Gli iniettivi a tre anni dall'inizio dell'uso nella pratica clinica

Antonio Di Biagio

Genova, 22 novembre 2024

Conflitti di Interesse

- **Advisory Board: ViiV**
- **Fondi per la Ricerca al mio Istituto: Gilead Sciences, ViiV**
- **Viaggi a congressi: Gilead Sciences**

Long acting antiretrovirali

Oggi

ART

Cabotegravir/rilpivirina (im)

Lenacapavir (sc/os)

PreP

Cabotegravir* (Classe Cnn) (im)

Domani

ART

Islatravir (os)

GS-5423 (os)

PreP

Lenacapavir (im)

Novembre 2024

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Islatravir

GS-5423

PreP

Lenacapavir

Novembre 2024

Cosa sappiamo oggi!

Cabotegravir/rilpivirine LA (CAB+RPV)

6 iniezioni per anno

European Guidelines (Oct 2021)	DHHS Guidelines (Feb 2022)	International AIDS Society (Oct 2020)
CAB + RPV LA Q8W	CAB + RPV LA Q8W and Q4W	CAB + RPV LA Q8W and Q4W

Dual therapies

In persons with suppression of HIV-VL < 50 copies/mL for the past 6 months these dual therapy strategies should only be given if there is
a) no historical resistance (recent data suggest possible use of DTG or DRV/b + XTC even when M184V is detected) and
b) HBV immunity with anti-HBs antibodies (if non-immune provide HBV Vaccination, if isolated HBc antibodies see the section on Treatment and Monitoring of Persons with HBV/HIV Co-infection for details)

Oral dual therapies supported by large randomized clinical trials or meta-analyses:

- DTG + RPV
- XTC + DTG
- XTC + DRV/b

In clinical trials, these strategies have not been associated with more virological rebounds than triple therapy. There were a few cases of resistance development on DTG + RPV

Long-acting intramuscular dual therapy CAB + RPV

- The use of oral lead-in (1 month) is optional
- Injections are administered every 2 months. In case of bridging, see the section on Drug-Drug Interactions after Oral and Intramuscular Administration of CAB and RPV

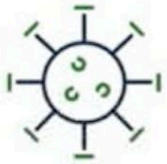
Initiation phase (start on day of last oral pills)	Continuation phase
Day 0: CAB 600 mg/ RPV 900 mg Month 1: CAB 600 mg/ RPV 900 mg	From month 2 onwards: CAB 600 mg/ RPV 900 mg every 2 months

The following baseline factors, when combined, are associated with risk of virologic failure and resistance:

- Archived RPV-associated mutations
- HIV subtype A6/A1 (Recent data suggest possible use in people with subtype A1)
- BMI ≥ 30 kg/m^2

Multivariable analysis: baseline risk factors for CVF

Archived RPV mutations



HIV-subtype A6

BMI ≥30 kg/m^2

Percentage of participants with CVF according to number of baseline factors

No baseline factors
n=4/970

Any one baseline factor†
n=8/404

≥2 baseline factors
n=11/57

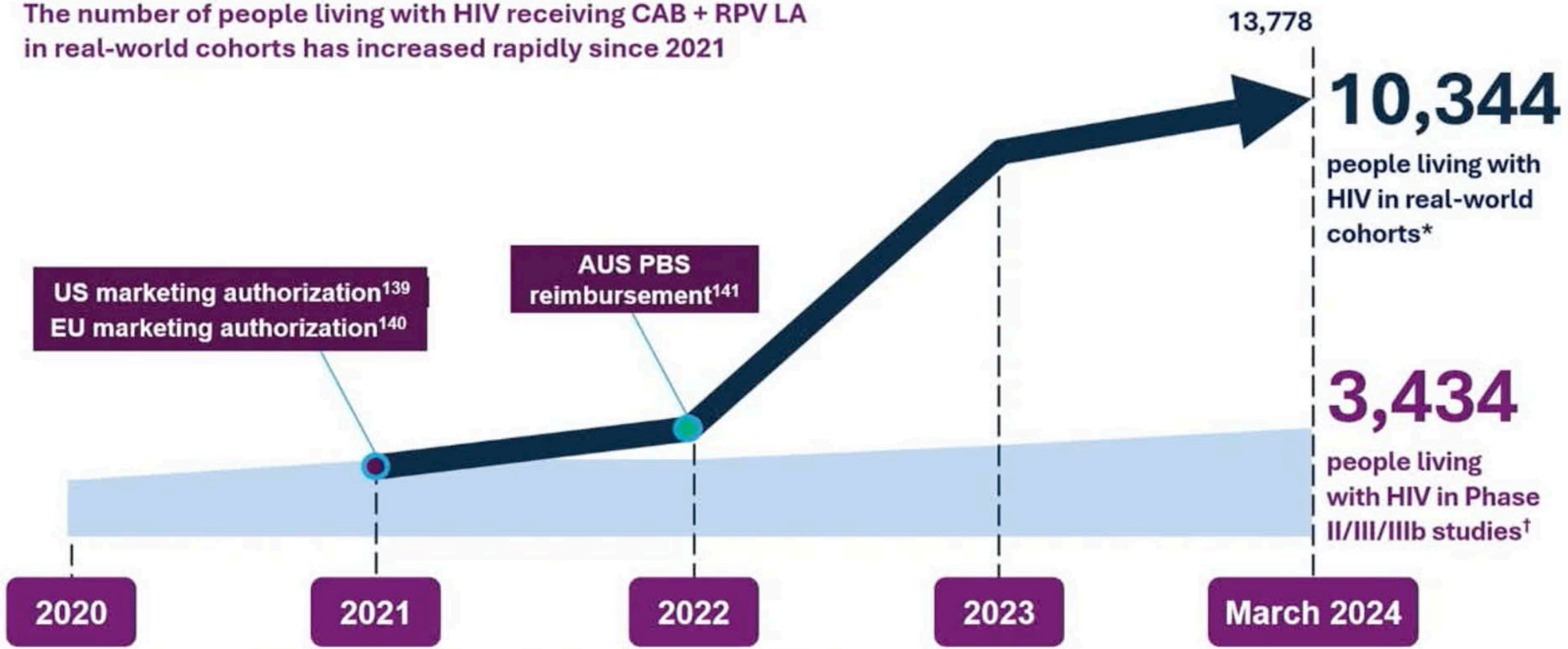
† Driven primarily by archived RPV RAMs and HIV-1 subtype A6

CVF occurred in 0.5% with high BMI ≥30 kg/m^2

*CVFs identified by Week 48 for ATLAS, Week 124 for FLAIR, and Week 152 for ATLAS-2M
NOTE: Prevalence of ≥2 baseline factors in Phase III study participants was low (4.0%) ;3.8% (n=6/157) of those with HIV-1 subtype A6/A1 only, and 3.2% (n=1/31) of those archived RPV RAMs only
BMI, body mass index; **CVF,** confirmed virologic failure; **RAM,** resistance-associated mutation

Orkin C, et al. CID 2023

>13,700 people living with HIV have received CAB + RPV LA across clinical trials and real-world cohorts



Potential overlap between real-world cohorts cannot be ruled out. Values represent people living with HIV who received injectable therapy

*Data reported based on real-world studies (both on- and off-label), as identified through literature searches; data reported per year using December 31st cut-off, except for 2024, which uses March 6th

†Clinical trial data reported at date of first published results, with December 31st cut-off point per year (except for 2024 which used March 6th, as per real-world studies)

EU, European Union; **US**, United States

See slide notes for references

Real Life Cabotegravir + Rilpivirina LA

High effectiveness and low rates of VF in real-world people with HIV are consistent with Phase III trials

	CROI 2024	AIDS 2024				BHIVA 2024
	OPERA[1,2]	SCohoLART[7]	COMBINE-2 C2C[4]	CARLOS[5]	ILANA[6]	SHARE-LAI[3]
	N=1,293 Median follow-up: 11 months (IQR: 8–14)* On-treatment analysis	N=504 Median follow-up 9.4 months (6.4–11.4)	N=374 Median follow-up: 3 months (IQR: 2.8–7.1)* On-treatment analysis	N=351 Month 12 follow-up ITT population	N=114 Month 12 follow-up On-treatment analysis	N=433 7.5 months (interquartile range 3.7–11.3)*
Virologically suppressed‡	95%	NR	98%	86%	NR	NR
CVF§	1.9% (n=25)	0.8% (n=4)	0.8% (n=3)	1.4% (n=5‖)	0.9% (n=1)	0.7% (n=3)

- *N indicates the number of individuals with follow-up VLs after first injection. In OPERA, median follow-up period is based on individuals who switched to Vocabria + Rekambys (n=1,362). In COMBINE-2 C2C, median follow-up period is based on individuals who remained on Vocabria + Rekambys at the time of analysis (n=453); †Consistent with label group only; ‡HIV VL <50 c/mL; §Two consecutive HIV-1 RNA ≥200 c/mL or a single HIV-1 RNA ≥200 c/mL followed by treatment discontinuation; ‖Previously reported: One additional participant had VF with off-label use of Vocabria + Rekambys (discovered *post hoc*; prior VF with an agent of NNRTI class) with NNRTI RAMs (K101E, Y181C, G190A) detected at failure
IQR, interquartile range; **ITT,** intention-to-treat; **NNRTI,** non-nucleoside reverse transcriptase inhibitor; **RAM,** resistance-associated mutation

1. Hsu RK, et al. CROI 2024. Poster 623; **2.** ViiV Healthcare. Data on File. REF-239143; **3.** Ring, K. et al. HIV Medicine, 2024. https://doi.org/10.1111/hiv.13679 ; **4.** Pozniak A, et al. AIDS 2024. Poster TUPEC278; **5.** Jonsson-Oldenbüttel C, et al. AIDS 2024. Poster TUPEB095; **6.** Orkin, C et. al, ILANA 12M poster, AIDS 2024 LB12. **7.** Muccini C, et al. AIDS 2024. Poster THPEB104;

Table 1. Clinical and demographic characteristics of the study population.

Baseline characteristics	*N* (%)	Missing data
Total PWH included	302	–
Mean age ± SD	48.2 ± 11.1	0
Sex		0
Female	69 (22.8)	
Male	231 (76.5)	
M to F	2 (0.7)	
Caucasian ethnicity	286 (94.7)	0
Risk factor for HIV infection		0
Heterosexual exposure	101 (33.4)	
IDU	30 (9.9)	
MSM	155 (51.3)	
Other	16 (5.3)	
HBsAg negative	302 (100)	
HCV positive serology	39 (12.9)	4
HIV-RNA > 30 copies/ml	8 (2.6%)	
Median viral load copies/ml (IQR)	57.5 (54.75–103.75)	0
Median CD4 cell/mm3 (IQR)	806.5 (580.0–1065.0)	0
$CD4^+$ >200 cell/mm^3	302 (100)	
Median $CD4^+$ nadir (IQR)	320 (144.5–460.0)	26
Median $CD4^+/CD8^+$ ratio (IQR)	1.1 (0.8–1.4)	16
Mean BMI kg/m^2 ± SD	25.1 ± 4.2	49
BMI >30 kg/m^2	24 (9.49)	
Mean total-cholesterol mg/dl ± SD	185.2 ± 35.8	3
Mean HDL-cholesterol mg/dl ± SD	53.2 ± 14.9	3
Median triglycerides mg/dl (IQR)	95.0 (70.0–127.0)	3
Mean glycemia mg/dl ± SD	88.7 ± 19.7	1
Mean eGFR ml/min ± SD	86.6 ± 23.1	0
Median ALT U/l (IQR)	23.0 (17.0–31.0)	3
Median AST U/l (IQR)	23.0 (19.0–28.0)	19
Comorbidities		
Type 2 diabetes	13 (4.3)	
Hypertension	53 (17.5)	
Depression	17 (5.6)	
Comedications		0
0	124 (41.1)	
1–2	123 (40.7)	
≥3	55 (18.2)	
Treatment-experienced	302 (100)	0
ART exposure years (IQR)	9.9 (5.8–15.9)	
Previous ART regimen		0
PIs	10 (3.3)	
NNRTIs	147 (48.7)	
INSTIs	234 (77.5)	
Previous exposure ART regimen		0
PIs	274 (90)	
months (IQR)	0 (0–34)	
NNRTIs	260 (86)	
months (IQR)	11.5 (0–84)	
INSTIs	253 (83.7)	
months (IQR)	43 (4–72)	
Oral lead-in phase	88 (29.1)	38
Treatment interruption	8 (2.6)	0
Reason for treatment interruption		0
Adverse reactions	7	
Injection site reaction	4	
Pancreatitis	1	
Neurologic symptoms	1	
Fever	1	
Pregnancy	1	

REAL-LIFE CISAI VS RCT

- Older age (mean 48.3 VS 42.0 years in ATLAS-2M and 37 years in SOLAR)
- Mean ART exposure 10.1 years VS 4.3 in ATLAS and 4.8 in ATLAS-2M
- 2 virological failures 0.4% VS 1.25% of the post-hoc analysis of FLAIR, ATLAS, ATLAS-2M
- Treatment interruptions for AE 3.2% VS 6% in SOLAR

Results: clinical and demographic characteristics of PWH in CAB/RPV in Icona cohort (n=506)

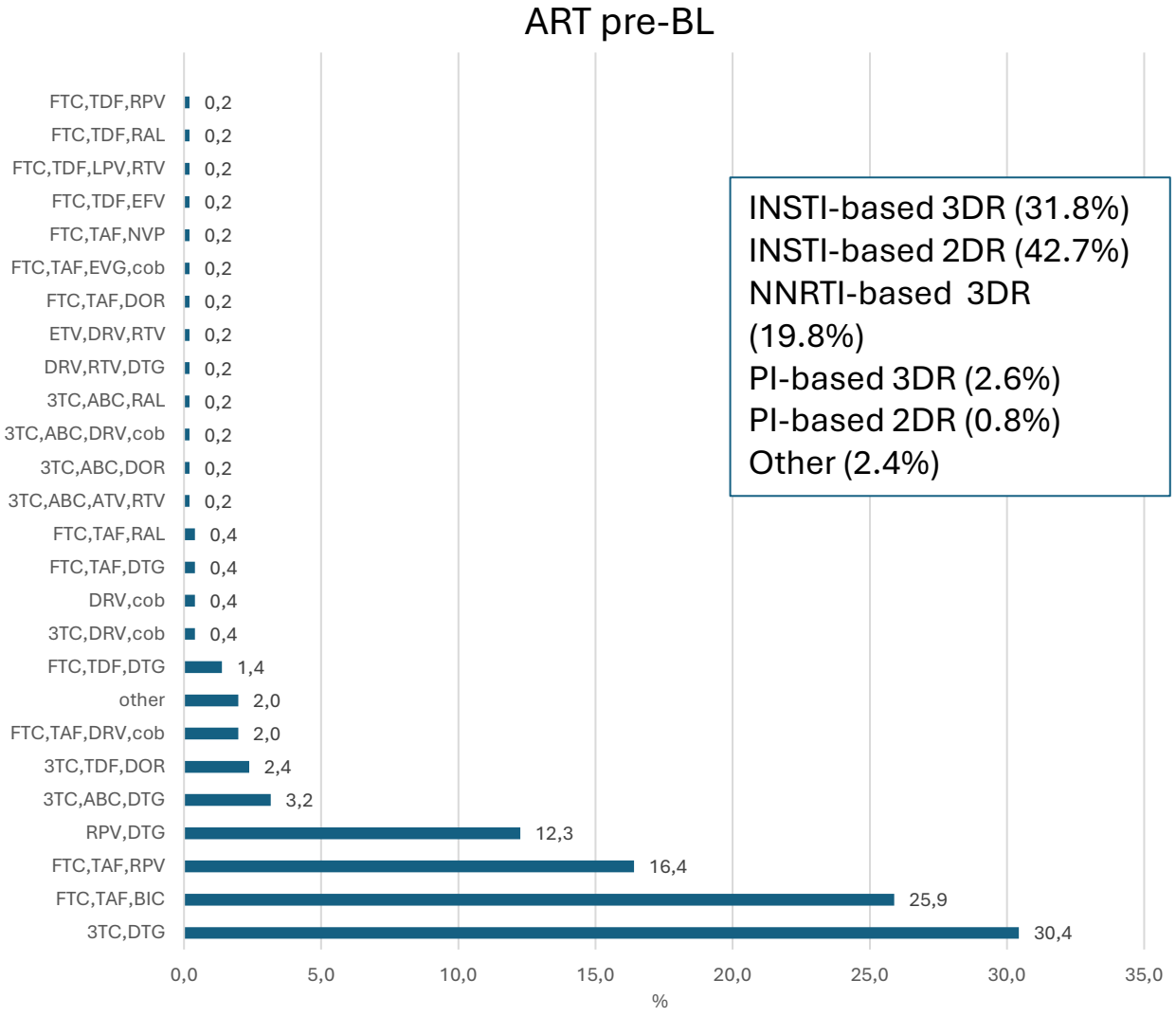
Gagliardini R.

Conceived by Professor Mauro Moroni
Fondazione Icona

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%)
Other/unknown	24 (4.7%)
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%)
Others*	71 (14.0%)
Missing	148 (29.2%)

*A6 = 0

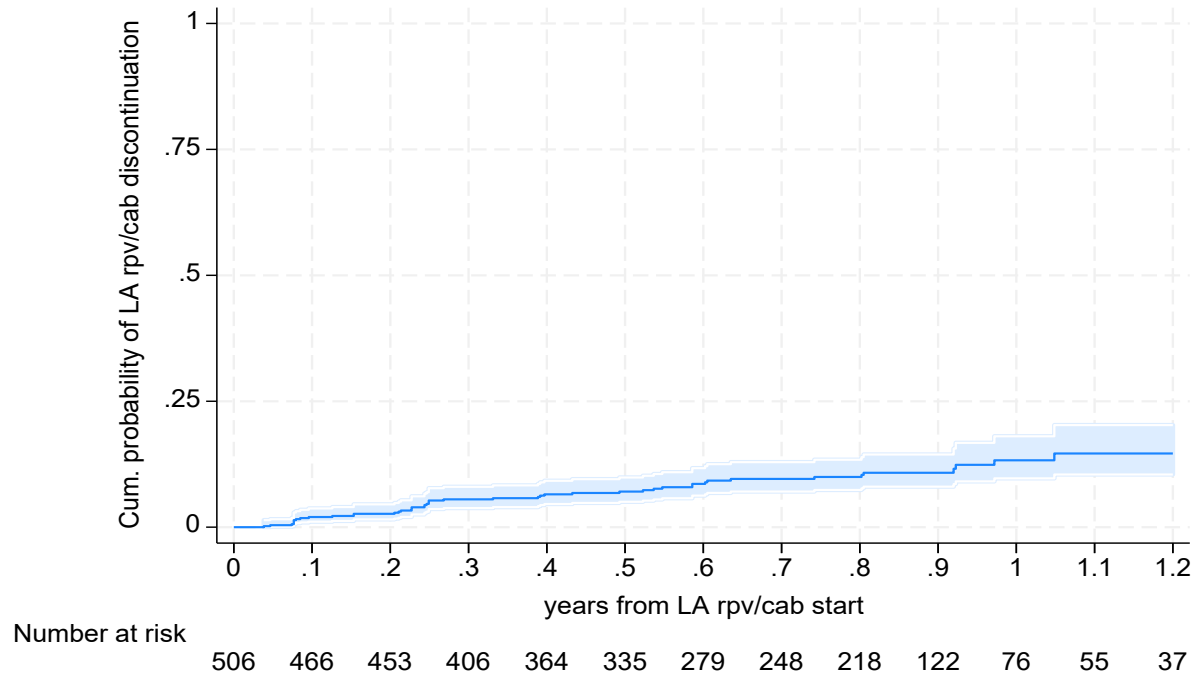
Oral lead-in: 78 (15%)



Treatment discontinuation

Gagliardini R.

- 47 treatment discontinuations
  - Incidence rate of TD:13.1 x 100 PYFU (95% CI, 9.8-17.4%)
  - 1-y cumulative probability of TD: **13.3%** (95% CI 9.7-18.1%)



ART started after discontinuation of CAB/RPV LA: DTG+3TC (40.4%), BIC/TAF/FTC (27.7%), DTG/RPV (10.6%), others (21.3%).

Causes of TD with CAB/RPV LA

	N (% over PWH included)
TOXICITY/EAs	33 (6,5%)
Arthro-myalgia	1 (0,2%)
Clinical contraindications	2 (0,4%)
Constitutional symptoms	1 (0,2%)
GI intolerance	3 (0,6%)
Allergic reactions	2 (0,4%)
Reactions injection site	17 (3,4%)
NPAEs	2 (0,4%)
Hepatic toxicity	2 (0,4%)
Pancreatic toxicity	1 (0,2%)
Metabolism issues	1 (0,2%)
Skin reactions	1 (0,2%)
PATIENT'S CHOICE	11 (2,2%)
OTHER	2 (0,4%)
Pregnancy	1 (0,2%)
DDI	1 (0,2%)
VIROLOGICAL FAILURE	1 (0,2%)

SCOLTA

Causes of discontinuation of CAB+RPV LA in an Italian cohort

- **Study Design:** SCOLTA (Surveillance Cohort Long-Term Toxicity Antiretrovirals) is an observational, multicenter, prospective cohort
  - The study aimed to describe the causes of CAB+RPV LA discontinuation in clinical practice
- Among those who initiated CAB+RPV LA between July 2022 and June 2024, 231 people with HIV-1 had at least one follow-up visit available and were enrolled in the study
  - 23% female, mean age 48.5 years, 66% polypharmacy, median time on ART 10 years
  - All were treatment experienced, and prior regimen included INI in 73%, NNRTI in 52%, both INI + NNRTI in 26% and PI in 1%
- 21 (9%) people discontinued CAB+RPV LA after a median of 2 months (range: 0-6)

Discontinuations due to AEs	Discontinuations due to other reasons
→15 individuals discontinued due to AEs • 6/15 were ISRs (grade 1, n=1; grade 2, n=4; grade 3, n=1) → The probability of AEs leading to discontinuation was not influenced by previous ART treatments, sex, BMI, CDC stage, age, risk factor for HIV, concomitant treatments or by oral lead-in (*P*>0.1 for all)	• Virologic failure (n=2) • Lost to follow-up (n=1) • Pregnancy (n=1) • Resistance to RPV (n=1)* • Inconvenience of injection schedule (n=1)

Short-term follow-up data show low rates of treatment discontinuation, mainly due to AEs, consistent with other RWE cohorts

Taramasso et al. AIDS 2024; Munich, Germany. Poster TUPEB102.

P074

Cabotegravir-rilpivirine long-acting injectable regimen: an analysis of the causes of interruption and impact of genotypic drug resistance in a multicentric cohort

G. Canavesi1, M. Mena1, E. Zaninetta2, L. Gazzola2, T. Bini2, G. Bo3, D. Arrue Diaz3, G. Orofino3, A. De Vito4, G. Madeddu4, C. Grillo5, C. Bartalucci6, F. Centorrino6, N. Squillace7, P. Bonfanti7, S. Rapino8, G. Tiecco8, E. Focà8, M. Menozzi9, F. Caldara Bonaura9, G. Guaraldi9, N. B. Bana, G. Cavazza, R. Rossotti, S. Lo Caputo5, A. Di Biagio6, S. Rusconi1

Table 2

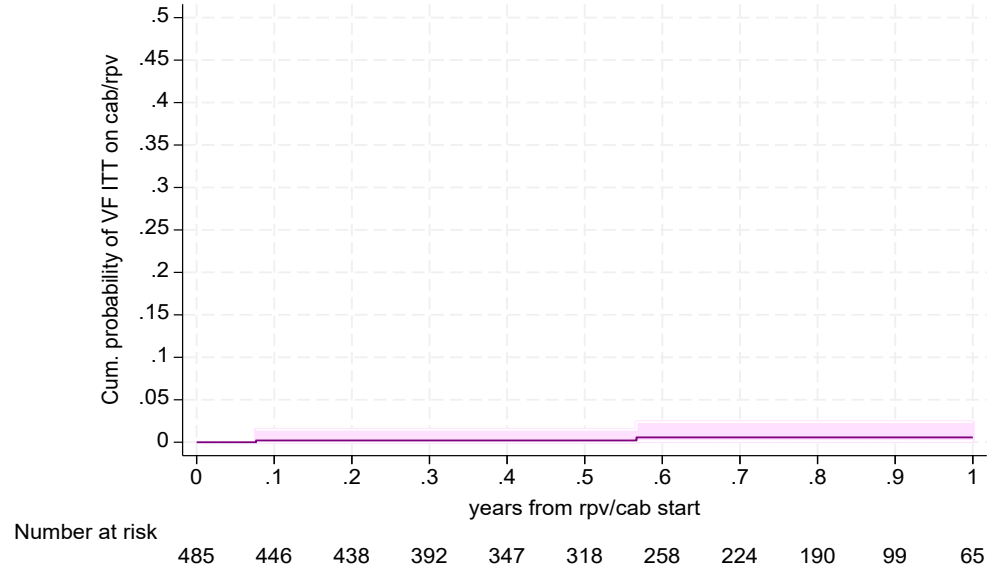
	NRTI mutations (basal GRT)	NRTI mutations (after VF GRT)	NNRTI mutations (basal GRT)	NNRTI mutations (after VF GRT)	PI mutations (basal GRT)	PI mutations (after VF GRT)	INSTI mutations (basal GRT)	INSTI mutations (after VF GRT)
PATIENT 1	0	0	0	0	0	0	0	0
PATIENT 2	NA	**M41L;D67N;L210V;T215Y**	0	0	0	0	0	0
PATIENT 3	0	0	0	0	10I	0	0	0
PATIENT 4	0	0	0	0	0	0	0	0
PATIENT 5	0	**151M;70R;65R**	138A	**181I;190A**	10F	**73S;90M**	0	**140S;148H**
PATIENT 6	0	0	0	**138K;179I**	0	**10V**	0	**148R**
PATIENT 7	0	**D67N;K70R;M184V**	0	**K103N;V108I;P225H**	0	**K70R**	0	**G140S;Q148K**
PATIENT 8	T69A;S68G	S68G	0	0	0	0	0	**E138EK;G140S;G163R**
PATIENT 9	0	**V21V/I;V35V/I;V60/VI;K122E;D123E**	0	**V245E/K;A272P;K281R**	0	**A71T;V77I**	0	0
PATIENT 10	NA	**M41L;D67N;L210V;T215Y**	NA	0	NA	0	NA	0
PATIENT 11	0	GRT in progress	0	GRT in progress	M36I; L63P;L89M	GRT in progress	0	GRT in progress
PATIENT 12	0	0	0	**S68GV,E138A,Y188H**	0	0	0	**E138EK, Q148R**
PATIENT 13	0	0	0	**E138K**	0	0	0	**N155NH, H51Y**
PATIENT 14	39A;41L;67N;210W;211K;215Y;218E;219Q;M41L;D67N;K70R;Q151L;T215Y;K219Q;M41L;L74V:M184V;K219Q	M41L;D67N;K70R;L74V;M184V;T215Y; K219Q	101P;103N;K101P;K103S;Y181C	**V106VI; N348I**	13V;30N;35D;36V 63P;71V;77I;88DR;D30N;L33F;I50L;A71V;V82A;N88D;D30N	N88D	0	**G140S;Q148H; D232DN**

Note: newly emerged mutations are in bold

	L	K	E	V	Y	Y	H	F	M
Rilpivirine[14]	**100**	**101**	**138**	**179**	**181**	**188**	**221**	**227**	**230**
	I	**E**	**A**	**L**	**C**	**L**	**Y**	**C**	**I**
		P	**G**		**I**				**L**
			K		**V**				
			Q						
			R						

Virological failure

- 2 VFs
  - Incidence rate of VF 0.59 x 100 PYFU (95%CI 0.15%-2.37%)
  - 1-year cumulative probability of VF 0.57% (95% CI 0.14-2.38%)



	HIV subtype	RAM NNRTI or INSTI	Nadir Cd4	Log10 HIV-RNA at zenith	Previous AIDS event	BMI, kg/m²	ART pre CAB/RPV	N° injections	VL at VF, cp/ml	RAM at VF	ART post CAB/RPV	VL<50 post-VF
VF1	B/F1	None	899	5,24	no	29.7	FTC/TAF/BIC	2	55, 69	NA	CAB/RPV	yes
VF2	B	None for NNRTI, not tested for INSTI	24	6,14	yes	24.9	FTC/TAF/BIC	5	636, 66500	K101E, E138A / E157Q	FTC,TAF,BIC, then DRV/c/TAF/FTC	no

Cosa stiamo imparando?

Con HIV RNA rilevato >50 Copie/mL?

Both IAS-USA guidelines (March 1, 2024) and DHHS guidelines (September 1, 2024) updated to include the use of LA-ART in those with adherence challenges/viremia

March 1, 2024

Updated Treatment Recommendation on Use of Cabotegravir and Rilpivirine for People With HIV From the IAS-USA Guidelines Panel

Paul E. Sax, MD[1]; Melanie A. Thompson, MD[2]; Michael S. Saag, MD[3]; et al

When supported by intensive follow-up and case management services, injectable cabotegravir and rilpivirine (CAB-RPV) may be considered for people with viremia who meet the criteria below when no other treatment options are effective due to a patient's persistent inability to take oral ART (rating AIIa under the conditions described).

- Unable to take oral ART consistently despite extensive efforts and clinical support
- High risk of HIV disease progression (CD4 cell count <200/μL or history of AIDS-defining complications)
- Virus susceptible to both CAB and RPV

If applicable, patients should also be referred for treatment of substance use disorder and/or mental illness.

JAMA®

Sax. JAMA. 2024; DHHS guidelines September 12, 2024

Updated: September 12, 2024
Reviewed: September 12, 2024

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV

Virologic Failure

Updates made to the Virologic Failure section include the following:

- For people who experience virologic failure while on their first ARV regimen of a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs), a salvage regimen of DTG plus boosted darunavir can be used **(AI)**. This recommendation is based on data from the D²EFT trial, a large randomized controlled trial comparing this regimen to a regimen of DTG plus two NRTIs.
- Some people with HIV cannot reach or maintain viral suppression on oral ART despite intensive adherence support. A complete regimen of long-acting injectable cabotegravir and rilpivirine (LA CAB/RPV) has been used in this population with some success, although long-term efficacy data are limited. Based on very limited data, the Panel recommends the use of LA CAB/RPV on a case-by-case basis in select individuals with persistent virologic failure despite intensive adherence support on oral ART, who have no evidence of resistance to CAB or RPV, and with shared decision-making between providers and people with HIV **(CIII)**. The Panel notes that people with HIV and their providers must be aware of the significant risk of developing resistance to NNRTIs, and particularly integrase strand transfer inhibitors (INSTIs) if virologic failure occurs on LA CAB/RPV. Such resistance may limit future treatment options and may also lead to HIV transmission.

48 week follow-up rates of 59 PWH starting LA CAB/RPV with viremia (95% VL<200)

48-week viral suppression rates in people with HIV starting long-acting CAB/RPV with initial viremia

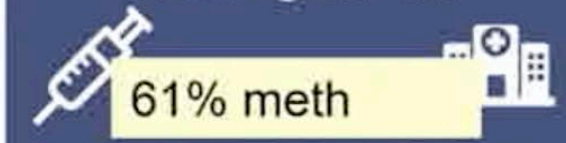
Hickey et al., 2024 | *Clinical Infectious Diseases*

IDSA Infectious Diseases Society of America

Retrospective Cohort

We sought to evaluate 48-week virologic outcomes following initiation of LA-CAB/RPV among PWH with baseline HIV RNA ≥50 copies/mL due to adherence challenges with oral ART

People with HIV at the Ward 86 HIV clinic in San Francisco who started LA-CAB/RPV with viremia due to oral adherence challenges (n=59)



Baseline clinical characteristics

- 53% experiencing homelessness/ unstable housing
- 49% with CD4 < 200
- Median baseline viral load 42,900 copies/mL (Q1 5,272, Q3 139,038)

48-week HIV RNA <50 copies/mL with persistence on LA-CAB/RPV: **80%**

48-week HIV RNA <50 copies/mL irrespective of ART regimen (LA-CAB/RPV or alternative ART): **92%**

- Early treatment-emergent resistance (at on-time 2nd injection; n=2) 3%
- Treatment-emergent resistance after late/missed injections (n=3) 5%
- Loss to follow-up without genotype data (n=1) 2%

} **10%**

Use of LA-CAB/RPV for people with HIV with viremia due to oral ART adherence challenges resulted in high levels of viral suppression out to 48 weeks. Up to 10% experienced treatment emergent resistance or loss to follow-up, though 92% were virally suppressed at 48 weeks.

Clinical Infectious Diseases

Hickey et al. CID October 2024

Popolazioni «speciali»

P065 Virtual	**Efficacy and safety of long-acting intramuscular cabotegravir and rilpivirine in women: a substudy of the RELATIVITY cohort** *Maria Jose Galindo Puerto, Noemí Cabello Clotet, Teresa Aldamiz-Echevarría Lois, Jara Llenas García,*
P064	**Long-acting injectable cabotegravir and rilpivirine outcomes in HIV-positive migrants in Spain: do they have worse outcomes?** *Jara Llenas-García, Roberto Pedrero Tome, Luis Ramos Ruperto, María José Galindo Puerto,*
P069	**Long-acting cabotegravir/rilpivirine as a safe antiretroviral therapy in solid organ transplanted HIV patients** *Ana Moreno, Santos Del Campo, Maria Jesus Perez-Elias, Jose Luis Casado, Miguel Garcia, Manuel Velez, Maria Jesus Vivancos, Santiago Moreno (Madrid, Spain)*
P058	**Long acting cabotegravir plus lenacapavir as a fully injectable maintenance antiretroviral regimen in people with HIV with adherence issues** *Romain Palich, Romain Manchon, Jérémy Zeggagh, Elisabete Gomes-Pires, Sophie Seang, Marc-Antoine Valantin, Marc Wirden, Marianne Burgard, Gilles Peytavin, Claudine Duvivier (Paris, France)*

Cosa dobbiamo migliorare ?

Gestione dei fallimenti virologici

Eventuali associazioni di LA non codificate

Exit Switch a viremia non rilevata (orale o LA)

Monitoraggio clinico HIV RNA ogni 2 mesi ?

Durabilità

Gestione degli eventi avversi