CRISTINA MUSSINI

# L’uso dei long acting in Italia

# HIV Guidelines

**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<br>Month 1: CAB 600 mg/ RPV 900 mg | From month 2 onwards:<br>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
- BMI ≥ 30 kg/m²

See the section on Drug-Drug Interactions after Oral and Intramuscular Administration of CAB and RPV for details, page 27

**EACS**

## 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

» Author Affiliations | Article Information

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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).

### Cabotegravir plus Rilpivirine

**DHHS**

Long-acting injectable CAB plus RPV is indicated in individuals with sustained (e.g., 3 to 6 months) virologic suppression (HIV-1 RNA <50 copies/mL) on a stable ARV regimen, with no history of treatment failure, and with no known or suspected resistance to either CAB or RPV.[36] CAB is an INSTI and a structural analogue of DTG. RPV is an NNRTI first approved in an oral tablet formulation in 2011. A tablet formulation of CAB was concurrently approved by the FDA to be used with RPV tablets as a 4-week oral lead-in therapy before initiation of the long-acting regimen and as oral bridging in the event of planned missed injections. The oral lead-in is now considered optional if going directly to long-acting formulations is preferred. The long-acting injectable combination can be given once monthly or as an every 2-month therapy. Clinical trial data supporting these regimens are discussed below.

# RWE evaluating cabotegravir and rilpivirine long-acting injectables in virologically suppressed individuals only

| Real-world cohort | Countries included | Participants (*n*) | Median follow-up [months (IQR)] | Virological failure rate [% (*n*)] |
|---|---|---|---|---|
| OPERA [31▪] | USA | 1543 | 7.4 (3.9–10.9) | 1.0 (16) |
| Dat'AIDS [32] | France | 1134 | 7 (3.5–9.6) | 1.1 (14) |
| COMBINE-2 [34] | France, Switzerland, Germany, UK, Netherlands | 472 | 3.0 (2.8–7.1) | 0.8 (3) |
| CARISEL [29] | Spain, France, Germany, Netherlands, Belgium | 430 | 12 (12–12) | 0.2 (1) |
| Maguire *et al.* [35] | USA | 374 | 9.1 (5.3–12.9) | 1.1 (4) |
| TRIO [36] | USA | 278 | 10 (5–13) | 0.9 (2) |
| BEYOND [37] | USA | 233 | 6 (6–6) | 1.3 (2) |
| CARLOS [38] | Germany | 200 | 6 (6–6) | 0.5 (1) |
| Ferre *et al.* [39] | France | 127 | 12.8 (8.5–26.7) | 4.7 (6) |
| CUSTOMIZE [28] | USA | 115 | NR | 0.0 (0) |
| Shankaran *et al.* [40] | USA | 75 | NR | 4.0 (3) |
| Rubenstein *et al.* [41] | France | 72 | 15 (NR) | 1.4 (1) |
| JABS [42▪▪] | Australia | 60 | 12 (12–12) | 0.0 (0) |
| Iannone *et al.* [43] | Italy | 38 | 7 (7–7) | 0.0 (0) |
| Keiju *et al.* [44] | Japan | 38 | NR | 0.0 (0) |
| Roberts *et al.* [45] | UK | 33 | NR | 0.0 (0) |
| Montalvo *et al.* [46] | USA | 30 | NR | 0.0 (0) |
| Masich *et al.* [47] | USA | 24 | NR | 4.1 (1) |

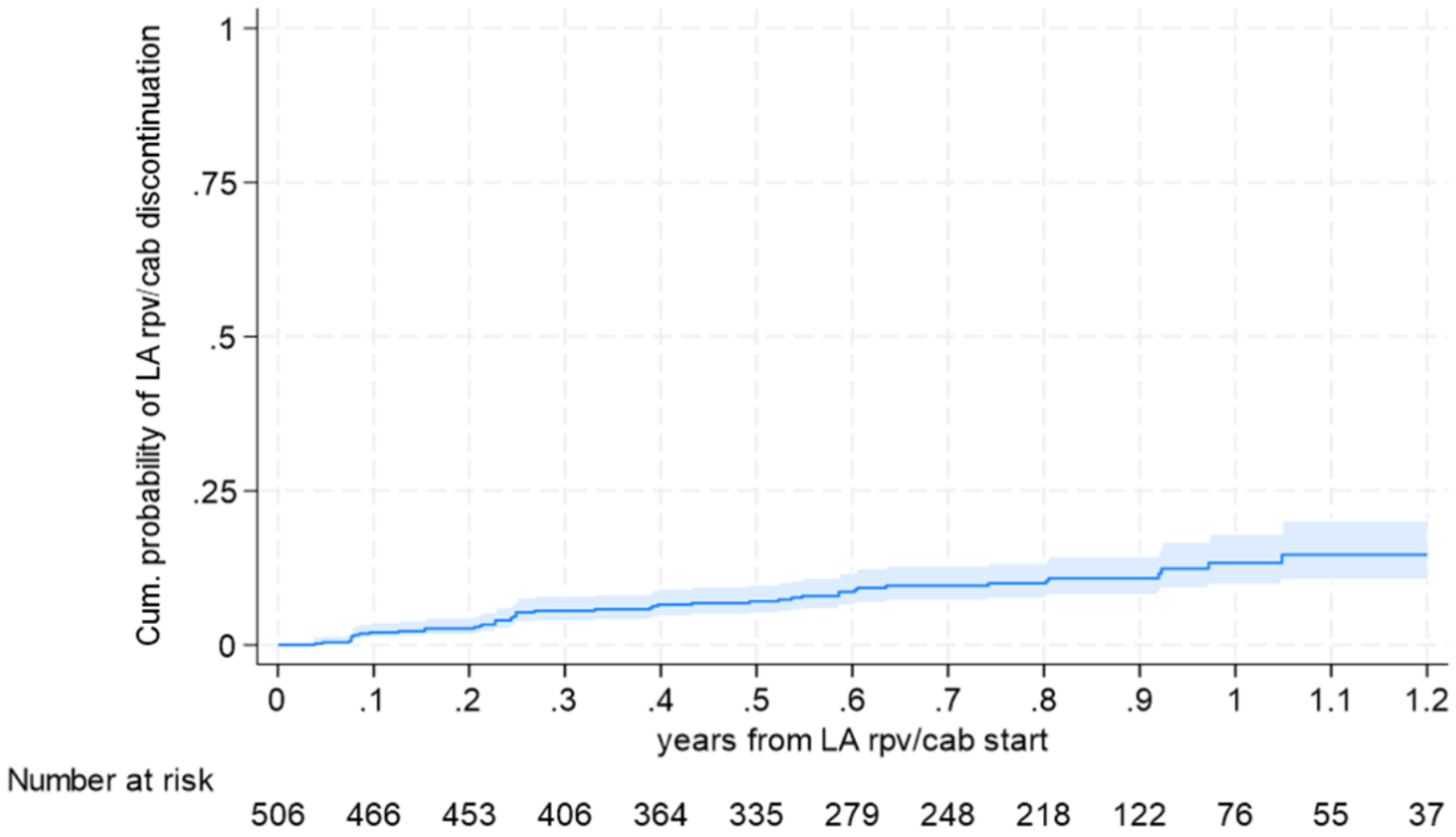
K. Ring, Curr Opin HIV AIDS, 2024

# ICONA Cohort 509 PLWHIV

## Participants

| | |
|---|---|
| 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%) |

## Treatment Discontinuations




R Gagliardini et al. ICAR 2024

# IRCCS San Raffaele Scientific Institute, Milan, Italy: SCohoLART cohort

GRUPPO OSPEDALIERO SAN DONATO

UNIVERSITÀ VITA-SALUTE SAN RAFFAELE

OSPEDALE SAN RAFFAELE

**Median follow-up time (IQR)**

**13.1 months** (9.1–15.5)

**Median age (IQR)**

**49 years** (40–56)

**Median BMI (IQR)**

**25 kg/m²** (23–27)

**Gender**

9% (n=47/514) Female

91% (n=467/514) Male

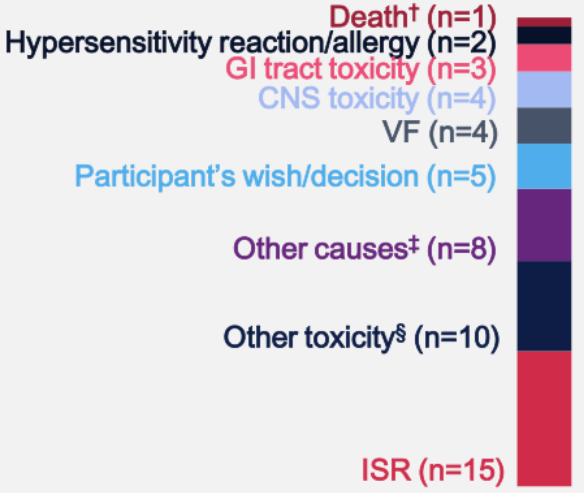
**514 people** living with HIV treated with CAB + RPV LA

**98%** (n=2,870/2,924) of injections administered within ±7-day dosing window

**4 virologic failures*** (0.8%)

- Three participants with NNRTI and INI RAMs at failure
- One participant with no RAMs at failure
- Regimens switched to: DRV/c/FTC/TAF (n=3), BIC/TAF/FTC (n=1); all resuppressed post-switch

**Reasons for discontinuation 10% (n=52)**




*Defined as: 2 consecutive VLs ≥50 c/mL or 1 VL ≥1,000 c/mL after initiation of CAB + RPV LA or at switching to another regimen; †One participant died from complications secondary to a metastatic biliopancreatic adenocarcinoma; ‡Other causes included: 2 personal commitments incompatible with scheduled injection visits, 1 transfer to another country, 1 HBV reactivation, 1 pregnancy, 1 viral blip, 1 enrolment in another study protocol, 1 chemotherapy-induced thrombocytopenia; §Other toxicity included: 3 pyrexia, 2 fatigue, 2 joint stiffness, 2 weight gain, 1 polyarthralgia. **/c,** cobicistat boosted; **BIC,** bictegravir; **BMI,** body mass index; **CAB + RPV LA,** cabotegravir + rilpivirine long-acting; **CNS,** central nervous system; **DRV,** darunavir; **FTC,** emtricitabine; **GI,** gastrointestinal; **HBV,** hepatitis B vírus; **INI;** integrase inhibitor; **IQR,** interquartile range; **ISR,** injection-site reaction; **NNRTI,** non-nucleoside reverse transcriptase inhibitor; **RAMs,** resistance-associated mutations; **TAF,** tenofovir alafenamide; **VF,** virological failure; **VL,** viral load

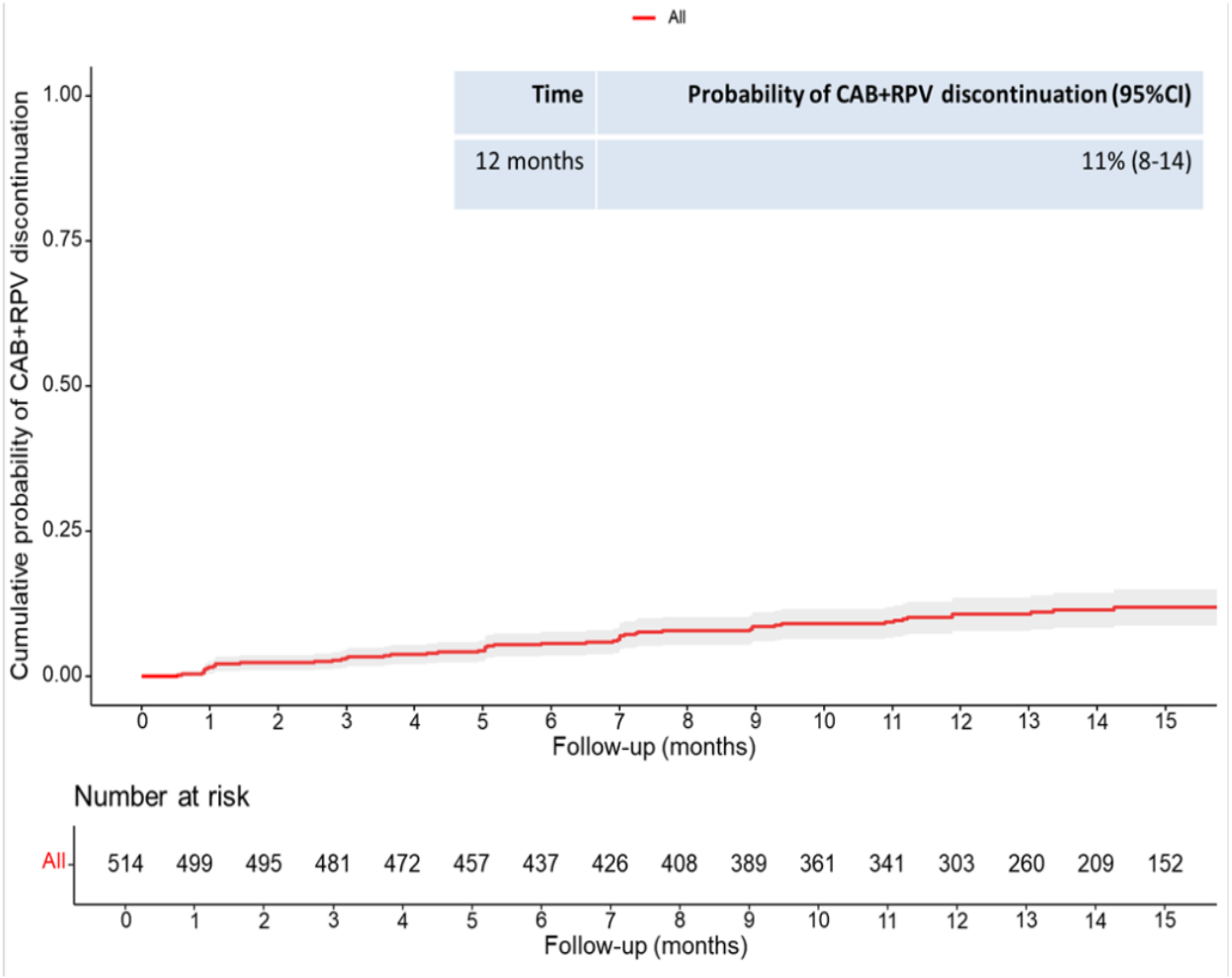
Muccini C, et al. Open Forum Infect Dis 2024;11:ofae326

# SCohoLART Study

## Participants

| | N=514 |
|---|---|
| Age, median (IQR) | 49 (40-56) |
| Male, n (%) | 467 (90.9) |
| Men who have sex with men, n (%) | 364 (70.8) |
| Years from HIV diagnosis, median (IQR) | 14.0 (8.8-20.5) |
| Years of ART, median (IQR) | 11.4 (7.9-17.4) |
| Previous AIDS diagnosis, n (%) | 52 (10.3) |
| CD4+ (cells/µL), median (IQR) | 794 (602-994) |
| Nadir CD4+ ≤200 cells/µL, n (%) | 120 (23.6) |
| HBcAb positive (%) | 122 (30.2%) |
| Years of the ART regimen in use at CAB+RPV switch, median (IQR) | 3.4 (2.2-5.4) |
| Number of drugs in the ART regimen in use CAB+RPV switch, median (IQR) | 3.00 (2.00-3.00) |
| 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) |
| 1 NRTI + 1 INSTI, n (%) | 124 (24.6) |
| 1 INSTI + 1 NNRTI, n (%) | 45 (8.8) |
| PI-monotherapy, n (%) | 5 (1.0) |
| Other, n (%) | 13 (2.5) |

## Treatment Discontinuations




C Muccini et al. Open Forum Infectious Diseases 2024

# IRCCS San Raffaele Scientific Institute, Milan, Italy: SCohoLART cohort

| 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<br>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<br>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<br>55 copies/mL | 70.8 ng/mL | / | **WT** for NNRTIs and INSTIs | B/F/TAF | <50 copies/mL after 1 week |

Muccini C et al. Open Forum Infectious Diseases. 2024.

# Hepatitis B Reactivation in PLWH With Anti-Core Antibody After Switch to an Anti-HBV Sparing Regimen

737

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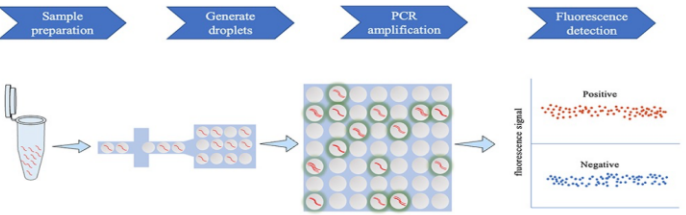
## BACKGROUND

- People living with HIV (PLWH) who show the presence of hepatitis B surface antigen (HBsAg) require antiretroviral treatment (ART) regimens containing nucleos(t)ide analogues [(NAs) tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF)], that are active against both HIV and hepatitis B virus (HBV).[1,2]
- Instead, PLWH who are anticore antibody (antiHBc) positive in the absence of HBsAg may have access to antiHBV sparing regimens (antiHBVsr).[1,2]
- However, loss of HBsAg in PLWH, with or without seroconversion to anti-HBsAg antibodies (HBsAb), could be due to ART containing drugs active against both viruses.[3]
- Furthermore, HBV reactivation has been described in individuals with isolated antiHBc and, in case of severe immunosuppression, with antiHBc and HBsAb.[4,5]

We investigated HBV reactivation in PLWH with antiHBc (isolated or with HBsAb) who switched from combination therapy containing drugs active against both viruses to antiHBVsr.

**Figure 1.** Workflow of ddPCR




Adapted from Fan Y, et al. **Application of Droplet Digital PCR to Detection of Mycobacterium tuberculosis and Mycobacterium leprae Infections: A Narrative Review.** Infect Drug Resist. 2022. doi: 10.2147/IDR.S349607.

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## CONTACT INFORMATION

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## METHODS

- Cohort study on PLWH with antiHBc (isolated or with HBsAb) who switched from NA-containing regimens to antiHBVsr dolutegravir/rilpivirine (DTG/RPV) or cabotegravir/rilpivirine long-acting (CAB/RPVLA). Follow-up accrued from the date of regimen switch [baseline (BL)] to the date of antiHBVsr discontinuation or the freezing date (August 29, 2023).
- HBV reactivation was initially assessed by ALT above the upper limit of normal range (normal value <60 IU/L) and in PLWH with ALT > normal levels by HBV-DNA quantification.
- In case of HBV reactivation and available plasma samples, HBV-DNA and HBV-RNA [as a surrogate marker for covalently closed circular DNA persisting in hepatocytes][6] were determined by highly sensitive digital droplet PCR (ddPCR; Figure 1) and HBV genotype by direct sequencing of the S gene.
- Data extracted from the database of Infectious Diseases, IRCCS San Raffaele Scientific Institute (CSLHIV Cohort) and from the SCohoLART study (single-center, prospective, phase IV, cohort study of people with HIV, treated with long-acting antiretroviral therapy; NCT05663580).

## RESULTS

- Overall, 34 PLWH with antiHBc and HBsAb and 7 with isolated antiHBc switched to an antiHBVsr (Table 1).
- Median follow-up after switch to antiHBVsr: 8.91 months [(IQR 6.78 - 24.14); in PLWH with HBsAb 8.96 months (IQR 6.78 - 24.14); in PLWH with isolated antiHBc 6.97 months (IQR 5.56 - 43.22); p=0.742].
- No reactivations in PLWH with antiHBc and HBsAb.

**Table 1.** Characteristics of PLWH with antiHBc at switch to antiHBVsr according to the presence or absence of anti-HBsAg

| BL Characteristics | Overall (n=41) | antiHBc positive (n=7) | antiHBc HBsAb positive (n=34) | p |
|---|---|---|---|---|
| Age (years) | 55.1 (50.2 - 62.2) | 57.8 (43.2 - 70.2) | 54.4 (50.2 - 61.5) | 0.690 |
| Male sex | 41 (100%) | 7 (100%) | 34 (100%) | - |
| Years of HIV infection | 15.4 (9.5 - 20.4) | 15.5 (10.1 - 26.4) | 15.3 (8.9 - 19.7) | 0.533 |
| HIV-RNA | | | | |
| <50 copies/mL | 40 (97.6%) | 7 (100%) | 33 (96.8%) | 0.661 |
| 50-200 copies/mL | 1 (2.4%)* | 0 (0%) | 1 (3.2%)* | |
| CD4⁺ cells count (cells/mm³) | 607 (460 - 772) | 693 (485 - 867) | 603 (459 - 772) | 0.726 |
| AntiHBVsr | | | | |
| DTG/RPV | 15 (36.6%) | 3 (42.9%) | 12 (35.3%) | 0.693 |
| CAB/RPVLA | 26 (63.4%) | 4 (57.1%) | 22 (64.7%) | |
| HBV-DNA <10 IU/mL (available in 26 PLWH) | 26 (100%) | 5 (100%) | 21 (100%) | - |
| ALT levels (IU/L) | 27.5 (21 - 32) | 28 (20 - 32) | 27 (21 - 39) | 0.763 |

*One participant had HIV-RNA >50, <200 copies/mL before switching to DTG/RPV

Of 7 PLWH with **isolated antiHBc**, 1 (14.3%) experienced **HBV reactivation** 3 months after switching to **CAB/RPVLA**

**Figure 2.** Trend of transaminases in the participant with HBV reactivation

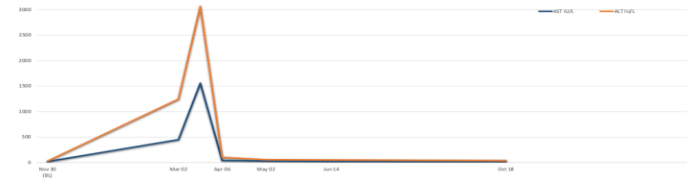
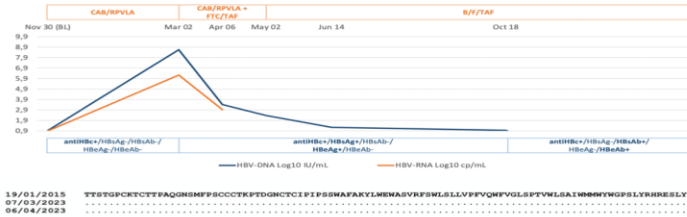


**Figure 3.** Trend of HBV-DNA, -RNA and serology in the participant with HBV reactivation. Alignment of the partia HBsAg before any ART and during HBV reactivation in the bottom




- In this individual (Figure 2 and Figure 3) we observed:
  - HBV-RNA positive at baseline (8 copies/mL) and very low levels of HBV-DNA (6 copies/mL) by ddPCR assay
  - Overt HBV infection assessed by HBsAg and hepatitis B e antigen (HBeAg) seroreversion and highly increased HBV-DNA
  - HBV genotype A2, with sequence identical to that obtained prior to any ART
  - Progressive decrease in HBV-DNA and normalization of transaminases after receiving emtricitabine/tenofovir alafenamide (FTC)/TAF.

## CONCLUSIONS

- HBV reactivation after switching to antiHBVsr is unlikely in PLWH with antiHBc and HBsAb.
- Close monitoring of ALT and possibly HBV-DNA is mandatory in PLWH with isolated antiHBc switching to antiHBVsr.

# CD4R/CD8R improvement after switch from a second-generation integrase inhibitor regimen to long-acting cabotegravir and rilpivirine

**Table 1. Crude mean changes per year in $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ during cabotegravir and rilpivirine and in the year before cabotegravir and rilpivirine.**

| *N* = 310<br>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 for comparison BIC/TAF/FTC vs. DTG/3TC vs. DTG/RPV |
|---|---|---|---|---|---|
| $CD4^+$ (cells/μl) 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/μl) 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), $P=0.39$ | $P<0.0001$ |
| $CD8^+$ (cells/μl) during CAB+RPV | −17 (−47, 12.9), $P=0.27$ | −30.77 (−74.8, 13.2), $P=0.17$ | −7.96 (−56.0, 40.1), $P=0.74$ | 2.84 (−75.8, 81.5), $P=0.94$ | $P=0.57$ |
| $CD8^+$ (cells/μl) in the year before CAB+RPV | 22.5 (1.13, 43.8), $P=0.04$ | 9.8 (−18.70, 38.3), $P=0.50$ | 40.7 (4.11, 77.4), $P=0.03$ | 26.8 (−40.5, 94.1), $P=0.43$ | $P=0.12$ |
| $CD4^+/CD8^+$ 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), $P=0.92$ | $P=0.78$ |

*P*-value for comparison (BIC/TAF/FTC vs. DTG/3TC vs. DTG/RPV, last column) corresponds to the type 3 test of fixed effects based on the calculation of Sum of Squares for each effect in the model. 3TC, lamivudine; BIC, bictegravir; CAB, cabotegravir; CI, confidence interval; DTG, dolutegravir; F, emtricitabine; RPV, rilpivirine; TAF, tenofovir alafenamide.

C. Muccini, AIDS 2024

# Improvement in high-density lipoprotein cholesterol in people with HIV who switched from a tenofovir alafenamide-containing regimen to cabotegravir plus rilpivirine

**Table 1**
Crude mean changes in metabolic parameters and weight in people with HIV treated with or without tenofovir alafenamide before starting cabotegravir + rilpivirine.

| 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), $P = 0.139$ | $P = 0.094$ |

PWH, people with HIV; TAF, tenofovir alafenamide; CAB, cabotegravir; RPV, rilpivirine; HOMA, homeostatic model assessment; HDL, high-density lipoprotein, LDL, low-density lipoprotein.

C. Muccini , IJAA 2024

# Studio Longitude

**Objectives**

• We herein present a multicenter real-world experience from 14 centers in Northern Italy, focusing on the implementation and outcomes associated with this novel treatment regimen (LONGITUDE Study).

# MATERIALS AND METHODS

**Padova**
Treviso
Belluno
Venezia-Mestre
Rovigo
Verona
**Vicenza**
Udine
**Bolzano**
**Trento**
Modena
**Bologna**
Pordenone
Aviano

- We included all individuals who received at least one dose of injectable cabotegravir and rilpivirine

- We collected demographic data and laboratory results, and assessed factors associated with treatment discontinuations (TD).

- Statistical assessments were conducted using Kaplan-Meier curves

- Logistic regression to identify significant predictors of TD.

# RESULTS

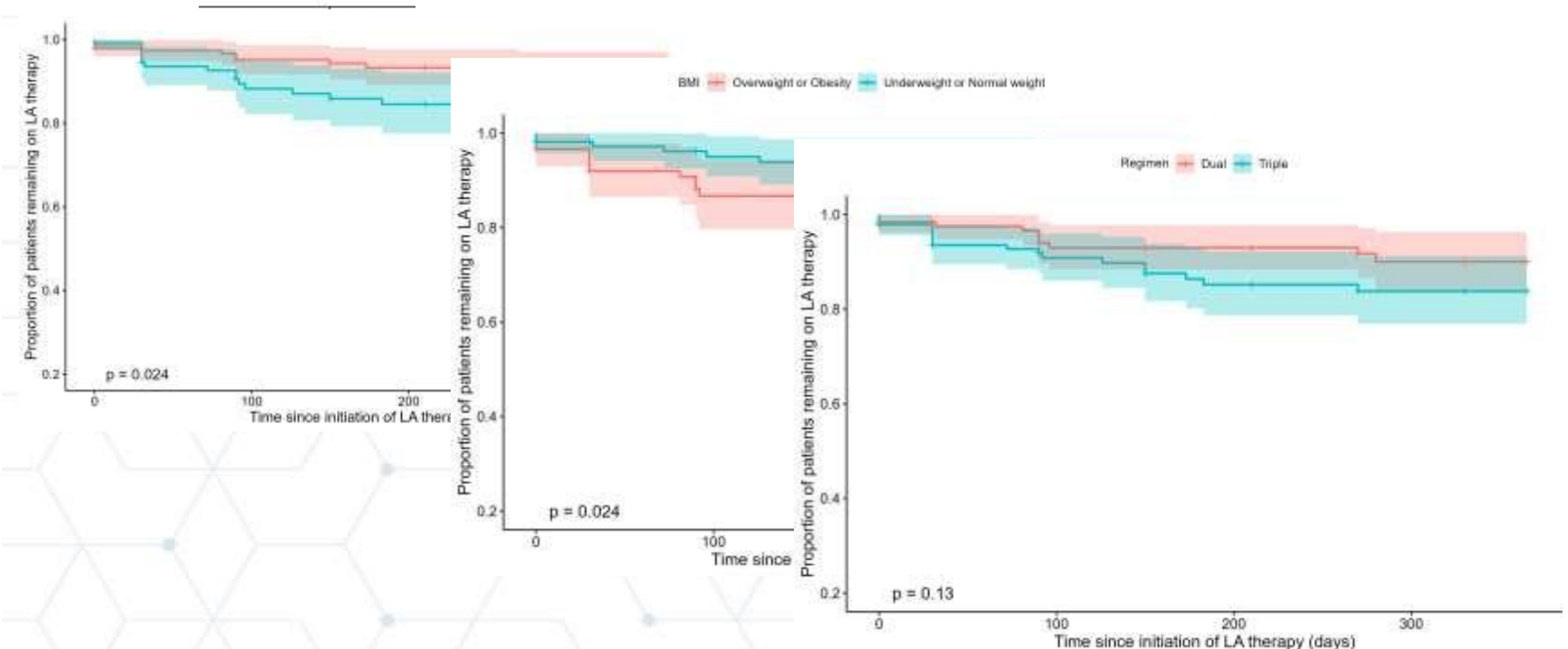
| Variables | Total (N = 270) |
|---|---|
| Caucasian ethnicity, n (%) | 243 (90) |
| Sex at birth, n (%) | 208 (77) |
| Age, years, median (IQR) | 49 (40-58) |
| Main risk factor for HIV acquisition, MSM, n (%) | 114 (70.4) |
| Years living with HIV, median (IQR) | 12 (7-20) |
| HIV subtype<br>Unkown<br>B<br>Others | <br>156 (57.8)<br>89 (33)<br>25 (9.2) |
| Main Reason for starting LA<br>Person's preference<br>Other medical reasons | <br>226 (83.7)<br>44 (16.3) |
| Nadir CD4+ T cell count, median (IQR) | 299 (174-439) |
| Past AIDS events, n (%) | 39 (14.5) |
| Previous HCV infection, yes | 39 (14.5) |
| Regular physical exercise, yes, n (%) | 81 (40.7) |
| Alcohol use disorders, | 7 (2.7) |
| Multimorbidity, n (%) | 87 (32.2) |
| Polypharmacy, n (%) | 51 (19.1) |

# RESULTS

**During the first year of follow-up 28 (10.4%) PWH discontinued the study regimen**

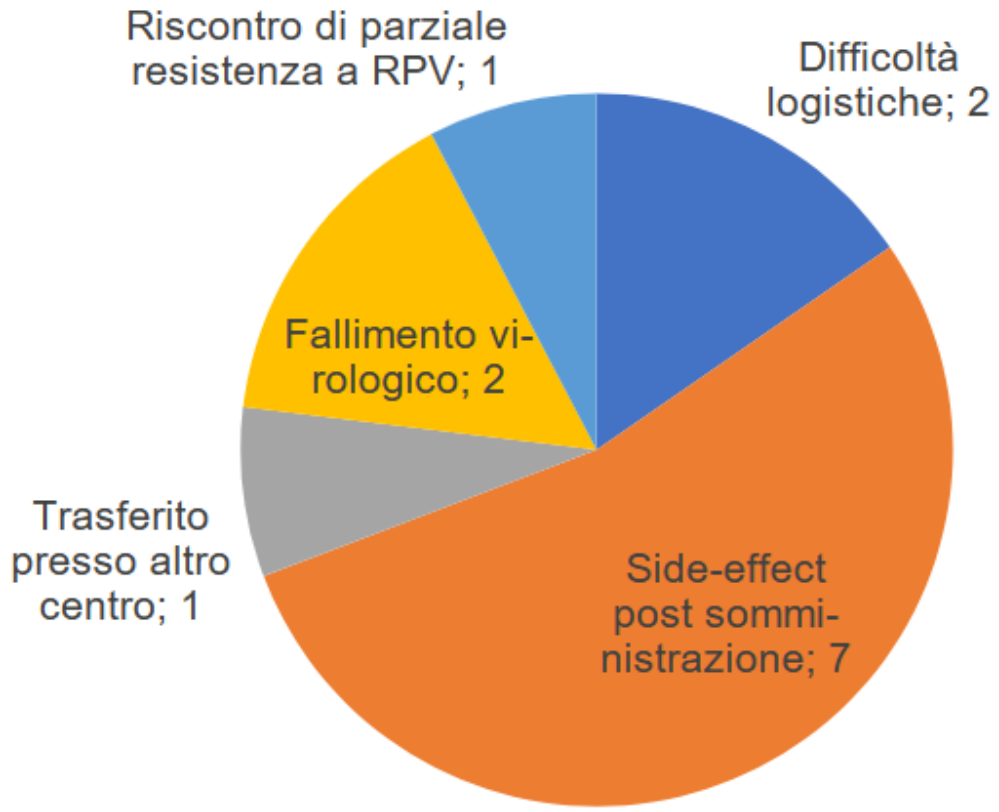
- **2VF**
- **1 acute HBV (acquired)**
- **1 not longer feasible with lifestyle**
- **4 pain**
- **20 not indicated by centers**

| Variable | OR | p-value |
|---|---|---|
| Years living with HIV | 1.06 | 0.005 |
| BMI | 1.17 | 0.022 |
| HCV Ab | 2.71 | 0.03 |



# Modena L-A Cohort (84 pts)

| Caratteristiche demografiche | |
|---|---|
| Età mediana in anni (IQR) | 53,5 (45-60) |
| Maschi | 68 (82,9%) |
| Provenienza da un regime INI-based | 64 (78%) |
| HbsAb con titolo protettivo | 47 (57,3%) |
| HbcAg positivo | 25 (30,5%) |
| HbsAb con titolo **non** protettivo e HbcAg positivo | 10 (12,2%) |
| VL ≤ 20 copie/ml prima dell'avvio del regime | 79 (96,3%) |
| Mediana CD4+ prima dell'avvio U/microl (IQR) | 801,6 (596,4 – 1007,37) |




*Motivi di interruzione del regime L-A*

13 cessazioni del regime per ogni causa (15,85%)

# VF1

Uomo di 57 anni , infezione da HIV nota dal 1992. Nadir di CD4+ 203 U/microl. Dal 2015 in terapia con DTG + RPV + MVC. BMI 22.5 kg/m2 nel febbraio 2023. Ultimo test di resistenza su DNA effettuato nel 2015: nessuna resistenza a INI o NNRTI.

**2015 - 2023**

- DTG/RPV + MVC. VL stabilmente ≤ 20 copie /ml, CD4+ stabilmente > 500 U/microl

**16/02/2023**

- Prima somministrazione di L-A CAB/RPV

**15/03/2023**

- Interruzione L-A per eccessivi SE riportati
- VL di controllo: 4230 copie/ml
- Ritorno a DTG/RPV + MVC

**22/06/2023**

- Test di resistenza su RNA (campione dl 15/03/2023): resistenza elevata a RPV e CAB, intermedia a DTG
- Avviato regime con DTG bid, MVC bid e DRV/c qd
- Ai successivi controllo VL ≤ 20 copie/ml

# VF2

Uomo di 48 anni , infezione da HIV nota dal 2002. Nadir di CD4+ 360 U/microl. Dal 2019 in terapia con DRV/c + 3TC. BMI 22.2 kg/m2 nel gennaio 2023.

**21/09/2023**
- DRV/c + 3TC. VL stabilmente ≤ 20 copie /ml, CD4+ stabilmente > 500 U/microl

**16/03/2023**
- Avvio lead-in orale con CAB + RPV

**13/04/2023**
- Prima somministrazione L-A CAB/RPV
- 11/03/2023: VL ≤ 20 copie /ml

**27/12/2023**
- VL 7975 copie /ml
- Test resistenza su RNA: resistenza moderata a RPV e CAB

**17/01/2024**
- Avvio di DRV/c/FTC/TAF
- Ai successivi controlli VL ≤ 20 copie /ml

| | | | |
|---|---|---|---|
| **DATA** | 06/07/2023 | NUM | |

| | | | | | |
|---|---|---|---|---|---|
| RT | Linfociti DNA | SUB | B | PRO | Linfociti DNA | SUB | B |
| ESITO | Nessuna mutazione significativa | | | ESITO | Nessuna mutazione significativa | | |
| RTaltro | 35I 123E 135M 177Ew 178M 211K | | | PROaltro | 10V 14Rw 15V 35D 37Dw 41Kw 62Vw 63P 69N 77Iw | | |
| Nulla | 3TC ABC AZT D4T DDI FTC TDF TAF EFV | | | Nulla | ATV/rtv DRV/rtv FPV/rtv IDV/rtv LPV/rtv | | |
| Trasc | | | | Trasc | | | |
| Mod | | | | Mod | | | |
| Cons | | | | Cons | | | |
| Elev | | | | Elev | | | |
| COM | Resistenza prevista - Elevata: . Consistente: . Parziale: . Trascurabile: . Nessuna: 3TC ABC AZT D4T DDI FTC TDF TAF EFV ETR NVP RPV DOR | | | COM | Resistenza prevista - Elevata: . Consistente: . Parziale: . Trascurabile: . Nessuna: ATV/rtv DRV/rtv FPV/rtv IDV/rtv LPV/rtv NFV SQV/rtv TPV/rtv | | |
| NOTE | | | | NOTE | | | |
| DATA | 21/07/2023 | | | DATA | 21/07/2023 | | |

| | | | |
|---|---|---|---|
| DATA INI | 21/07/2023 | DATAV3 | |
| INI SUB | B | V3 SUB | |
| TIPO INI | DNA Linfociti | V3 RECETTORE | |
| INI ESITO | None | V3 FPR | 0 |
| INI ALTRO | E10ED,S17SN,A21S,A23V,S119ST,M154I,V165I,V201I,L234V,S283SG | V3 NOTE | |
| | | TIPO V3 | |
| | | V3 COMM | |
| INI NOTE | | V3_ALL | |

| | | | |
|---|---|---|---|
| **DATA** | 17/01/2024 | NUM | |

| | | | | | |
|---|---|---|---|---|---|
| RT | RNA plasma | SUB | B | PRO | RNA plasma | SUB | B |
| ESITO | 138K | | | ESITO | Nessuna mutazione significativa | | |
| RTaltro | 123E 135M 178M 179I 207A 211K 246Pw | | | PROaltro | 10V 15V 35D 60E 63P 69N | | |
| Nulla | 3TC ABC AZT D4T DDI FTC TDF TAF DOI | | | Nulla | ATV/rtv DRV/rtv FPV/rtv IDV/rtv LPV/rtv | | |
| Trasc | EFV ETR NVP | | | Trasc | | | |
| Mod | | | | Mod | | | |
| Cons | RPV | | | Cons | | | |
| Elev | | | | Elev | | | |
| COM | Resistenza prevista - Elevata: . Consistente: RPV. Parziale: . Trascurabile: EFV ETR NVP. Nessuna: 3TC ABC AZT D4T DDI | | | COM | Resistenza prevista - Elevata: . Consistente: . Parziale: . Trascurabile: . Nessuna: ATV/rtv DRV/rtv FPV/rtv IDV/rtv LPV/rtv NFV SQV/rtv TPV/rtv | | |
| NOTE | | | | NOTE | | | |
| DATA | 30/01/2024 | | | DATA | 30/01/2024 | | |

| | | | |
|---|---|---|---|
| DATA INI | 30/01/2024 | DATAV3 | |
| INI SUB | B | V3 SUB | |
| TIPO INI | RNA Plasma | V3 RECETTORE | |
| INI ESITO | Q148R | V3 FPR | 0 |
| INI ALTRO | E10D,A21S,A23V,L45V,E96K,M154I,V165I,V201I,L234V | V3 NOTE | |
| INI NOTE | | TIPO V3 | |
| | | V3 COMM | |
| | | V3_ALL | |

# Use of long-acting injectable cabotegravir/rilpivirine in people with HIV and adherence challenges

| | Setting/design | Number of PWH | Required VS prior to LA-CAB/RPV | Clinical outcomes: % with viral suppression (VS) and/or number/% experiencing virologic failure (VF) | Treatment emergent CAB/RPV resistance associated mutations | Notes |
|---|---|---|---|---|---|---|
| ACTG 5939 (LATITUDE) | Network randomized trial in 33 US sites | Step 1, 434; Step 2, 146 LA-CAB/RPV vs. 148 oral ART | Yes | 6 cases of VF in LA-CAB/RPV arm vs. 28 cases of VF in SOC oral ART arm (7.2% cumulative probability of VF in LA-CAB/RPV arm vs. 25% in SOC oral ART) | 2/6 cases of VF<br>Participant 1: RT: K103R; INSTI: E138EK, G140GS, Q148K;<br>Participant 2: RT: K20KR; M230ML; INSTI: E138K; Q148K | Economic incentives for VS prior to randomization |
| Ward 86 Clinic | Academic Ryan White-funded clinic; Observational | 59 (32% VL >100K) | No | 92% with VL<50 c/ml at 48 weeks (VS estimate includes use of alternate ART)<br>7 cases of adverse virologic outcomes (includes those LTFU) | 5/6 cases of VF<br>Patient 1: RT: E138K; INSTI: R263K<br>Patient 2: RT: L100I, Y181I<br>Patient 3: RT: K101E; INSTI: Q148R<br>Patient 4: RT: K101E, E138K, Y181F/I/N, M230L<br>Patient 5: RT: E138A/K/T, Y181C | One-third receiving care in a low-barrier drop-in primary care model |
| University. of Mississippi | Academic Ryan White-funded clinic; Observational | 12 (mean VL 150K) | No | 100% with VL<50 c/ml (50% w/1 year f/u) | None | Half started with Q8 week dosing |
| University of North Carolina | Academic Ryan White-funded clinic; Observational | 6 | No | 83% with VL<50 c/ml<br>2 cases of VF (1 with low-level rebound viremia after VS) | 1/2 cases of VF<br>Patient 1: RT: Y181C | |
| Owen Clinic | Academic Ryan White clinic; Observational | 63 (44 with VL>50 c/ml; 7 with VL >10 000 c/ml | No | 90% with VL <200 c/ml at 24 weeks; 89% with VL <200 c/ml at 48 weeks (VS estimates include use of alternate ART)<br>6 cases of VF | 3/6 cases of VF, mutations not reported in abstract | 9 patients also initiated LA-CAB/RPV with lenacapavir |
| San Francisco Street Medicine | Public health program (San Francisco); Observational | 14 with VL >30 c/ml | No | 93% <30 c/ml (mean follow up 11 months)<br>2 cases of VF | 2/2 cases of VF<br>Patient 1: RT: V179D, M230, Y181C,<br>Patient 2: RT: V108I, K101K, K103R, E138K, Y181C; INSTI: E138K, G140S, Q148R | 2 patients also initiated LA-CAB/RPV with lenacapavir |
| Boston Medical Center | Harm reduction site (Boston); Observational | 5 (VS required prior to start) | Yes | 1/5 persisted with injections over 6 months | Unknown | Loss of trusted practitioner may have been a factor |
| OPERA Cohort | 84 clinics across 18 US states; Observational | 229 VL >50 c/ml (93 VL >200 c/ml) | No | 94% VL<200 c/ml (median f/u 6 months)<br>7 (4%) VF | Not reported | 75% achieved VL <50 c/ml |

KA Christopoulos, COHA, 2024

# Coorte LAT H Civico Palermo

UOSD Patologie Infettive Popolazioni Vulnerabili

Civico Di Cristina Benfratelli
Azienda di Rilievo Nazionale ad Alta Specializzazione

start 01/2023 dati aggiornati al 10/12/2024 – **Pazienti: 59**

| | | |
|---|---|---|
| Età media anni | 33 | |
| Femmine | 31 | (52,5%) |
| Maschi | 27 | (45,5%) |
| M > F | 01 | (1,7%) |
| Italiani: | 28 | (47,5%) |
| Africani: | 31 | (52,5%) |

# LAT: tempo di trattamento

## 48 settimane: 27 Pazienti

VL < 20 copie/ml:100%
2 bleep
3 interruzioni per scelta non correlata ad eventi avversi
1 Paziente naive* ha presentato VL < 20 copie/ml dopo 8 settimane

* da sempre incapace di assumere terapia per OS

# LAT: tempo di trattamento

## 24 settimane: 17 Pazienti

VL < 20 copie/ml:100%
nessun bleep
nessuna interruzione

## < 24 settimane: 8 Pazienti

VL < 20 copie/ml:100%
nessun bleep
nessuna interruzione

# LAT: eventi avversi

## grado 1-2: 6 Pazienti (11.5%)

dolore in sede di inoculo

un Paziente ha anche lamentato dolore articolare e muscolare prolungato (in corso di valutazione – ha cominciato 4 settimane fa)

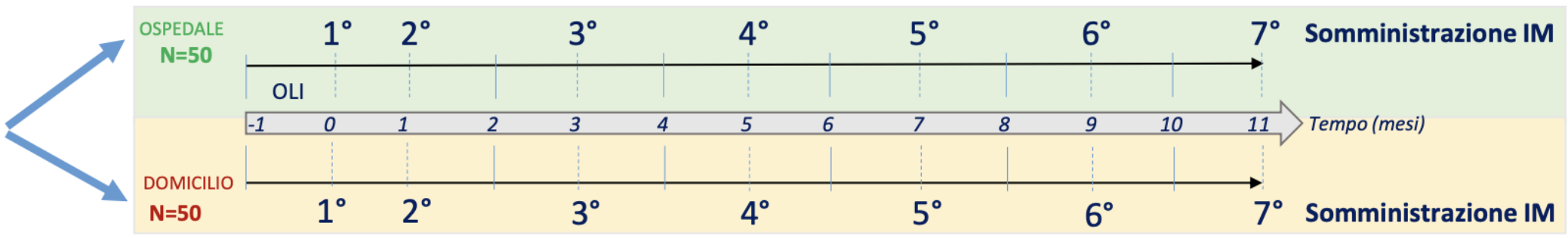
# LAT: differenze tra Pazienti italiani e africani?

NESSUNA!

# Antiviral Long-Acting Drugs Landing in people living with HIV (ALADDIN)

| Screening e arruolamento dei partecipanti | OLI opzionale | Trattamento con CAB LA + RPV LA |
|---|---|---|
| Durata di 1 mese | | Durata di 11 mesi: *somministrazione IM ai mesi 0, 1, 3, 5, 7, 9 e 11* |

**100** Persone con HIV-1 in soppressione virologica (HIV-1 RNA <50 copie/mL) per almeno 12 mesi verranno randomizzati (**1:1**) in due bracci di studio




**Obiettivo primario:** valutare la fattibilità, l'accettabilità e l'appropriatezza della somministrazione del trattamento, come percepito dai pazienti, in un contesto domiciliare o in un contesto ospedaliero.

Primo paziente randomizzato 2 dicembre 2024

I.R.C.C.S. Ospedale San Raffaele
Gruppo San Donato

UNIVERSITÀ VITA-SALUTE SAN RAFFAELE
UniSR
QUID EST HOMO?

# Long-acting injectable antiretrovirals for HIV treatment in the ICONA cohort: physicians' and nurses' points of view

**A. Cingolani [1,2]*, A. Tavelli[3], S. De Benedittis[3], I. Mastrorosa[4], C. Muccini [5], T. Bini[6], A. Carraro[6], M. Compagno[7], M. Mazzitelli [8], M. Guastavigna[9], M. Cernuschi[5,10], C. Torti[1,2], A. Antinori[4] and A. d'Arminio Monforte[3]; on behalf of ICONA Foundation Study group†**

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**Background:** Implementation level of long-acting injectable agents cabotegravir/rilpivirine (LAI CAB/RPV) for human immunodeficiency virus (HIV) treatment in Italy is still not known. The aim of this study is to identify the status of implementation of LAI CAB-RPV and its barriers.

**Materials and methods:** A cross-sectional online survey was conducted among infectious diseases (ID) physicians and nurses belonging to the ICONA network in Italy. Three validate 4-items measures were used: Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM) and Feasibility of Intervention Measure (FIM).

**Results:** Out of 61 ICONA centres, 38 (62%) completed the survey: 57.9% were academic centres, 42.1% were hospital-based. In total, 104 respondents were ID physicians (57.4%), 77 were nurses (42.5%); 4.5% of all PWH followed at the 38 centres started LAI CAB/RPV at time of study. Centres taking care of >1000 PWH reported 95% application of procedures for LA implementation, higher than other centres ($P=0.009$). Mean score of AIM was (16.0, standard deviation, SD, 3.3), of IAM (16.0, SD 3.0) and FIM (16.0, SD 2.9). A linear correlation was found between AIM and the number of people with HIV who started LAI CAB/RPV (25–50 versus <25, coefficient of correlation [b] 2.57, 95%CI 0.91–4.60, $P=0.004$), academic versus hospital-based centres (b −1.59, 95%CI −2.76–0.110044, $P=0.007$) and the absence of preliminary systematic assessment of staff (b −1.98, 95%CI −3.31–0.65, $P=0.004$). Implementation barriers were not significantly different according to the number of PWH/centre.

**Conclusions:** LAI CAB/RPV implementation was low, with a great variability according to centre size. Tailored and centre-specific interventions to address barriers and to optimize the LA treatment implementation should be designed.

*J Antimicrob Chemother* 2024; **79**: 2662–2667

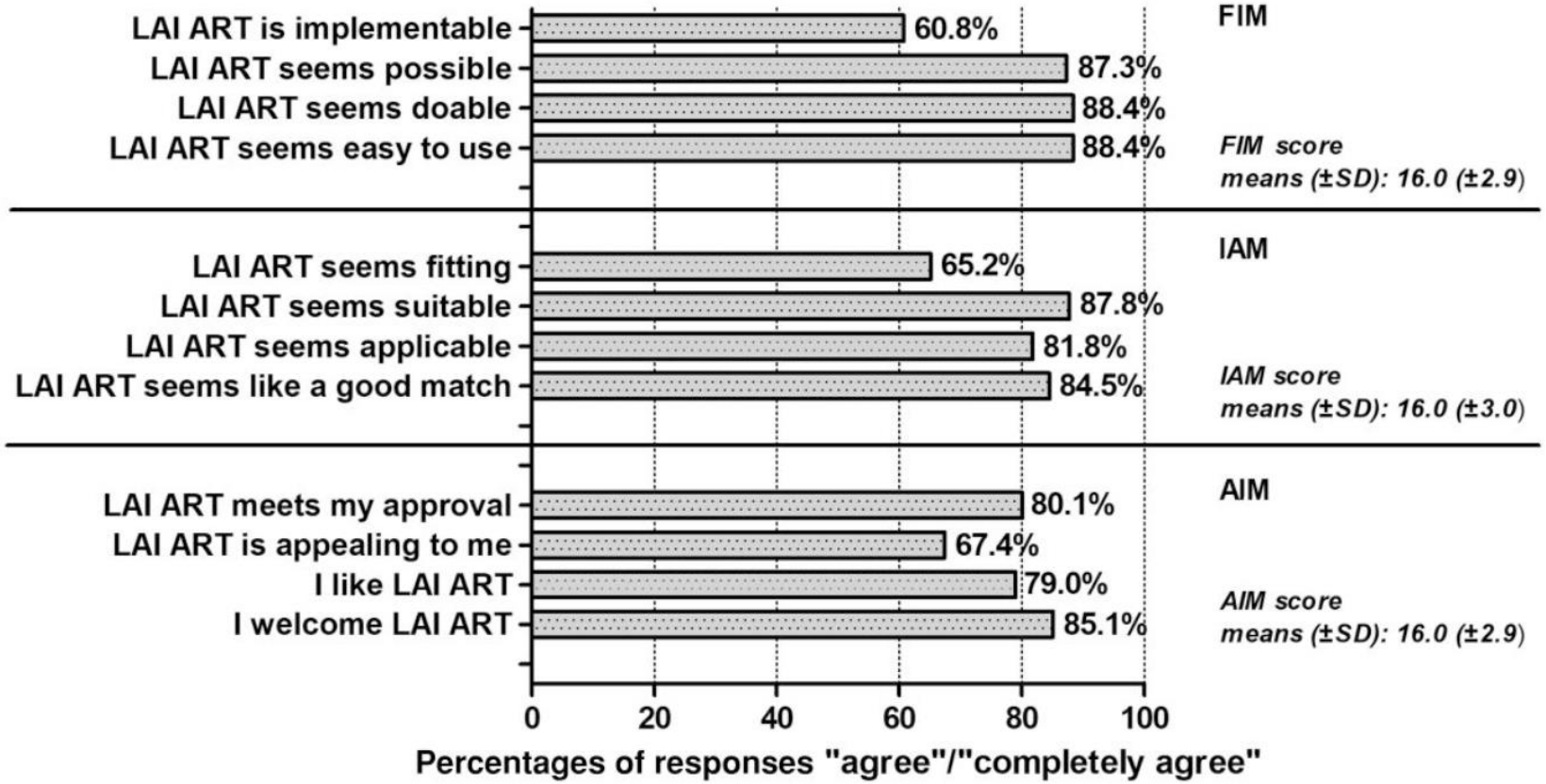



**Figure 1.** Percentage of participants who responded 'agree'/'completely agree' on the 1–5 Likert scale for each item of the FIM, IAM and AIM. The two answers are summed together to express the proportion of participants with a positive response to each question. Mean scores with ±SD are also reported for the three implementation measures (scale 4–20).

# Sfide per l'infermiere

- Ambulatorio dedicato
- Personale dedicato
- Frigo nelle vicinanze
- Approvvigionamento
- Stoccaggio
- Tempo di preparazione e somministrazione
- Gestione agende per appuntamenti

# Inizio training e organizzazione

Inizio gennaio 2023 – 3 infermiere hanno eseguito il training

84 pazienti arruolati ad oggi nell'ambulatorio *long-acting*

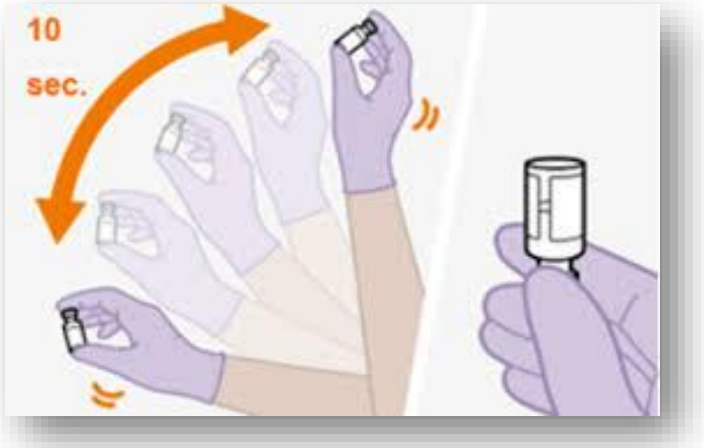
Le sedute si tengono il mercoledì e il giovedì, un paziente ogni 30 minuti, max 7 al giorno

Le sedute si svolgono in presenza di personale medico, infermieristico e di un farmacista

# Modalità di somministrazione

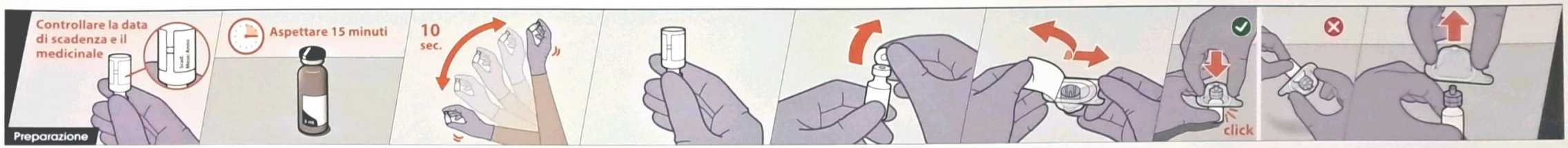
# Preparazione

**Cabotegravir**




**Rilpivirina**


Discioglimento




**1. Ispezionare il flaconcino**[1,2]
- Controllare che la data di scadenza non sia passata.[1,2]
- Ispezionare il flaconcino immediatamente. Se si vedono corpi estranei, non usare il medicinale.[1,2]

**Nota**: il flaconcino di cabotegravir ha un vetro di color marrone.[1] Non usare se la data di scadenza è passata.[1,2]

**2. Aspettare 15 minuti**[1,2]
- Attendere almeno 15 minuti prima di procedere con l'iniezione di rilpivirina, per permettere al medicinale di raggiungere la temperatura ambiente.[1,2]
- Se la confezione di cabotegravir è stata conservata in frigorifero, toglierla e aspettare almeno 15 minuti prima di procedere con l'iniezione, per permettere al medicinale di raggiungere la temperatura ambiente.[1]

**3. Agitare energicamente**[1,2]
- Tenere il flaconcino saldamente e agitare energicamente per 10 secondi interi come illustrato nella figura.[1,2]

**Nota**: si sconsiglia di creare bolle d'aria.[3]

**4. Controllare la sospensione**[1,2]
- Capovolgere il flaconcino e controllare la risospensione. Deve avere un aspetto uniforme. Se la sospensione non è uniforme, agitare di nuovo il flaconcino.[1,2]
- È normale vedere piccole bolle di aria.[1,2]

**Nota**: l'ordine di preparazione del flaconcino non è importante.[1,2]

**5. Rimuovere la capsula del flaconcino**[1,2]
- Rimuovere la capsula dal flaconcino.[1,2]
- Passare sul tappo di gomma un tampone imbevuto di alcol.[1,2]

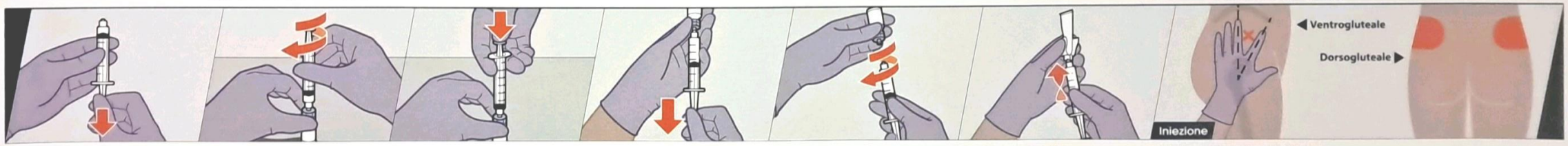
**Non** permettere che nulla venga in contatto con il tappo di gomma dopo averlo pulito.[1,2]

**6. Aprire il contenitore dell'adattatore per flaconcino**[1,2]
- Staccare la carta di protezione dal contenitore dell'adattatore per flaconcino.[1,2]

**Nota**: **non** rimuovere l'adattatore dal suo contenitore per la fase successiva. L'adattatore **non** cadrà se la confezione è capovolta.[1,2]

**7. Fissare l'adattatore al flaconcino**[1,2]
- Posizionare il flaconcino su una superficie piana.[1,2]
- Premere l'adattatore direttamente sul flaconcino come illustrato nella figura.[1,2]
- L'adattatore del flaconcino deve agganciarsi saldamente con uno scatto.[1,2]

**8. Sollevare il contenitore**[1,2]
- Sollevare il contenitore dell'adattatore per flaconcino come illustrato nella figura.[1,2]




**9. Preparare la siringa**[1,2]
- Estrarre la siringa dalla sua confezione.[1,2]
- Aspirare 1 mL di aria nella siringa. Questo faciliterà il prelievo del liquido nella fase successiva.[1,2]

**10. Fissare la siringa**[1,2]
- Tenere saldamente l'adattatore e il flaconcino come illustrato nella figura.[1,2]
- Avvitare saldamente la siringa sull'adattatore per flaconcino.[1,2]

**11. Premere lo stantuffo**[1,2]
- Premere lo stantuffo fino in fondo per spingere l'aria nel flaconcino.[1,2]

**12. Aspirare lentamente la dose**[1,2]
- Capovolgere la siringa e il flaconcino e aspirare lentamente tutto il liquido possibile nella siringa. Potrebbe esserci più liquido nel flaconcino della dose necessaria.[1,2]

**Nota**: tenere la siringa in posizione verticale per evitare fuoriuscite di liquido.[1,2]

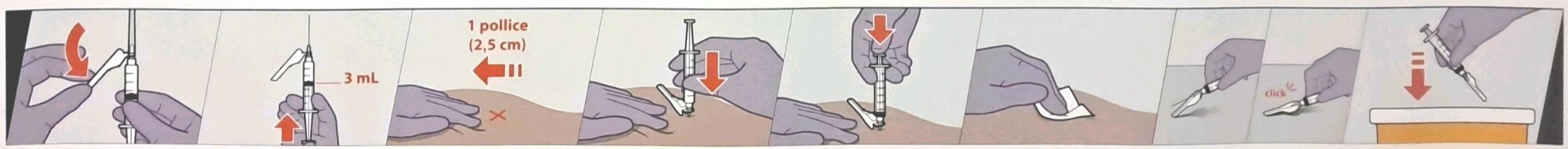
**13. Svitare la siringa**[1,2]
- Tenere lo stantuffo della siringa saldamente in posizione come mostrato nella figura per evitare fuoriuscite di liquido. È normale avvertire una certa resistenza.[1,2]
- Svitare la siringa dall'adattatore per flaconcino, tenendo l'adattatore come illustrato nella figura.[1,2]

**Nota**: controllare che la sospensione sia uniforme e di colore da bianco a rosa chiaro per cabotegravir.[1] Controllare che la sospensione abbia un aspetto uniforme e un colore bianco lattescente per rilpivirina.[3]

**14. Attaccare l'ago**[1,2]
- Aprire parzialmente la custodia dell'ago in modo da esporne solo la base.[1,2]
- Tenendo la siringa in posizione verticale, inserirla saldamente nell'ago.[1,2]
- Rimuovere la custodia dall'ago.[1,2]

**15. Preparare la sede dell'iniezione**[1,2]
- Le iniezioni devono essere somministrate in sede glutea. Scegliere tra le seguenti aree dove praticare l'iniezione:[1,2]
  - ventrogluteale (raccomandata)[1,2]
  - dorsogluteale (quadrante superiore esterno).[1,2]

**Nota**: solo per uso intramuscolare in sede glutea.[1,2] **Non** iniettare in vena.[1,2]




**16. Togliere il cappuccio**[1,2]
- Piegare il salva ago verso l'esterno allontanandolo dall'ago.[1,2]
- Togliere il cappuccio dell'ago da iniezione.[1,2]

**17. Rimuovere il liquido in eccesso**[1,2]
- Tenere la siringa con l'ago puntato verso l'alto. Premere lo stantuffo fino all'indicazione della dose di 3 mL per rimuovere il liquido in eccesso ed eventuali bolle d'aria.[1,2]

**Nota**: disinfettare il sito di iniezione con un tampone imbevuto di alcol. Lasciare asciugare la pelle all'aria prima di proseguire.[1,2]

**18. Tendere la cute**[1,2]
- Utilizzare la tecnica di iniezione del tratto z per ridurre al minimo il rischio di fuoriuscita di medicinale dal sito di iniezione.[1,2]
- Tendere con decisione la cute che copre il sito di iniezione, spostandola di circa un pollice (2,5 cm).[1,2]
- Mantenere la cute in questa posizione per praticare l'iniezione.[1,2]

**19. Inserire l'ago**[1,2]
- Inserire l'ago per l'intera lunghezza o per una profondità sufficiente a raggiungere il muscolo.[1,2]

**20. Iniettare la dose**[1,2]
- Continuando a tenere la cute ben tesa, premere lentamente lo stantuffo fino in fondo.[1,2]
- Assicurarsi che la siringa sia vuota.[1,2]
- Estrarre l'ago e rilasciare immediatamente la cute tesa.[1,2]

**21. Esaminare la sede di iniezione**[1,2]
- Applicare pressione sul sito di iniezione utilizzando una compressa di garza.[1,2]
- In caso di sanguinamento, si può applicare un cerotto.[1,2]

**Non** massaggiare l'area.[1,2]

**22. Mettere in sicurezza l'ago**[1,2]
- Piegare il salva ago sopra l'ago.[1,2]
- Applicare una lieve pressione sul salva ago, spingendolo contro una superficie rigida, in modo da bloccarlo in posizione.[1,2]
- Il salva ago si blocca con un «click».[1,2]

**23. Smaltire in modo sicuro**[1,2]
- Smaltire aghi, siringhe, flaconcini e adattatori per flaconcini usati in conformità alle disposizioni locali in materia di salute e sicurezza.[1,2]

# Problemi

Dolore nei giorni successivi in sede di iniezione
Febbre (tipicamente 2-3 gg dopo l'iniezione)

Inosservanza degli appuntamenti

Difficile organizzazione nei periodi festivi

# Consigli ai pazienti

- Riposo e astenersi dall'attività fisica (GAG) per 2-3 giorni
- Dopo le prime somministrazioni si tiene il paziente in attesa 15-20 minuti
- Eventuale terapia antidolorifica (tachipirina o FANS per os)
- In caso di dolore intenso e persistente tornare a visita (ECO tessuti molli?)
- Riduzione del dolore avanzando con le somministrazioni (componente psicologica e assuefazione fisica)
- Alert informatico per non dimenticare gli appuntamenti (?)

# Conclusioni

- ✓ I pazienti sono in generale soddisfatti della terapia che risulta anche molto efficace anche in popolazioni con situazioni teoricamente più complesse.

- ✓ Permangono problematiche organizzative, che però stiamo tutti risolvendo.