR	11 (5, 18)	13 (7, 18)
	>12 months Follow-up	549 (46)	8 (53)
	>24 months Follow-up	101 (8)	3 (20)
Gender	Age at Start	43 (34, 54)	49 (36, 52)
	Male	921 (77)	6 (40)
	Female	269 (22)	8 (53)
Race	Another or Unknown Gender	8 (1)	1 (7)
	White	500 (42)	4 (27)
	Black or African American	573 (48)	9 (60)
Payer	Another or Unknown Race	125 (10)	2 (13)
	Hispanic Ethnicity	244 (20)	1 (7)
	Commercial Payer	622 (52)	12 (80)
	Medicare/Medicaid Payer	330 (28)	2 (13)
	Other or Unknown Payer	246 (21)	1 (7)

BMI	Years since HIV Diagnosis	4 (1, 8)	3 (1, 4)
	Body mass index (BMI kg/m ²)	28 (24, 32)	31 (26, 37)
	Obese I (BMI 30-39)	357 (30)	5 (33)
CD4	Obese II (BMI ≥40)	68 (6)	3 (20)
	Absolute CD4 (cells/μL)	677 (488, 882)	657 (430, 833)
	Nadir CD4 (cells/μL)	437 (284, 631)	321 (194, 480)
Baseline resistance	INSTI	6/314 (2)	0/3 (0)
	CAB	2/314 (<1)	0/3 (0)
	NNRTI	61/314 (19)	0/3 (0)
	RPV	15/314 (5)	0/3 (0)
	Both CAB and RPV	1/314 (<1)	0/3 (0)

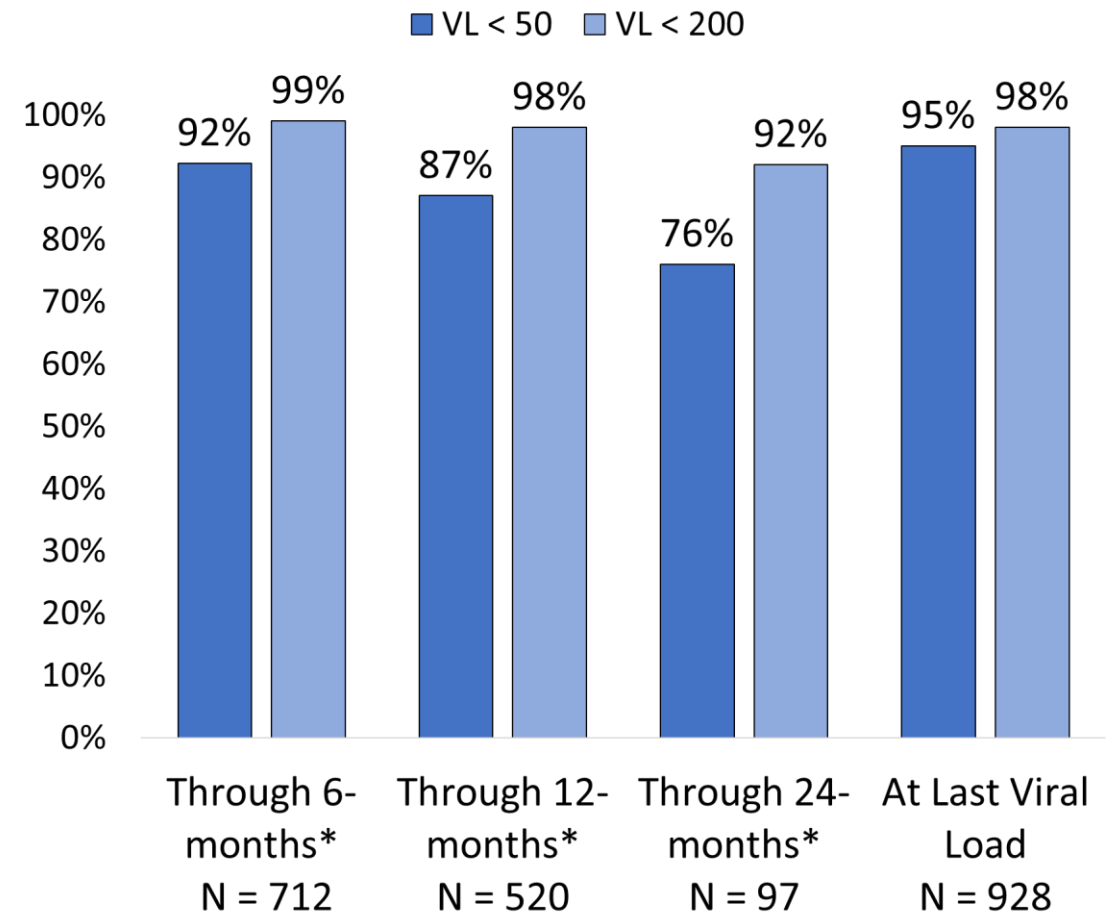
Outcomes in CAB/RPV in TRIO Health US Cohort

Adherence to and durability of CAB/RPV regimen



* Includes 21 who re-initiated CAB+RPV and remained on CAB+RPV through end of follow-up

Maintenance of viral suppression on CAB/RPV

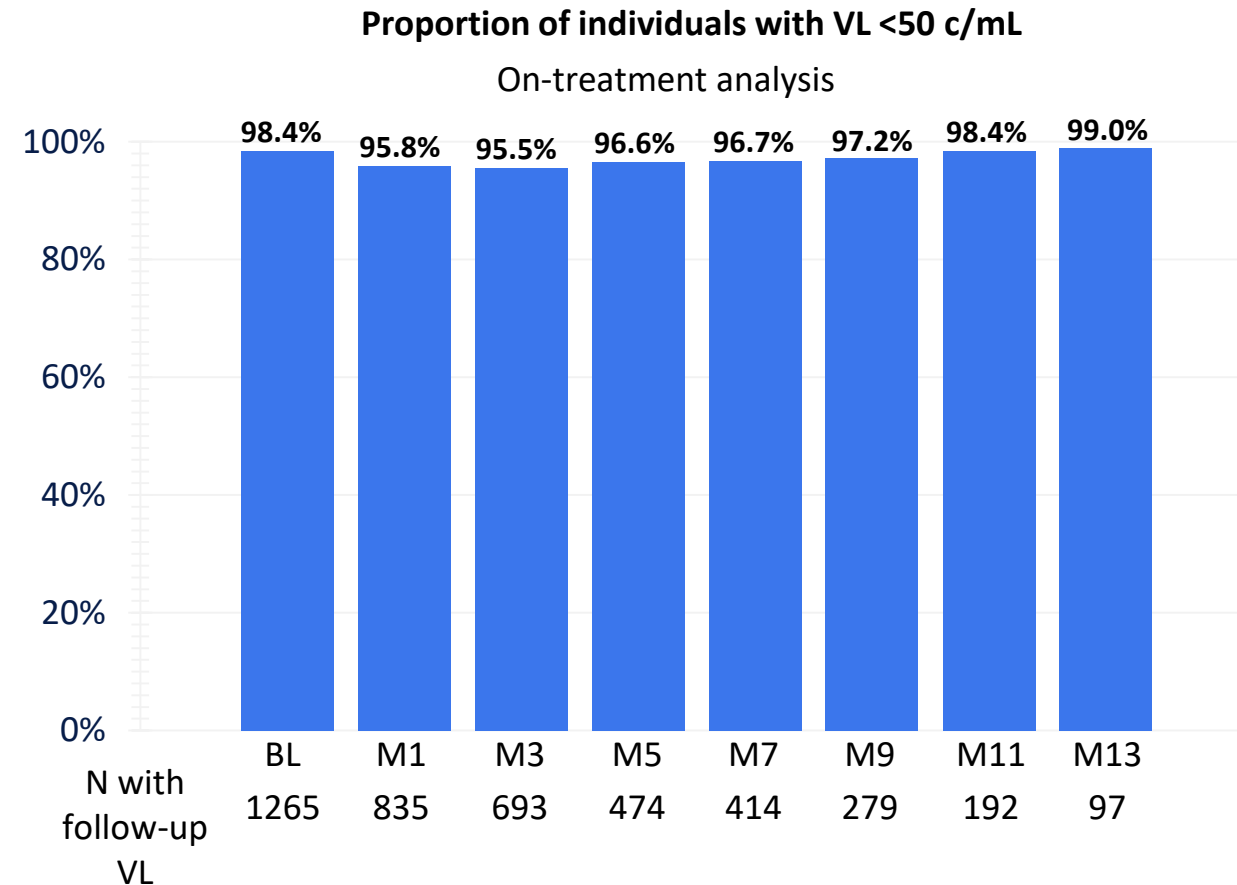


* VL < 50 or VL < 200 at all viral loads through time period

European Cohorts

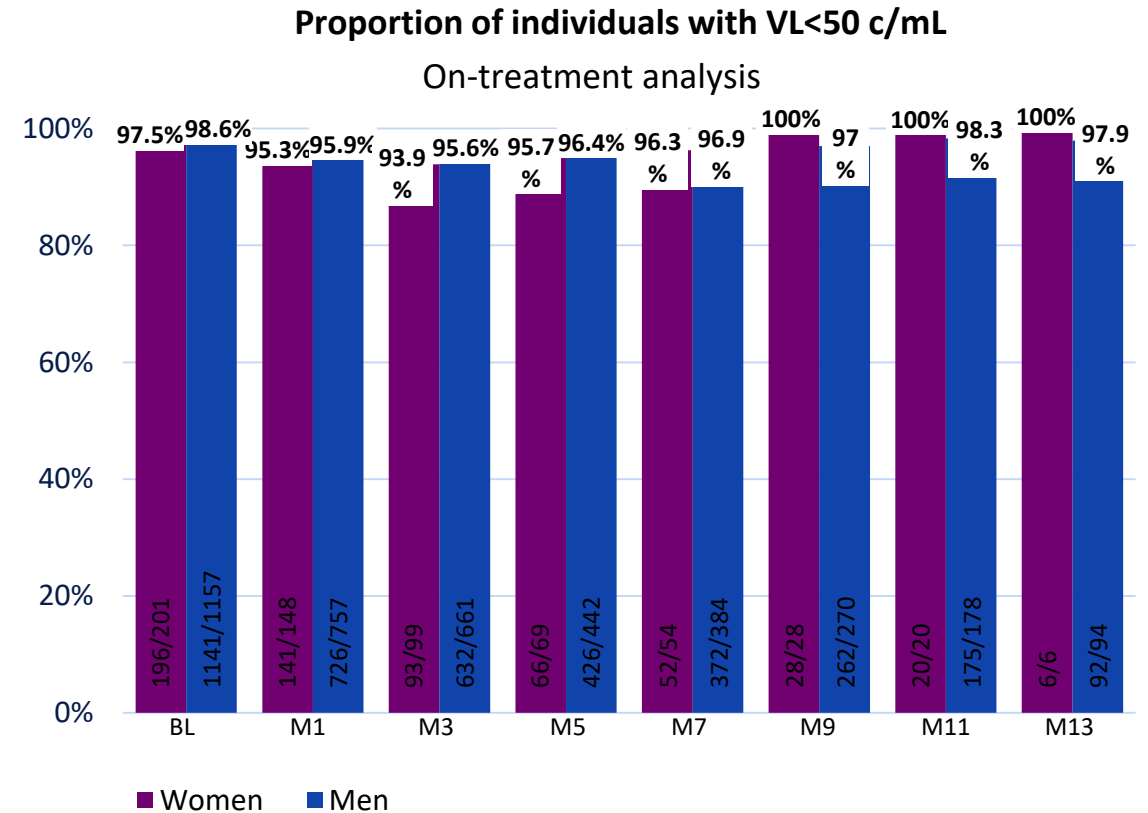
RELATIVITY

- Multicenter cohort from Spain
- 1285 people with HIV-1 were included in this analysis
 - 85.7% male, median age 45 years, median 9 years on ART
 - 1.7% viraemic, 9.3% with NNRTI RAMs and 0.7% INI RAMs
 - Previous ART: 44% DTG/3TC, 23% DTG/RPV, 21% BIC/FTC/TAF
- Proportion of individuals with VL<50 c/mL ranged between 95.5% and 99% throughout the follow-up time (median 7.6 months)
- 65 (5%) discontinued treatment, including 6 (0.5%) due to VF:
 - 3 experienced VF with no emergent resistance, 2 had INI RAMs only and 1 had INI and NNRTI RAMs at VF
 - 2/6 screening failures due to previous VF with probable INI RAMs unnoticed, and INI/NNRTI RAMs not known at switch
 - 5/6 resuppressed on INI or PI-based STRs



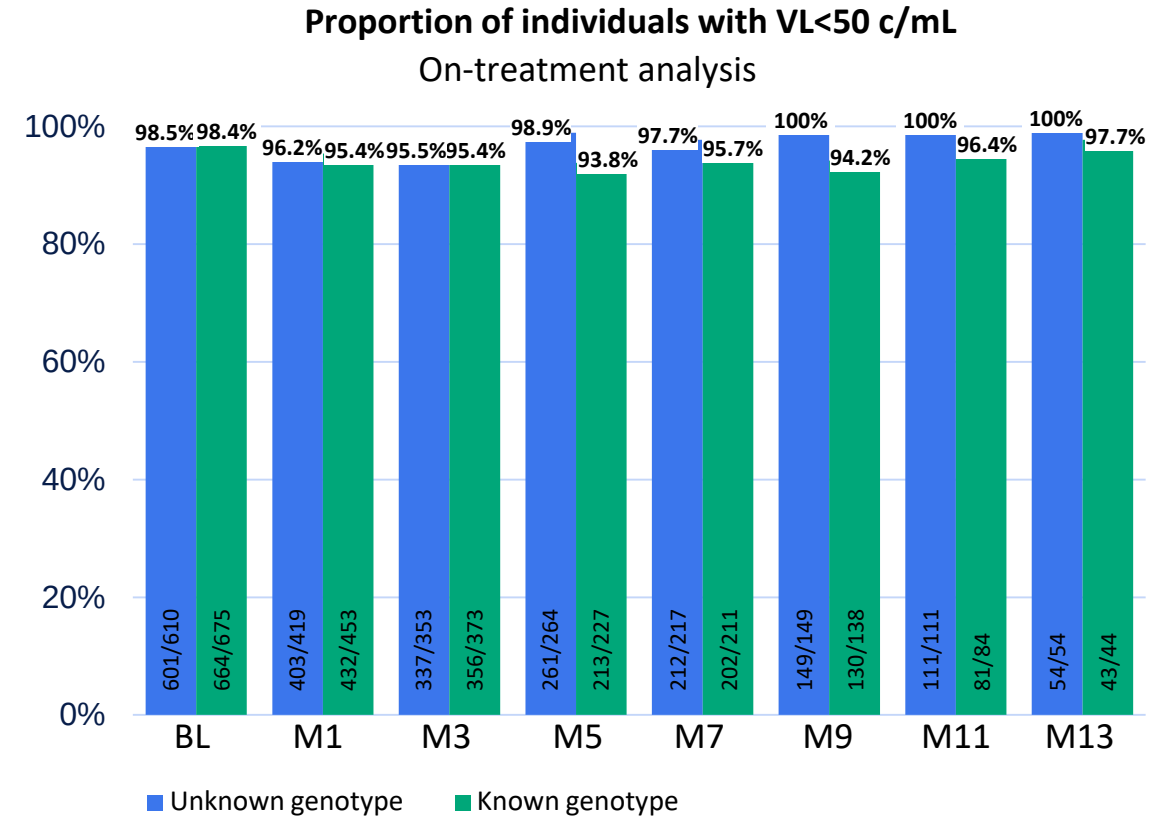
RELATIVITY

- Substudy on CAB+RPV LA in women with HIV
- Of 1358 PWH, 201 (14.8%) were women
 - Women were older, had more comorbidities, higher prevalence of AIDS, longer time on ART, and had a higher rate of prior VF
 - Follow-up period was shorter for women (7.2 vs 7.7 months)
- Virologic suppression and virologic failure rates were comparable between women and men
- VL<50 c/mL among women ranged between 93.9% and 100%, with 1 individual (0.5%) experiencing VF
- Discontinuation rates and rates of ISRs were higher for women vs men
 - 18 women discontinued CAB+RPV, due to ISRs (7, 3.5%), systemic adverse events (3, 1.5%), VF (1, 0.5%), and other reasons (6, 3.0%)



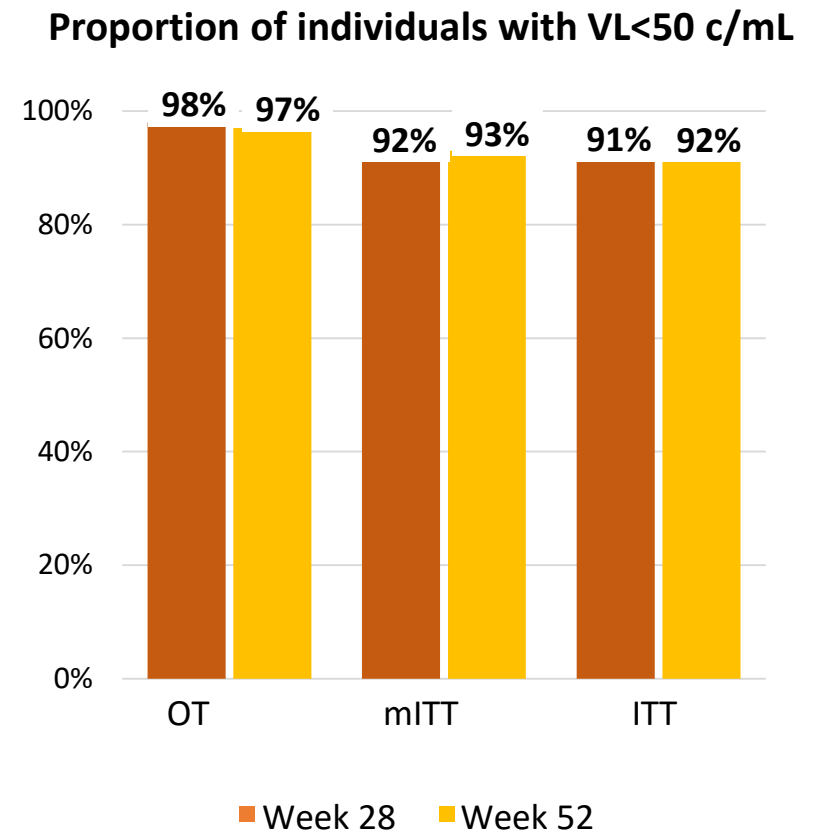
RELATIVITY

- Of 1285 PWH included in the RELATIVITY cohort, 610 (47%) switched to CAB+RPV LA without a previous genotype test result
- People in this subgroup were significantly older with a lower prevalence of psychiatric disorders, previous blips, and documented virological failures
- Switching from DTG/RPV was more frequent when genotyping was not available
- High virologic suppression rates observed for both subgroups through a median of 7.6 months, regardless of the availability of previous genotype test results
- Of the 6 (0.5%) individuals experiencing VF in this cohort, only 1 had no previous genotype available at initiation



Hospital Clínic Barcelona

- Observational, prospective, single-center study
- 533 individuals were enrolled in the study, of which 318 (60%) and 99 (19%) reached W28 and W52 of follow-up
 - 92% male, 11% BMI >30 kg/m², median 9 years on ART (IQR 4-15)
 - 98% had VL <50 c/mL at initiation
- High virologic suppression rates observed at W28 and W52: 98% and 97%
- 96% injection administered within the ± 7 -day window and 2% were delayed
- 4 (1.3%) individuals experienced virological failure, all with LLV (VL <200 c/mL)



High virologic suppression and adherence rates observed up to W52, with low virological failure rate

ANRS CO3 AquiviH-NA Cohort

- A retrospective analysis of 374 PWH who received their first CAB+RPV LA injection between January 1, 2022, and June 30, 2024
- Median age was 47 years (range 20-81), 26% (98/374) were female
- 90% (336/374) participants continued CAB+RPV LA injections at 12M
- 3.5% (12/374) experienced virological failure at month 12, with 6/12 having low-level viremia (VL >50 and <200 copies/mL)
- 10.2% (38/374) discontinued treatment at 12 months, mainly due to AEs, including ISRs, and physician choice
- No significant changes in BMI or LDL cholesterol were observed at month 12

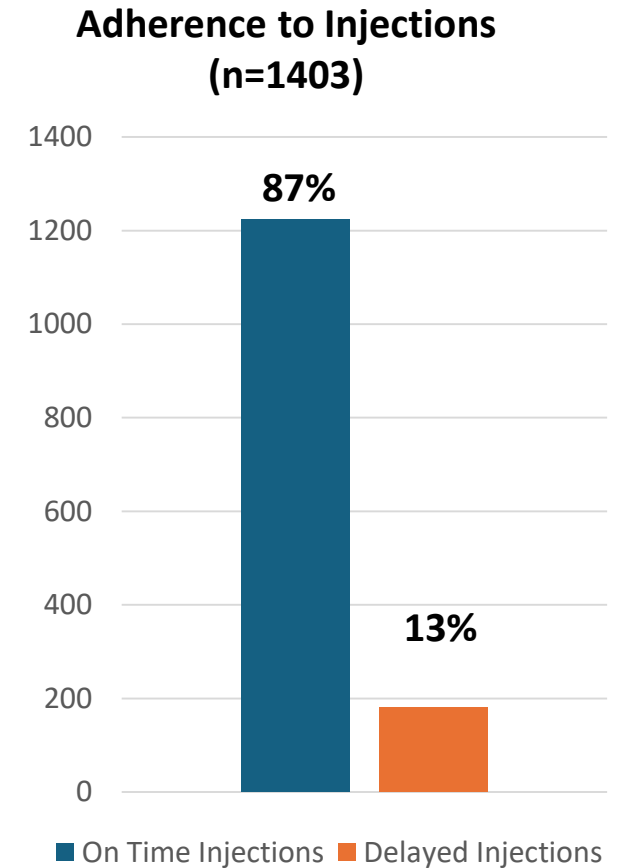
Comparison of cumulative viral load characteristics from initiation of treatment to month 12

Characteristics	Total N=374	
At least 1 virological failure since baseline, n (%)		
No	334	(96.5)
Yes	12	(3.5)
Type of virological failure, n (%)		
Low level viremia (2 consecutive VL>50 cp/mL)	6	(50.0)
High level viremia (at least 1 VL >200cp/mL if 2 consecutive VL>50 cp/mL)	3	(25.0)
For unsuppressed at baseline patient, No VL<50 between 3 and 12 months	3	(25.0)
Delay of first virological failure, Median (IQR) in month	4.9	(1.8;6.9)
At least 1 Blip (VL>50cp/mL after VL≤50cp/mL) since baseline, n (%)	346	
No	319	(92.2)
Yes	27	(7.8)

High durability and neutral impact on metabolic parameters through 12 months

University Medical Center Hamburg-Eppendorf

- Retrospective study
- 106 people were included:
 - 19% female, median 49 years
 - Median 7.5 years on ART, with 80% previously on INI-based regimens
- Virological suppression was achieved in 96.2% of participants at final measurement, with 94.3% maintaining an undetectable viral load throughout the study period
- One individual (0.7%) experienced virological failure, having started treatment with a detectable viral load at initiation
- 18 participants (17.0%) discontinued treatment, with main reasons being injection site pain (44.4%)



High virologic suppression for a median of 30 months despite 13% non-adherence in this real-world cohort

Italian Cohorts

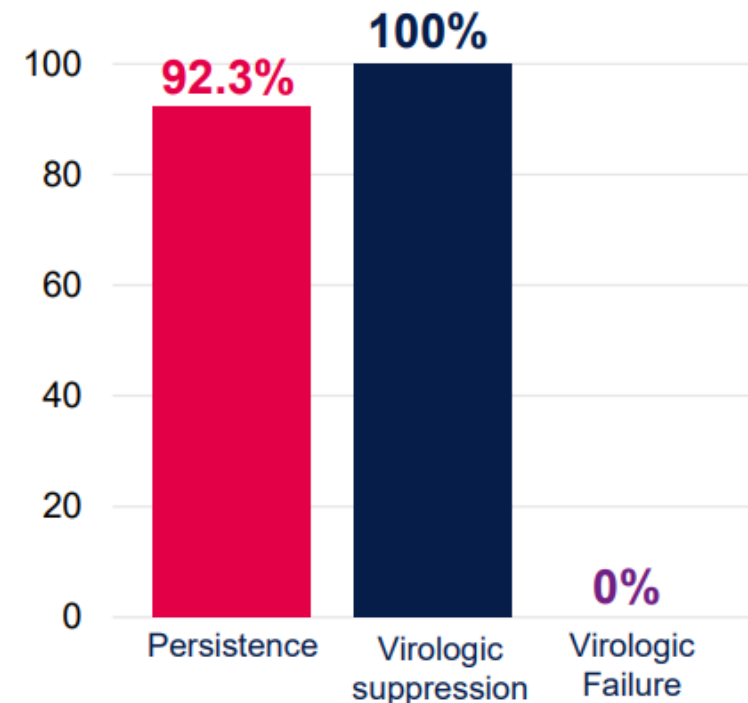
Real-life Data from the GEPPPO Cohort

Baseline characteristics

	N or median	Percentage or IQR
Age (years)	66.7	65-70
Male sex at birth	59	75.9%
Body Mass Index, BMI (Kg/m²)	24.8	23.6-27.3
Years of HIV infection	20	14.0-28.5
Years of antiretroviral treatment	19	13.0-22.0
HIV RNA at baseline		
<20 copies/mL	70	89.7%
20-50 copies/mL	1	1.3%
>50 copies/mL	3	3.8%
Not available (6 mm window)	4	5.1%
Nadir CD4 cell count: n/mm3	270	105-410
Multimorbidity	48	61.9%
Polipharmacy	25	31.9%

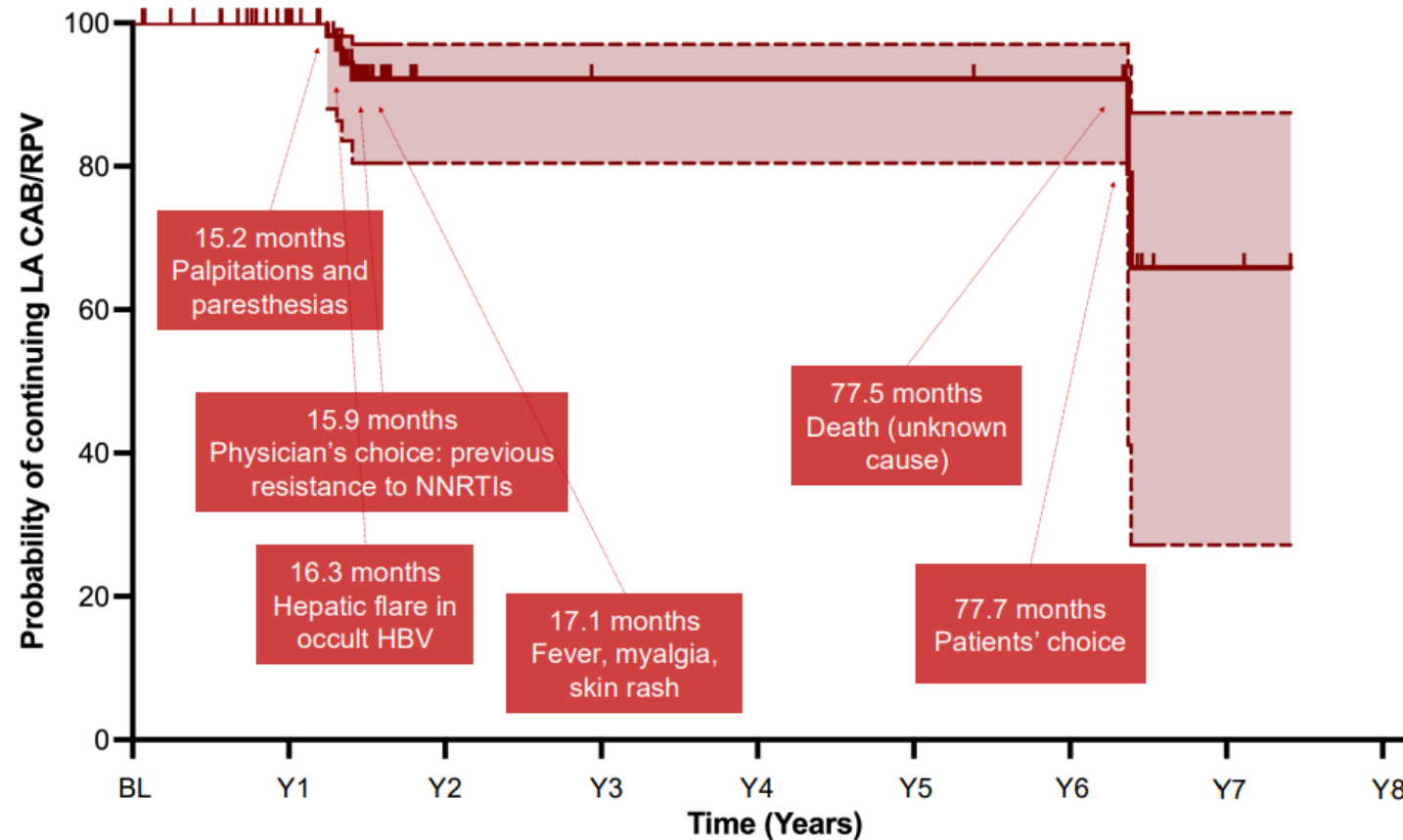
Persistence and virologic outcomes, n=78

Median follow-up time: 17.29 months (CI 95%: 16.74-17.60)



Real-life Data from the GEPPPO Cohort

Reasons for discontinuation in 6 participants



Real-life Data from the ICONA Cohort

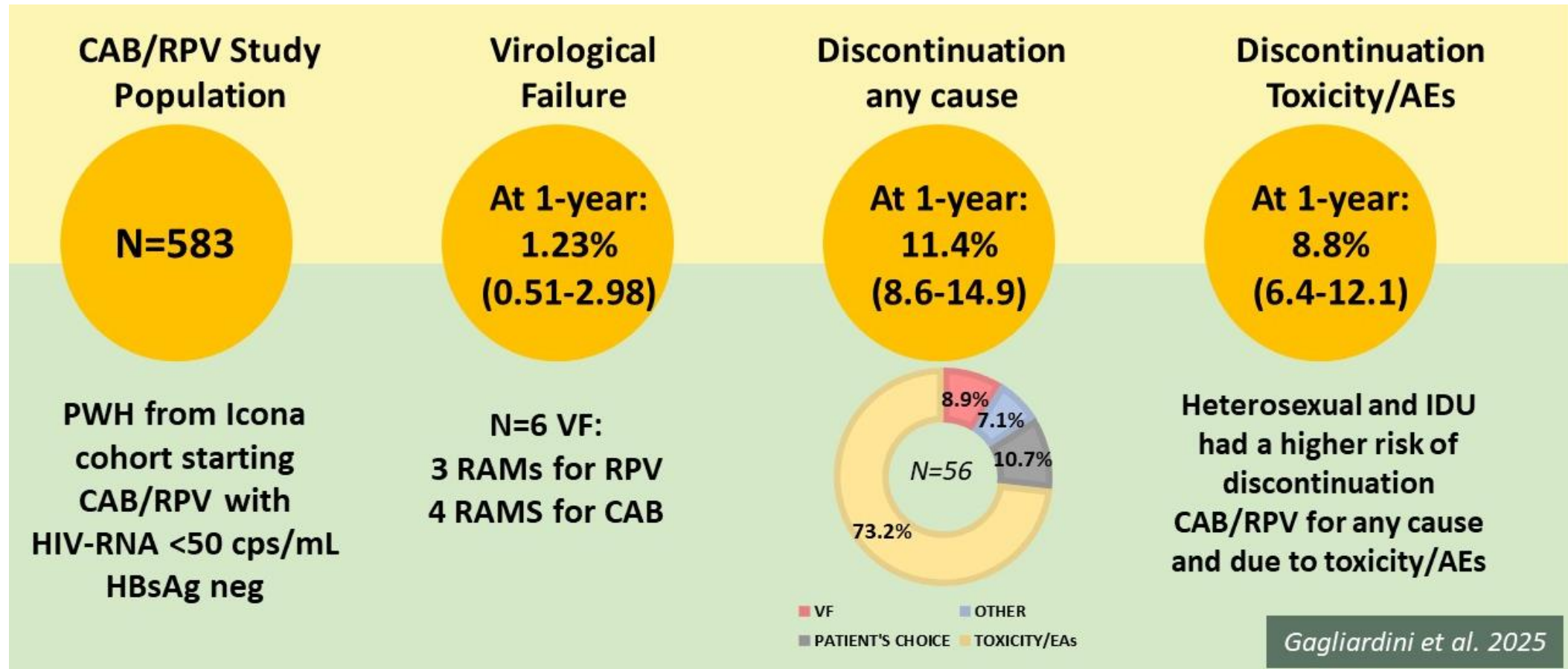


Baseline characteristics

Female sex, n(%)	57 (11.3%)
Italian nationality, n (%)	452 (88.7%)
Mode of HIV transmission, n(%)	
Heterosex	129 (25.5%)
IDU	9 (1.8%)
MSM	344 (68.%)
BMI, median (IQR)	24.4 (22.7-26.8)
BMI > 30, n(%)	39 (7.7%)
CD4 at BL, median (IQR)	766 [590-959]
CD4 at nadir, median (IQR)	387 (243-532)
CD4< 200 at nadir, n(%)	98 (19.4%)
Age, median (IQR)	46 [37-54]
Age > 50 ys	165 (32.6%)
Years of viral suppression, median (IQR)	7.0 (3.7-9.6)

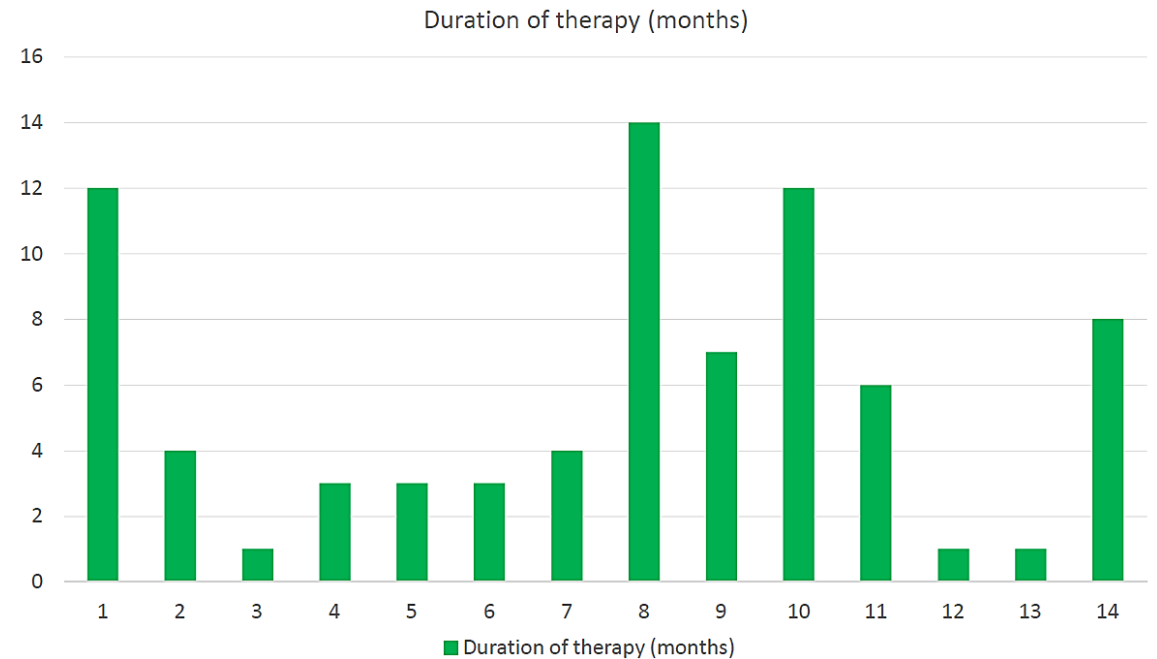
ART exposure, years, median (IQR)	7.3 (4.4-10.2)
Previous AIDS event, n (%)	42 (8.3%)
HBcAb positive, n (%)	79 (19.8%)
HCVAb positive, n(%)	35 (7.2%)
ART line, median (IQR)	4 [3-5]
GRT RT pre-CAB/RPV, n (%)	415 (82.0%)
RPV fully susceptible, n(%)	405 (97.6%)
GRT INSTI pre-CAB/RPV, n (%)	231 (45.7%)
CAB fully susceptible, n (%)	231 (100%)
HIV subtype, n(%)	
A1	7 (1.4%)
B	280 (55.3%)

Real-life Data from the ICONA Cohort



Real-life Data from a Multicentric Cohort

- A descriptive analysis of the causes of treatment interruption and the impact of genotypic drug resistance among PWH receiving CAB + RPV across 10 infectious disease units in Italy
- 758 individuals were included (average age, 53 years; average BMI, 25.26 kg/m²)
- Average duration of LA therapy was 5.23 months
- 66 PWH (8.7%) interrupted treatment, 14 (1.8%) due to VF
- 46 individuals had GRT before starting CAB + RPV, with 5 harboring NNRTI resistance
- Post-VF GRT revealed new mutations in 8 individuals



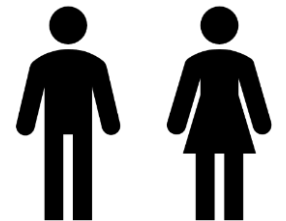
SCohoLART Study

- ✓ Single-center, prospective, phase IV, cohort study of people with HIV, treated with long-acting antiretroviral therapy
- ✓ **Aim:** to collect clinical data, in order to optimize, during a long-term follow-up, the clinical management of people with HIV, treated with long-acting antiretroviral therapy
- ✓ **Primary study endpoint:** cumulative proportion of people with treatment failure over 48 weeks.

Treatment failure is defined by the occurrence of virological failure (VF, 2 consecutive HIV-RNA values >50 copies/mL or a single HIV-RNA value >1000 copies/mL after the start of cabotegravir and rilpivirine) or discontinuation for any reason of the regimen.

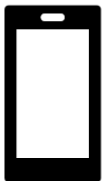
Inclusion criteria:

- HIV infection;
- age > 18 years;
- HIV-RNA <50 copies/ml;
- Stable ART;
- Planned start of cabotegravir and rilpivirine;
- Written informed consent provided.



SCohoLART Study

- ✓ Cabotegravir 600 mg i.m. + Rilpivirine 900 mg i.m. at T0, M1, M3 and then every 2 months, with or without oral lead-in
- ✓ Laboratory and clinical monitoring
 - HIV RNA testing was monitored at month 1, 3 and 6 and then every 6 months
 - HBV-DNA quantification in HBsAg-neg/HBcAb+ participants
- ✓ Genotypic resistance testing in case of virological failure
- ✓ Drug concentration at every blood drawn
- ✓ W-BQ16 questionnaire at T0 and after one year (or at treatment discontinuation)
- ✓ Blood stored at T0 and after one year (or at treatment discontinuation)



To ensure **maximum adherence** to scheduled injections, visits for CAB+RPV administration were managed via an **app** that could be freely downloaded from any mobile device

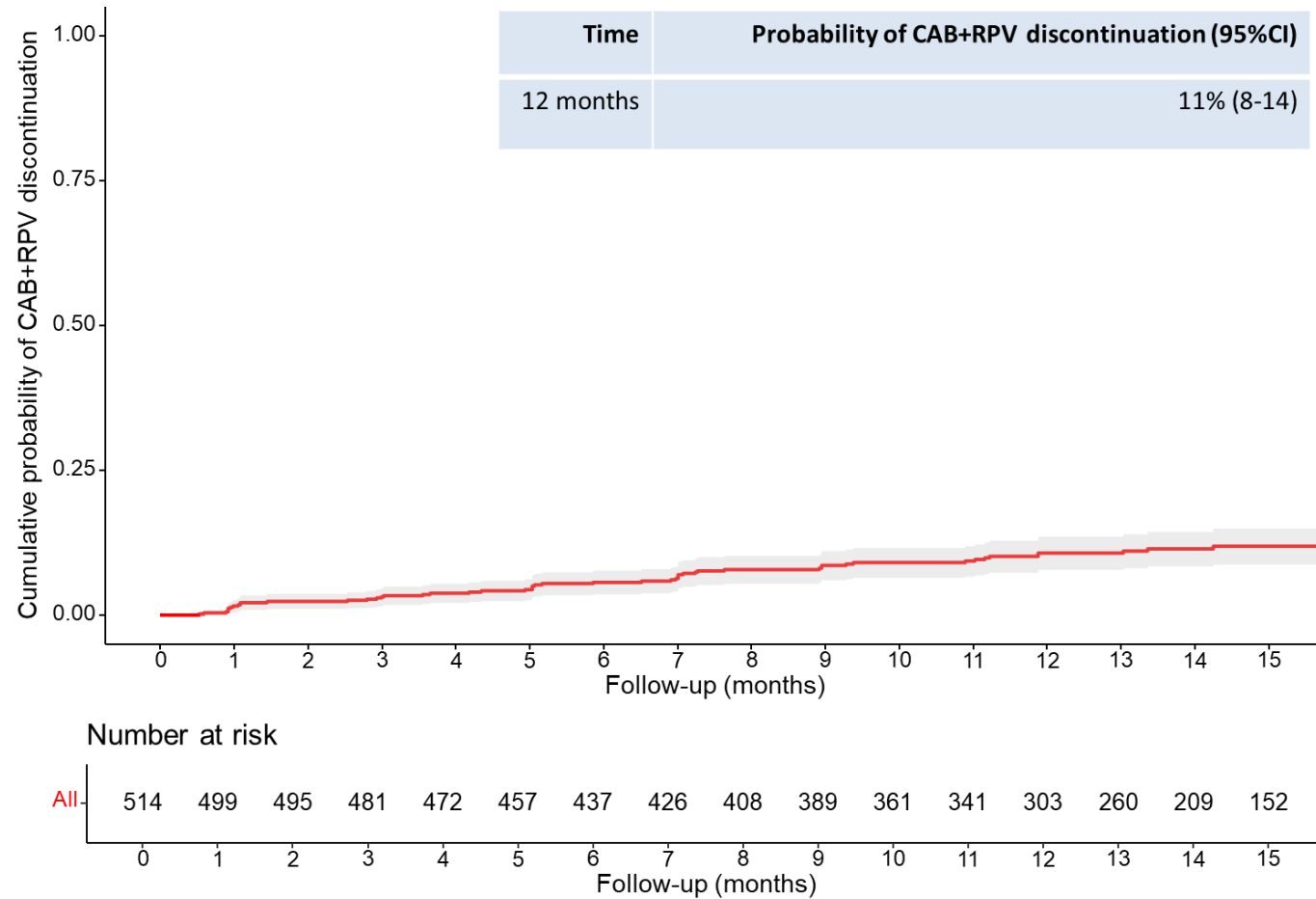
Real-life Data from the SCohoLART Study

Baseline characteristics

	N=514
Age, median (IQR)	49 (40-56)
Male, n (%)	467 (90.9)
HIV risk factor:	
Men who have sex with men, n (%)	364 (70.8)
Heterosexuals, n (%)	58 (11.3)
People who inject drugs, n (%)	11 (2.1)
Other, n (%)	81 (15.8)
Years from HIV diagnosis, median (IQR)	14.0 (8.8-20.5)
Years of ART, median (IQR)	11.4 (7.9-17.4)
CD4+ (cells/ μ L) , median (IQR)	794 (602-994)
Nadir CD4+ (cells/ μ L):	
>200 cells/ μ L, n (%)	389 (76.4)
$\leq$ 200 cells/ μ L, n (%)	120 (23.6)
CD8+ (cells/ μ L) , median (IQR)	850 (643-1114)
Years of the ART regimen in use at CAB+RPV switch, median (IQR)	3.4 (2.2-5.4)
Type of ART regimen in use at CAB+RPV switch:	
2 NRTI + 1 PI, n (%)	14 (2.8)
2 NRTI + 1 NNRTI, n (%)	124 (24.6)
2 NRTI + 1 INSTI, n (%)	179 (35.5)
2-drug regimen, n (%)	175 (34.7)
PI-monotherapy, n (%)	5 (1.0)
Other, n (%)	7 (1.4)

Real-life Data from the SCohoLART Study

Probability of treatment discontinuation



Real-life Data from the SCohoLART Study

Reasons of treatment discontinuation

	N=52
Death*, n (%)	1 (1.9)
Hypersensitivity reaction/allergy, n (%)	2 (3.8)
Injection site reaction, n (%)	15 (28.8)
Participant's wish/decision, n (%)	5 (9.6)
Gastrointestinal tract toxicity, n (%)	3 (5.8)
Central nervous system toxicity, n (%)	4 (7.7)
Other toxicity, n (%)**	10 (19.2)
Virological failure, n (%)	4 (7.7)
Other causes, n (%)***	8 (15.4)

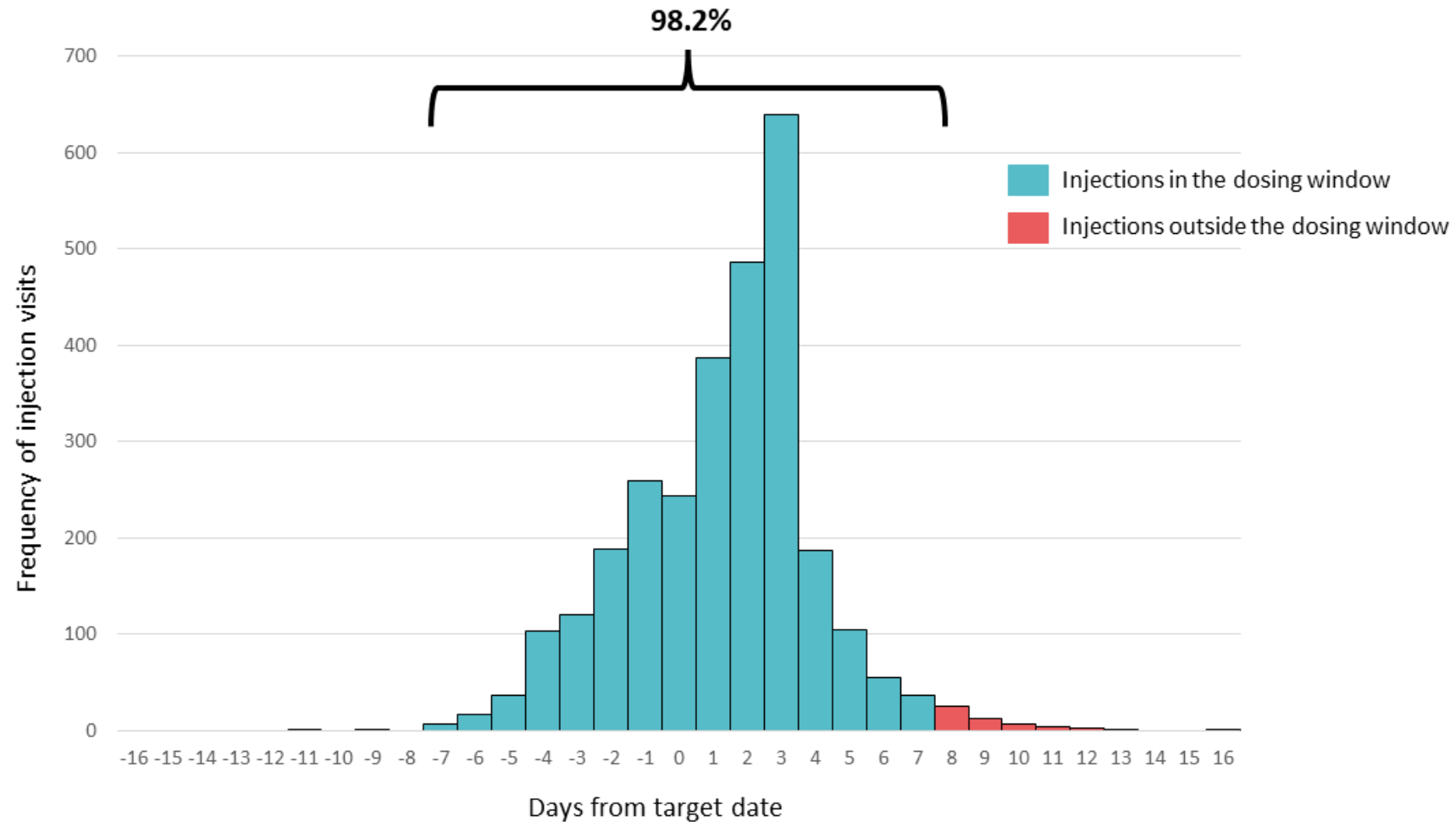
* One participant died from complications secondary to a metastatic biliopancreatic adenocarcinoma

** Other toxicity included: 3 pyrexia, 2 fatigue, 2 joint stiffness, 2 weight gain, 1 polyarthralgia

*** Other causes included: 2 personal commitments incompatible with injection visits, 1 transfer to another country, 1 HBV reactivation, 1 pregnancy, 1 viral blip, 1 enrollment in another study protocol, 1 chemotherapy-induced thrombocytopenia

Real-life Data from the SCohoLART Study

Probability of treatment discontinuation



Virological Failures

Participant	Year of HIV diagnosis	Subtype	Body mass index (kg/m ²)	Pre CAB+RPV regimen	HIV RNA at virological failure	RPV at failure	STI at failure	Genotypic resistance testing at failure	Post CAB+RPV regimen	HIV RNA post CAB+RPV switch
1. Male, 50 years	2005	B	22.2	DTG/ABC/3TC	371 copies/mL 436 copies/mL	121.8 ng/mL	Gonococcal urethritis	NNRTI (RNA) E138A NNRTI (DNA) E138EA INSTI (RNA) E138EK, Q148R INSTI (DNA) Q148QR	DRV/c/F/TAF	<50 copies/mL after 4 weeks
2. Male, 41 years	2007	B	25.7	DTG/RPV	34300 copies/mL	170.5 ng/mL	Gonococcal urethritis	NNRTI (RNA) K101PQ, E138A INSTI (RNA) E138K, Q148R	DRV/c/F/TAF	<50 copies/mL after 32 weeks
3. Male, 56 years	2012	B	24.6	B/F/TAF	636 copies/mL 66500 copies/mL	50.5 ng/mL	Primary syphilis	NNRTI (RNA) K101E, E138A NNRTI (DNA) K101KE, E138EA INSTI (RNA/DNA) E157Q	DRV/c/F/TAF	<50 copies/mL after 20 weeks
4. Male, 57 years	2018	B	25.3	B/F/TAF	276 copies/mL 55 copies/mL	70.8 ng/mL	/	WT for NNRTIs and INSTIs	B/F/TAF	<50 copies/mL after 1 week

CD4+/CD8+ Improvement during Long-acting Regimen

Variable	Overall crude mean change per year (95%CI)	Crude mean change per year among people treated with BIC/F/TAF (95%CI)	Crude mean change per year among people treated DTG/3TC (95%CI)	Crude mean change per year among people treated with DTG/RPV (95%CI)	p-value BIC/TAF/FTC vs. DTG/3TC vs. DTG/RPV
CD4+ (cells/ μ L) during CAB+RPV	28.84 (0.89, 56.79), p=0.04	22.10 (-19.00, 63.18), p=0.29	31.07 (-14.30, 76.43), p=0.18	43.41 (-30.00, 116.81), p=0.25	p=0.23
CD4+ (cells/ μ L) in the year before CAB+RPV	41.11 (21.30, 60.93), p<0.001	34.48 (7.70, 61.16), p=0.01	56.30 (22.41, 90.18), p=0.001	26.27 (-34.19, 86.73), p=0.39	p<0.0001
CD4+/CD8+ during CAB+RPV	0.08 (0.05, 0.11), p<0.0001	0.08 (0.034, 0.13), p<0.001	0.09 (0.04, 0.14), p=0.001	0.06 (-0.02, 0.15), p=0.15	p<0.0001
CD4+/CD8+ in the year before CAB+RPV	0.01 (-0.01, 0.03), p=0.32	0.01 (-0.02, 0.04), p=0.49	0.01 (-0.02, 0.05), p=0.45	0.00 (-0.06, 0.06), p=0.92	p=0.78

HDL Cholesterol Improvement during Long-acting Regimen

Variable	Crude mean change (slope) per year among PWH treated with TAF pre-CAB+RPV start (95% CI)	Crude mean change (slope) per year among PWH treated without TAF pre-CAB+RPV start (95% CI)	p-value (TAF vs. non-TAF)
Glucose (mg/dL)	-2.38 (-8.71,3.96), p=0.461	-3.69 (-9.04,1.67), p=0.177	p=0.305
HOMA index	0.59 (-0.49,1.66), p=0.278	-0.39 (-1.19,0.41), p=0.330	p=0.334
Triglycerides (mg/dL)	-4.93 (-16.55,6.68), p=0.404	-3.1 (-12.44,6.24), p=0.514	P=0.569
Cholesterol (mg/dL)	1.82 (-5.1,8.75), p=0.605	2.27 (-3.38,7.92), p=0.430	p=0.640
HDL cholesterol (mg/dL)	2.79 (0.23,5.35), p=0.033	1.64 (-0.56,3.85), p=0.144	p=0.034
LDL cholesterol (mg/dL)	1.37 (-4.92,7.66), p=0.668	6.81 (1.56,12.07), p=0.011	p=0.035
TOT/HDL cholesterol	-0.31 (-0.78,-0.68), p=0.18	-0.26 (-0.68,0.16), p=0.21	p=0.186
Weight (Kg)	1.24 (-0.25,2.73), p=0.102	0.8 (-0.45,2.04), p=0.206	p=0.112
Body Mass Index (kg/m ²)	0.39 (-0.1,0.88), p=0.119	0.31 (-0.1,0.73), p=0.139	p=0.094

Conclusions

- ✓ Efficacy and safety of long-acting regimen are confirmed by data from clinical practice
- ✓ Long-acting therapy can be considered a valid strategy for a large number of PWH in real-life
- ✓ Longer-term real world data are needed to evaluate the CAB/RPV regime over time
- ✓ The future of research on the treatment of HIV infection is directed towards the long-acting strategy



Thanks for your attention!

