ARCOBALENOAIDS ODV

Tori-No AIDS 2025: incontri con l'esperto su HIV

Giovedì 25 settembre ore 18:15
Sala Polivalente
Vol.To, Via Giolitti, 21 - Torino

LE TERAPIE ANTI HIV LONG ACTING: FACCIAMO IL PUNTO

Relatore: dr. Giancarlo Orofino
Infettivologo Ospedale Amedeo di Savoia Torino

Moderatore: dr. Pietro Altini
Presidente ARCOBALENO Aids ODV

Per informazioni: 3517552585 - arcobalenoaidsto@gmail.com

TORINO

Un farmaco long acting è una formulazione farmaceutica a rilascio prolungato che permette di mantenere un'azione terapeutica costante nell'organismo per un periodo di tempo più lungo rispetto alle formulazioni convenzionali, spesso tramite somministrazione iniettabile periodica. Questi farmaci garantiscono una copertura farmacologica più stabile, migliorano l'aderenza al trattamento e possono ridurre le ricadute e le ospedalizzazioni, come si osserva negli antipsicotici long acting injectable (LAI) per la schizofrenia.

FIG. **1** Simulazione grafica del profilo farmacocinetico di una terapia orale e di una terapia long-acting iniettabile

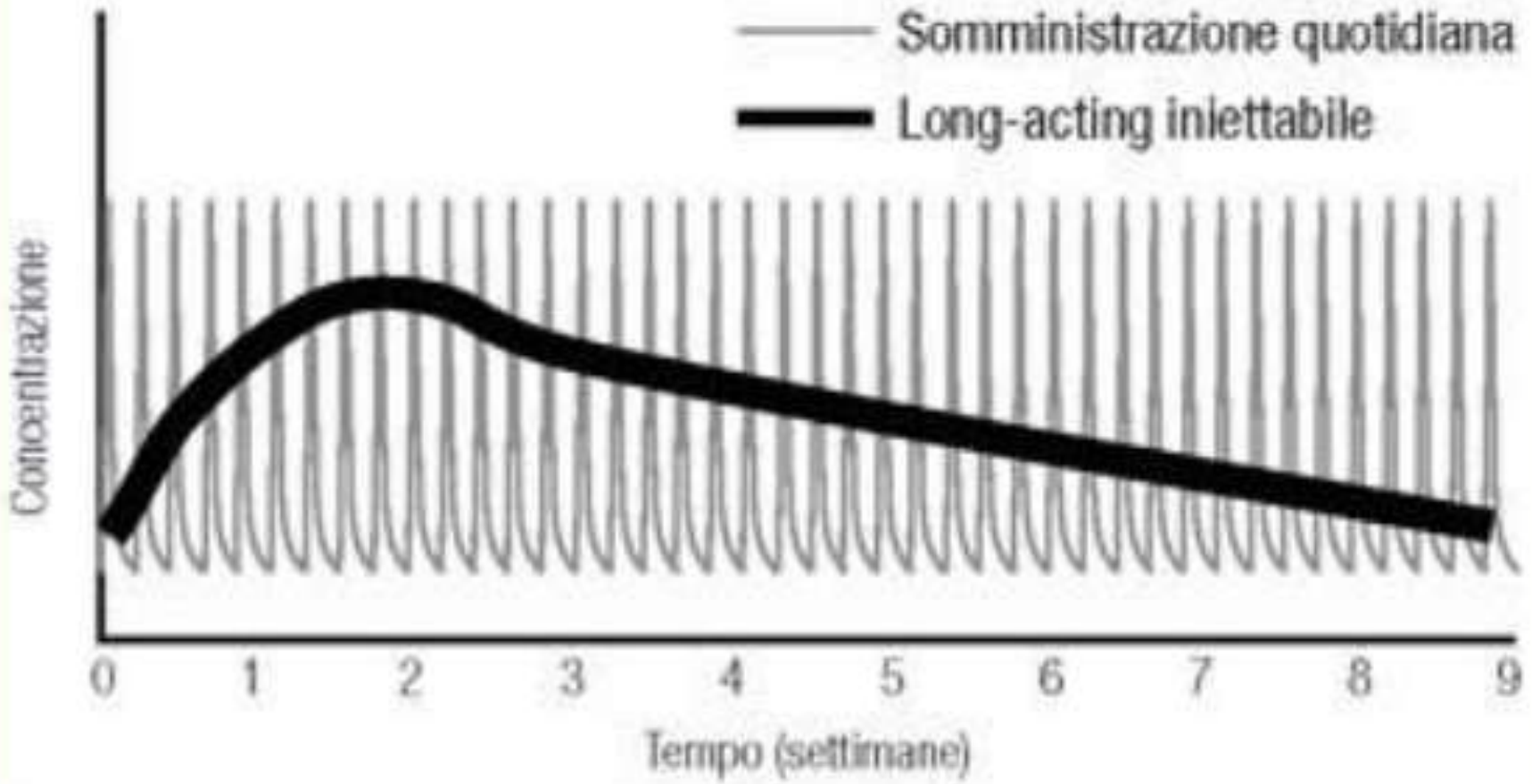
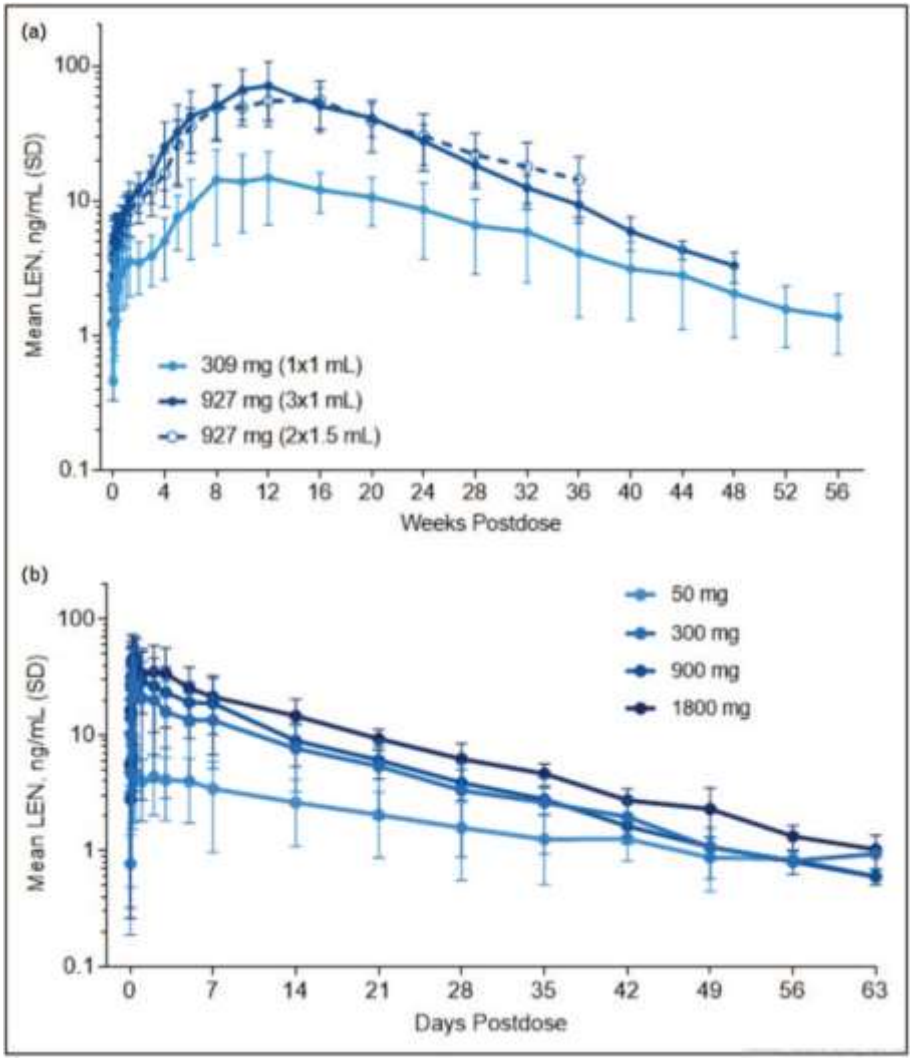


FIGURE 2



[Lenacapavir: a first-in-class HIV-1 capsid inhibitor]

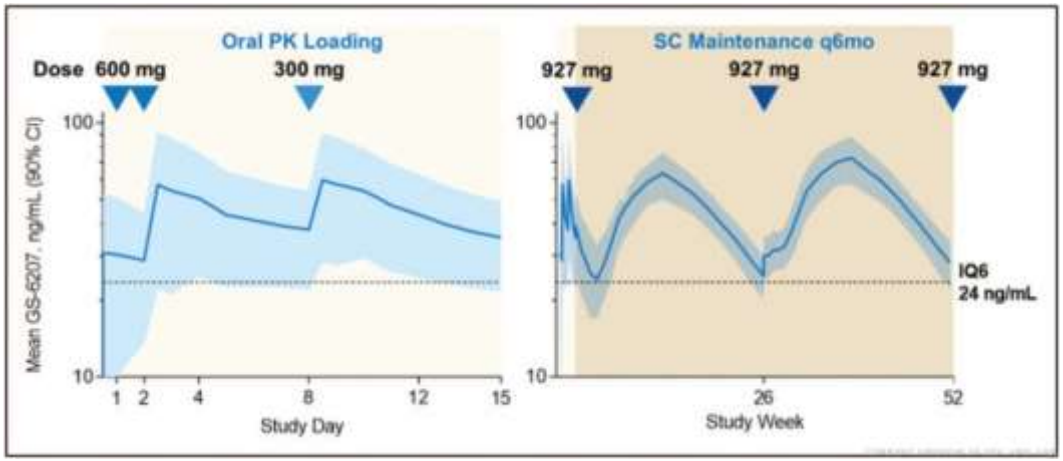
Dvory-Sobol, Hadas; Shaik, Naveed; Callebaut, Christian; Rhee, Martin S.

Current Opinion in HIV and AIDS17(1):15-21, January 2022.

doi: 10.1097/COH.0000000000000713

Observed lenacapavir plasma concentrations following oral (a) and subcutaneous (b) administration. Adapted from [10▪,11▪].

FIGURE 3



Predicted lenacapavir pharmacokinetics for phase 2/3 oral and subcutaneous combination regimens in healthy volunteers. Adapted from [10▪].

Lenacapavir: a first-in-class HIV-1 capsid inhibitor

Dvory-Sobol, Hadas; Shaik, Naveed; Callebaut, Christian; Rhee, Martin S.

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Perché i long acting ?

Per cercare di arginare il decadimento nel tempo dell'aderenza alla terapia, tipico delle patologie croniche …. e HIV (per fortuna !!!) è patologia cronica

Per venire incontro ad una caratteristica peculiare della terapia antiretrovirale : lo stigma , sia reale che percepito

L'uso dei Farmaci in Italia

Rapporto Nazionale

Anno 2023

OSSERVATORIO NAZIONALE SULL'IMPIEGO DEI MEDICINALI

AIFA
AGENZIA ITALIANA DEL FARMACO

Figura 3.2.1d Tempo (in giorni) alla discontinuazione del trattamento con antipertensivi nella popolazione di età ≥45 anni stratificato per sesso, le curve sono aggiustate per età (il modello di Cox è stato utilizzato per la stima delle curve di persistenza). L'area geografica del nord non comprende l'Emilia Romagna.

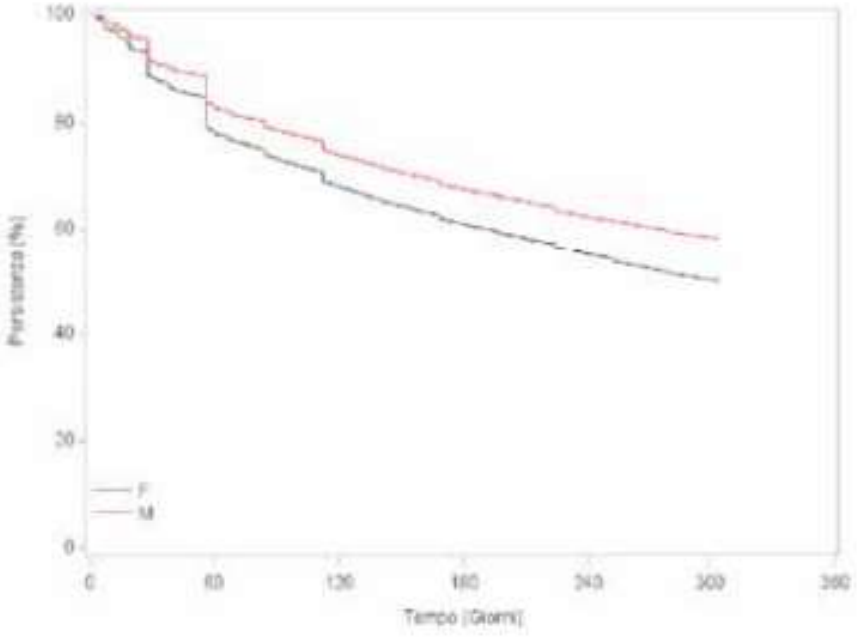
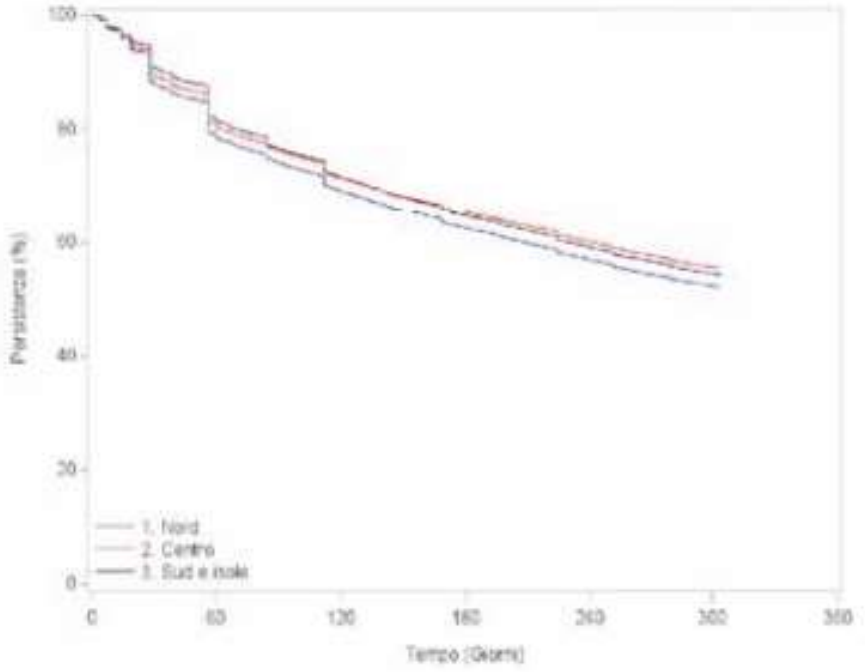
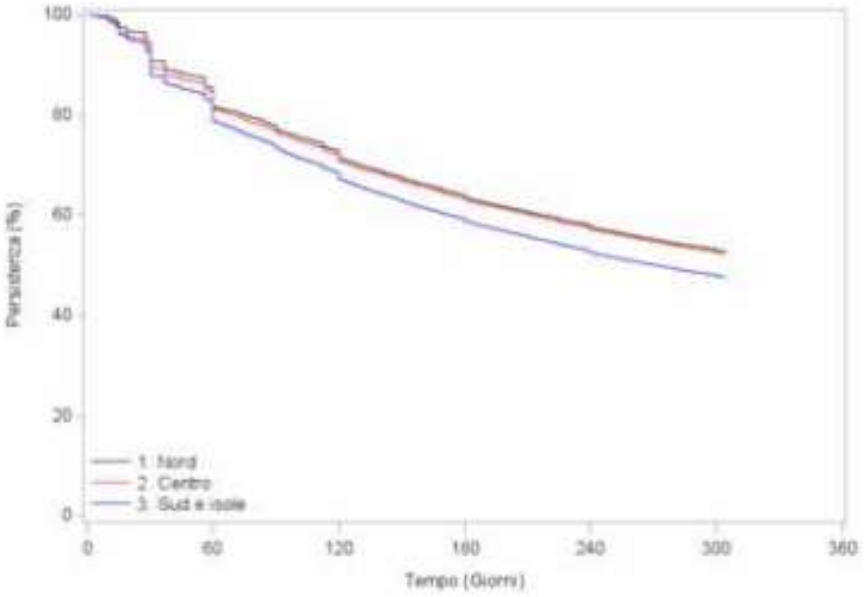


Figura 3.2.1e Tempo (in giorni) alla discontinuazione del trattamento con antipertensivi nella popolazione di età ≥45 anni stratificato per area geografica, le curve sono aggiustate per sesso ed età (il modello di Cox è stato utilizzato per la stima delle curve di persistenza). L'area geografica del nord non comprende l'Emilia Romagna.



antiipertensivi

Figura 3.2.2d Tempo (in giorni) alla discontinuazione del trattamento con ipolipemizzanti nella popolazione di età ≥45 anni stratificato per area geografica, le curve sono aggiustate per sesso ed età (il modello di Cox è stato utilizzato per la stima delle curve di persistenza)



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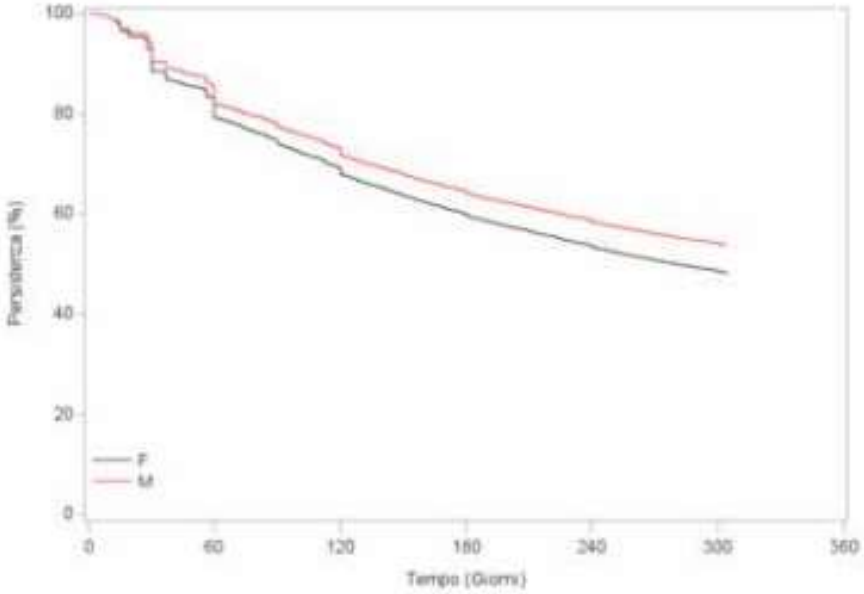


ipolipemizzanti

Figura 3.3.1d Tempo (in giorni) alla discontinuazione del trattamento con antidiabetici nella popolazione di età ≥45 anni stratificato per sesso, le curve sono aggiustate per età (il modello di Cox è stato utilizzato per la stima delle curve di persistenza). L'area geografica del nord non comprende l'Emilia Romagna

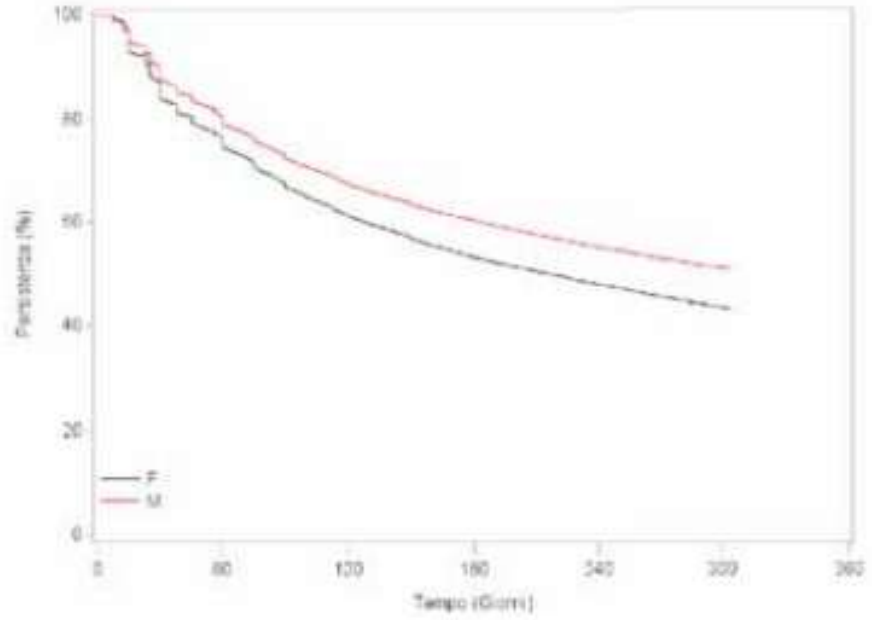
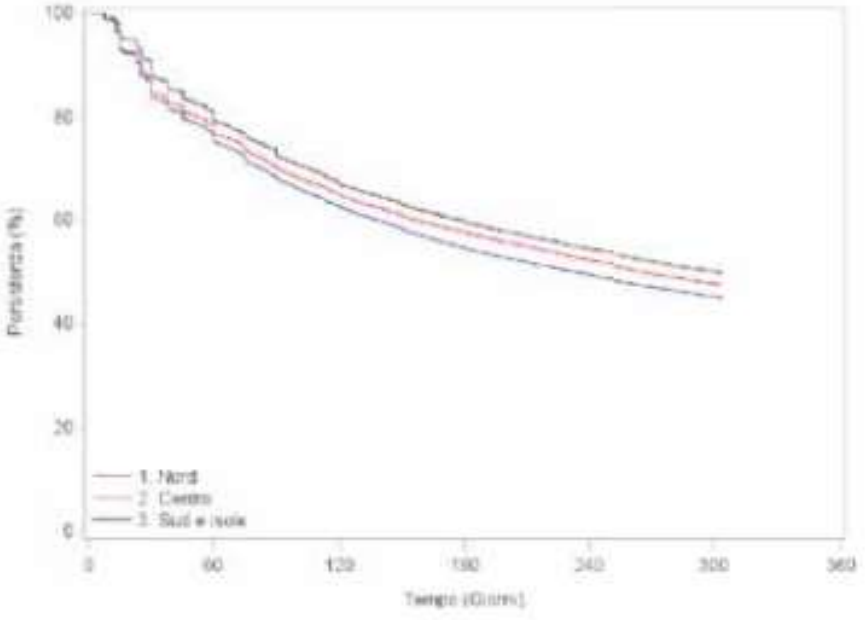
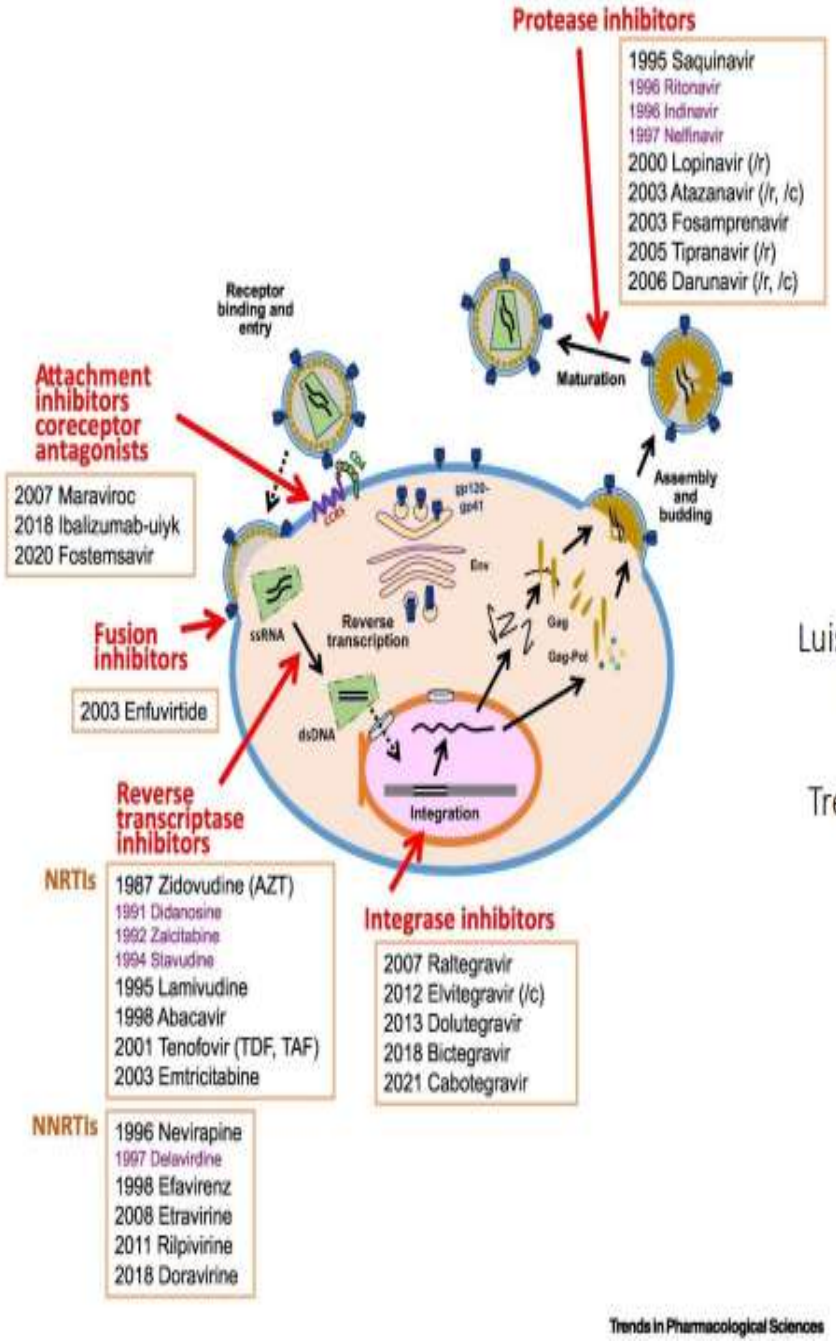


Figura 3.3.1e Tempo (in giorni) alla discontinuazione del trattamento con antidiabetici nella popolazione di età ≥45 anni stratificato per area geografica, le curve sono aggiustate per sesso ed età (il modello di Cox è stato utilizzato per la stima delle curve di persistenza). L'area geografica del nord non comprende l'Emilia Romagna



antidiabetici

CICLO DI REPLICAZIONE VIRALE E TARGET TERAPEUTICI



Luis Menéndez-Arias, Rafael Delgado,
Update and latest advances in antiretroviral therapy,
Trends in Pharmacological Sciences,
Volume 43, Issue 1,
2022

7. *Horizon Scanning* sullo sviluppo di nuove terapie per il trattamento dell'infezione da HIV

Tendenze *nuove* - Numero Speciale 2020

Tabella 2 - Molecole a lunga durata d'azione in sviluppo per la terapia dell'HIV

Classe	Meccanismo d'azione	Somministrazione: tipo e frequenza
MOLECOLE CHIMICHE		
Cabotegravir LA	INSTI	Sospensione di nanocristalli im ogni 2 mesi
Rilpivirina LA	NNRTI	Sospensione di nanocristalli im ogni 2 mesi
Islatravir	NRTTI	Orale settimanale
MK-8504 / MK-8583	NRTI	Orale settimanale
GS-6207 (lenacapavir)	CI	sc ogni 3-6 mesi
GSK '937	MI	Sospensione di nanocristalli im ogni 2-3 mesi
Elsulfavirina	NNRTI	im o sc mensile
Albuvirtide	FI	singola infusione ev settimanale
MOLECOLE BIOLOGICHE		
leronlimab; 3BNC117; 10-1074; PGDM1400; PGT121; 10E8; N6 LS; VR07-523LS	bNAbs EI	ev o s.c somministrati da ogni 1-2 sett. a ogni 2-3 mesi
Combinectin (GSK3732394)	Adnectina EI/FI	sc ogni 2-4 sett.

(Legenda - LA: long acting; INSTI = inibitore dell'integrasi; NRTI:inibitore nucleosidico della trascrittasi inversa; NNRTI: inibitore non nucleosidico della trascrittasi inversa; NRTTI: inibitore nucleosidico della traslocazione della trascrittasi inversa; MI: inibitore della maturazione; FI: inibitore della fusione; EI: inibitore dell'entry; bnAb: anticorpo ampiamente neutralizzante; im: intramuscolare; sc: sottocutaneo; ev: infusione endovenosa)

Tabella 3 - Regimi a due farmaci long-acting in sviluppo per la terapia dell'HIV

Molecole	Meccanismo d'azione	Fase di sviluppo
Elsufavirina	NNRTI + *TBD*	I
GS-6207 (lenacapavir)	CI + *TBD*	I
Albuvirtide+3BNC117	IF+bNAb	II
3BNC117+10-1074	bNAb + bNAb	I
CAB+VRC07-523LS	INSTI+bNAb	II
CAB+N6 LS	INSTI+bNAb	I
CAB+GSK937	INSTI+MI	FTIH
CAB-LA+RPV-LA	INSTI+NNRTI	FDA/EMA submitted

Tabella 4 - Molecole e regimi in sviluppo commercializzabili entro i prossimi 10 anni come molecole *long-acting* (LA) e/o regimi a due soli farmaci (2DR)

Molecola/Regime	Approvazione (*)	Via di sommin.	2DR	LA
DTG/RPV	2019	orale	SI	NO
DTG/3TC	2020	orale	SI	NO
CAB+RPV	2021	orale	SI	SI
Islatravir/doravirina	2023	orale	SI	NO
GS6207 (CI) + tbd	2024	sc	TBD	SI
GSK254 (MI)+ DTG	2025	orale	SI	NO
CAB + N6LS	2027	im - sc	SI	SI
10E8+VR07-523LS	2027-30	ev - sc	SI	SI
Elsulfavirina	2027-30	Im - sc	TBD	SI
Islatravir + tbd	2027-30	orale	SI	SI
Combinectina+tbd	2027-30	sc	SI	SI
GSK937 (MI)+CAB	2027-30	im	SI	SI
GS-9722+PGT-121	2027-30	ev - sc	SI	SI

(*) La previsione di approvazione regolatoria è basata sulle attuali informazioni disponibili e può variare significativamente sulla base dei programmi di sviluppo.

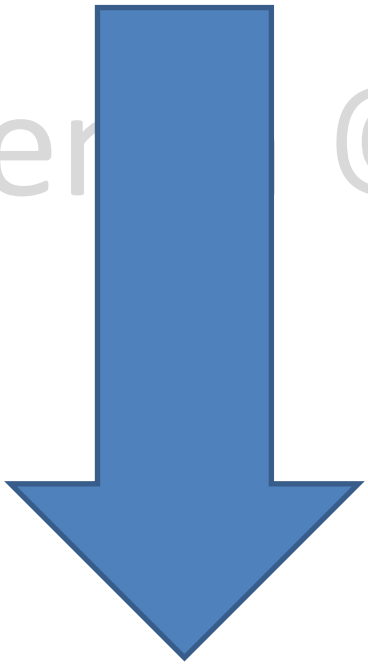
Di cosa parliamo

- Vocabria © + Rekambys ©
- Sunlenca ©

- Non parlerò di PrEP !!!

Di cosa parliamo

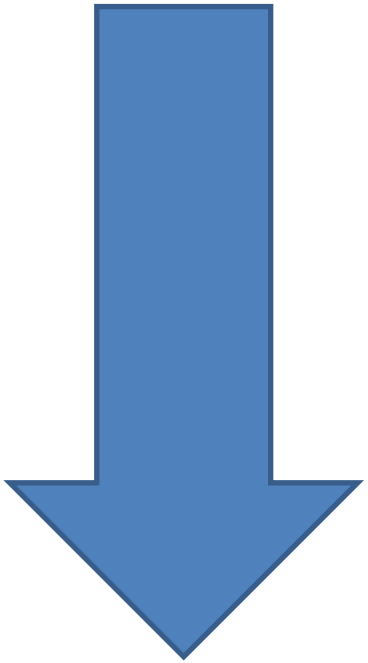
- Vocabria © + Rekambys ©
- Sunlenca ©



Cabotegravir (inibitore integrasi)

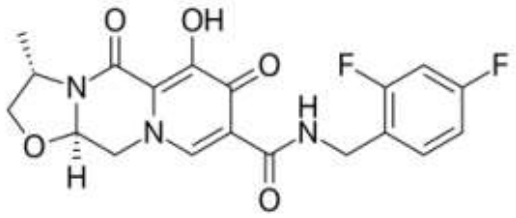
Di cosa parliamo

- Vocabria © + Rekambys ©
- Sunlenca ©



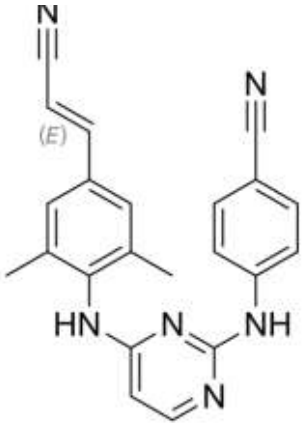
Rilpivirina (inibitore n.n. TrI)

Cabotegravir e Rilpivirina



- INSTI
- Strutturalmente simile a Dolutegravir e Bictegravir
- Formulazione orale (30 mg cp) e iniettabile (600 mg 3 mL)
- Non dovrebbe essere somministrato con rifampicina, rifapentina, carbamazepina, oxacarbazepina, fenitoina o fenobarbital per induzione dell'enzima UGT1A1
- Emivita 41 ore per la formulazione orale; emivita 5,6-11,5 settimane per la formulazione iniettabile
- 99% legato alle proteine plasmatiche
- Inattivazione per glucurorinidazione

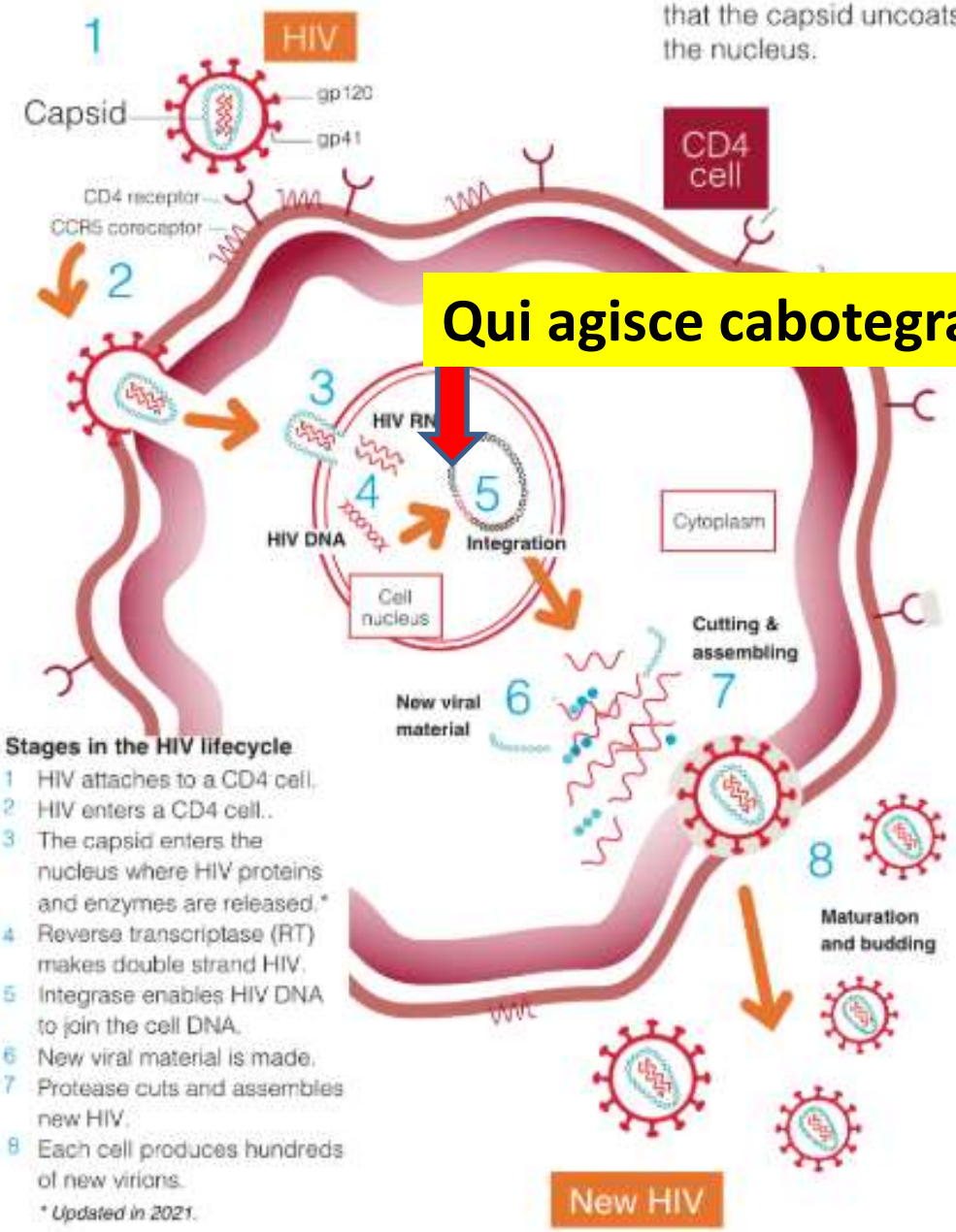
Questo regime terapeutico a due farmaci (CAB-RPV) rappresenta attualmente un'opzione di switch per le persone con HIV (PLWH) virologicamente soppresse, non in gravidanza e non in allattamento, di età superiore ai 18 anni e senza una storia di fallimento virologico o mutazioni associate alla resistenza (RAM), ad eccezione della mutazione NNRTI K103N, se presente da sola



- NNRTI
- Formulazione orale (25 mg cp) e iniettabile (900 mg 3 mL)
- Non dovrebbe essere somministrato con rifampicina, rifapentina, carbamazepina, oxacarbazepina, fenitoina o fenobarbital per induzione dell'enzima CYP3A4

HIV lifecycle (2021)

Note: In March 2021, researchers accepted that the capsid uncoats in the nucleus.

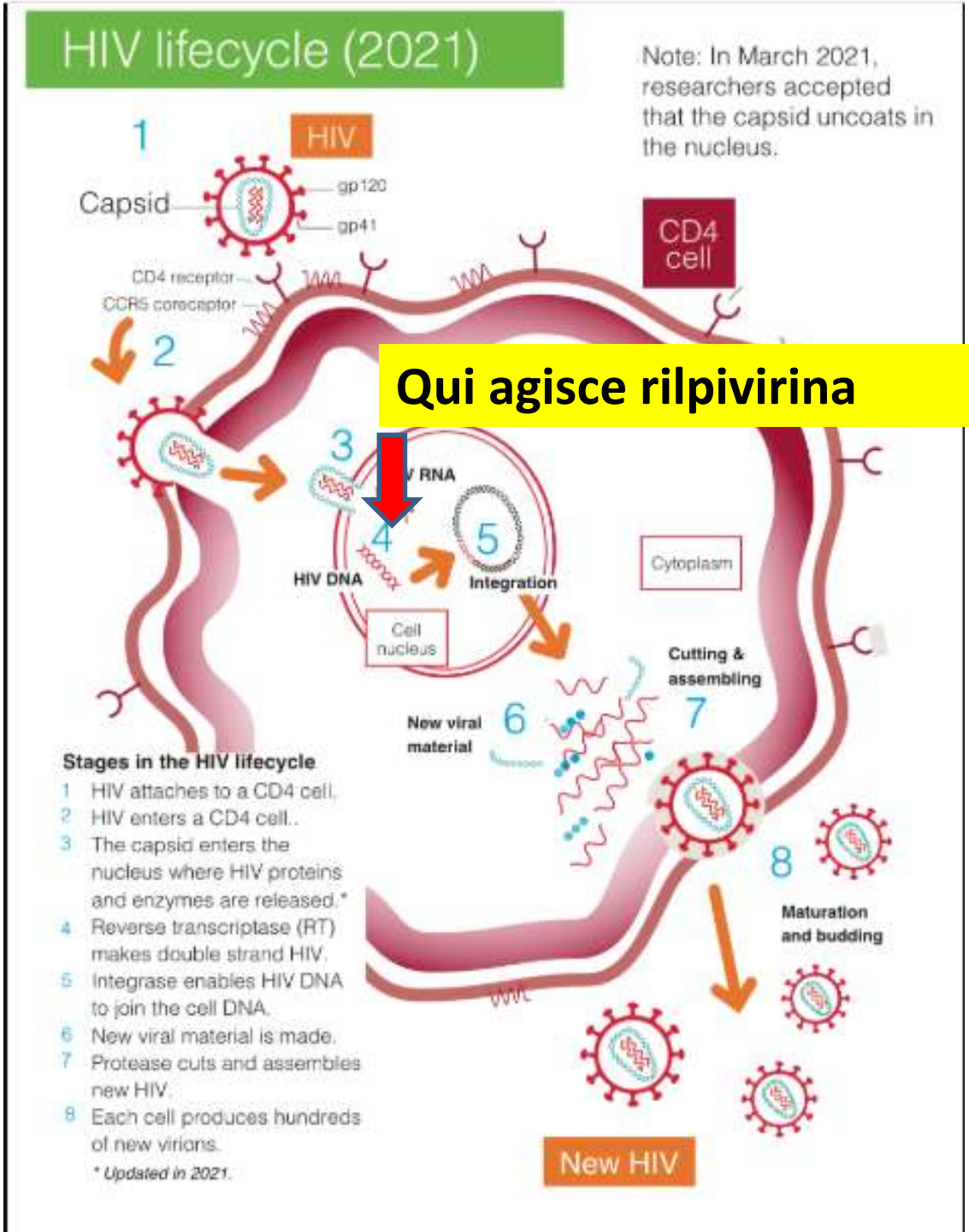


Qui agisce cabotegravir

Stages in the HIV lifecycle

1. HIV attaches to a CD4 cell.
2. HIV enters a CD4 cell..
3. The capsid enters the nucleus where HIV proteins and enzymes are released.*
4. Reverse transcriptase (RT) makes double strand HIV.
5. Integrase enables HIV DNA to join the cell DNA.
6. New viral material is made.
7. Protease cuts and assembles new HIV.
8. Each cell produces hundreds of new virions.

** Updated in 2021.*

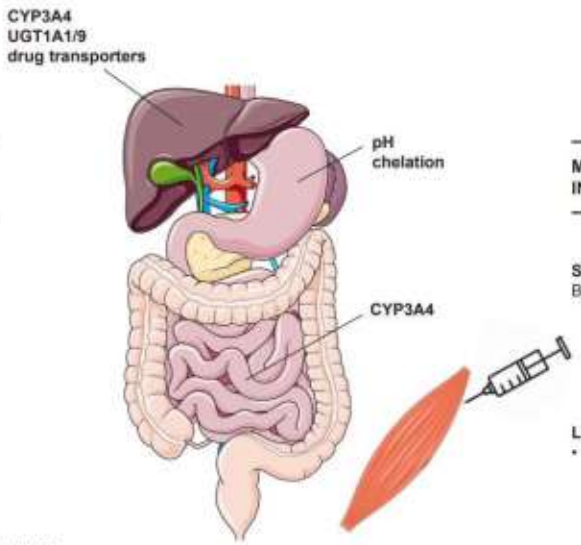

HIV lifecycle (2021)
Note: In March 2021, researchers accepted that the capsid uncoats in the nucleus.
1
HIV
Capsid
gp120
gp41
CD4 receptor
CCR5 coreceptor
CD4 cell
2
Qui agisce rilpivirina
3
V RNA
4
HIV DNA
5
Integration
Cytoplasm
Cell nucleus
Cutting & assembling
7
New viral material
6
8
Maturation and budding
New HIV
Stages in the HIV lifecycle
1 HIV attaches to a CD4 cell.
2 HIV enters a CD4 cell..
3 The capsid enters the nucleus where HIV proteins and enzymes are released.*
4 Reverse transcriptase (RT) makes double strand HIV.
5 Integrase enables HIV DNA to join the cell DNA.
6 New viral material is made.
7 Protease cuts and assembles new HIV.
8 Each cell produces hundreds of new virions.
* Updated in 2021.

Drug-Drug Interactions after Oral and Intramuscular Administration of CAB and RPV

Mechanisms of DDIs after ORAL administration

Stomach/intestine
- Change gastric pH
- Chelation divalent cations
- Inhibition/induction of CYP3A4, drug transporters

Liver
- Inhibition/induction of CYP3A4, UGT1A1/9, drug transporters



Mechanisms of DDIs after INTRAMUSCULAR administration

Stomach/intestine
Bypassed

Liver
- Inhibition/induction of CYP3A4, UGT1A1/9, drug transporters

Adapted from Hodge D et al. Clin Pharmacokinet 2021

Examples of medications interacting with the oral but not the intramuscular administration of RPV

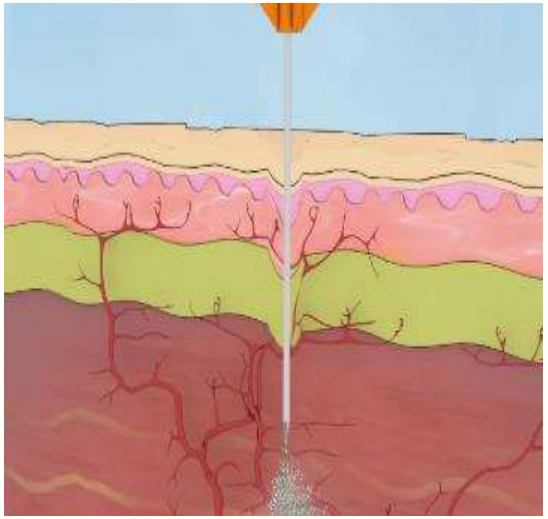
- Antacids
- famotidine
- lansoprazole
- liraglutide
- omeprazole
- orlistat
- pantoprazole
- rabeprazole
- ranitidine

Examples of medications interacting with the oral but not the intramuscular administration of CAB

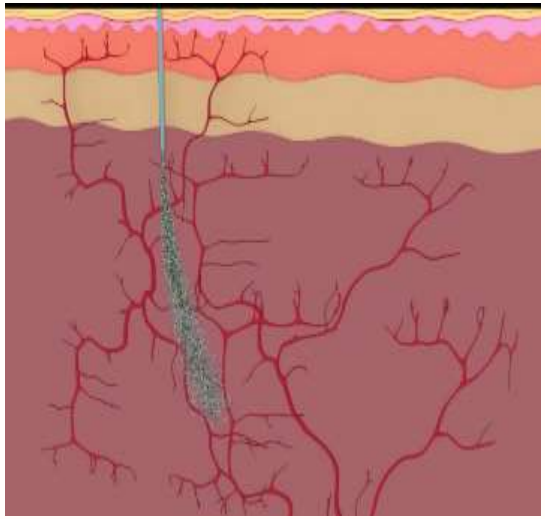
- Antacids
- calcium
- iron
- magnesium
- multivitamins containing divalent cations
- orlistat
- strontium ranelate

CAB + RPV LA formulation allows for monthly or every 2-month dosing

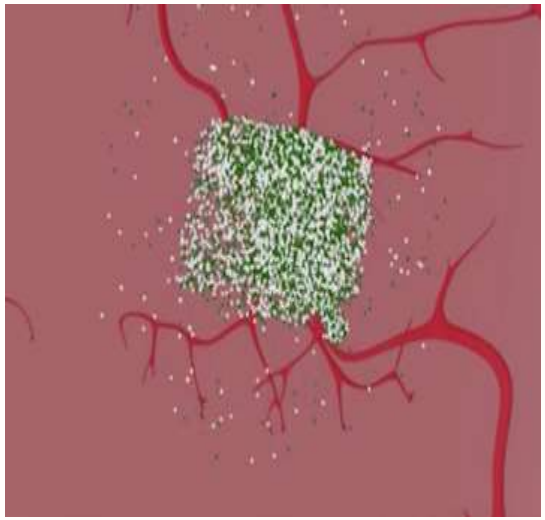
CAB + RPV extended-release suspensions contain finely-milled drug particles suspended in an aqueous vehicle that supports LA dosing:



CAB + RPV LA is administered as separate IM gluteal injection



LA suspension forms a drug depot in the muscle

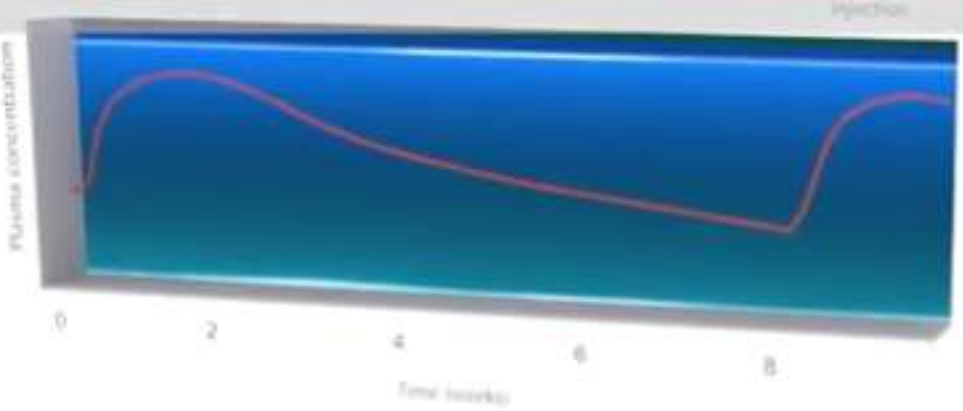


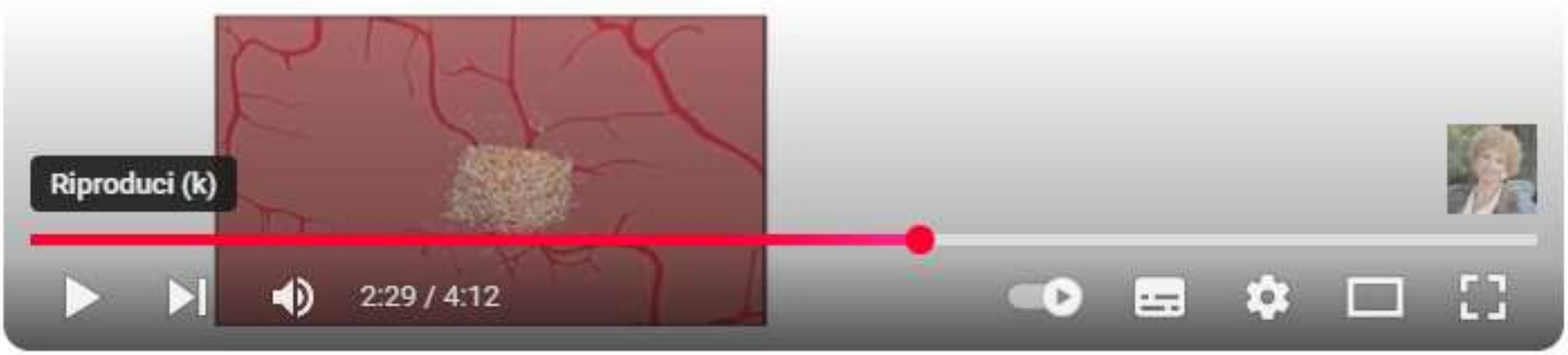
Medications are slowly absorbed from the depot site into the bloodstream

IM, intramuscular

- Trezza C, et al. Curr Opin HIV AIDS 2015;10:239–45

Slow release from the depot yields an absorption-limited half-life of at least 40 days, versus approximately 40 hours when compared with oral dosing of the drugs.[1, 2]





VOCABRIA (cabotegravir) + REKAMBYS (rilpivirine) Mechanism of Action as Long-Acting Regimen for HIV

CAB + RPV LA is recommended by guidelines as a strategy to improve QoL for some people with HIV

DHHS guidelines[1]

"[Consider] switch to a long-acting injectable regimen for convenience, to relieve pill fatigue or to decrease potential stigma or disclosure concerns associated with taking daily oral medications"

IAS–USA guidelines[2]

"Injectable CAB + RPV LA is recommended for persons who experience stigma or other adverse consequences of taking pills daily or in response to strong patient preference"

EACS guidelines[3]

"The objectives of treatment modification should be to improve AEs, facilitate adequate treatment of comorbid conditions and improve QoL. Intramuscular CAB + RPV LA, among other dual therapies, is a recommended switch strategy"

AE, adverse event

1. DHHS. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Sep 2024
2. Gandhi RT, et al. JAMA 2025;333:609–28
3. EACS. Guidelines Version 12.1. Nov 2024

schema

- Si può iniziare assumendo due compresse al giorno per 1 mese oppure inziare subito con le iniezioni, una per ogni gluteo
- Le prime due sono a distanza di un mese, poi ogni 2 mesi
- La “ forchetta “ di somministrazione è di + o – 7 giorni
- In casi selezionati, possibilità di sostituire la puntura con la terapia orale (due compresse al giorno) per 1 mese , poi bisogna ritornare alle iniezioni o cambiare terapia

Cabenuva (CAB IM and RPV IM)	**Cabenuva 600-mg/900-mg kit contains:** • CAB 600-mg/3-mL vial and RPV 900-mg/3-mL vial **Cabenuva 400-mg/600-mg kit contains:** • CAB 400-mg/2-mL vial and RPV 600-mg/2-mL vial	**Optional Lead-in with Oral CAB and RPV** • CAB 30 mg PO and RPV 25 mg PO once daily with food for 4 weeks **Monthly IM CAB and RPV** • Loading dose: CAB 600 mg/3 mL IM × 1 dose and RPV 900 mg/3 mL IM for 1 dose • Continuation phase: CAB 400 mg/2 mL IM every 4 weeks and RPV 600 mg/2 mL IM every 4 weeks **Every 2-Month IM CAB and RPV** • Loading dose: CAB 600 mg/3 mL IM and RPV 900 mg/3 mL IM **once monthly** for 2 doses • Continuation phase: CAB 600 mg/3 mL IM and RPV 900 mg/3 mL IM every 2 months

Oral Lead In

- precauzione per possibili eventi avversi
- 28 giorni di terapia orale
- assunzione con il cibo
- no PPI, no multivitaminici o antiacidi
- opzionale

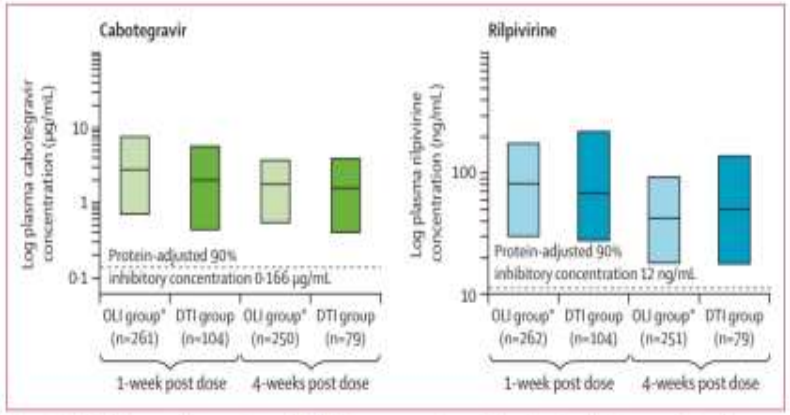


Figure 2: **Initial plasma cabotegravir and rilpivirine concentrations following first injections as DTI and after OLI**

Data are median (5th and 95th percentiles). DTI=direct-to-injection. OLI=oral lead-in. *Historical data: participants who were randomly assigned to receive long-acting cabotegravir plus rilpivirine in the maintenance phase.

Initiation of long-acting cabotegravir plus rilpivirine as direct-to-injection or with an oral lead-in in adults with HIV-1 infection: week 124 results of the open-label phase 3 FLAIR study

Chloe Orkin, Enrique Bernal Morell, Darrell H S Tan, Harald Kastner, Hans-Jürgen Stellbrink, Elena Belonosova, Rebecca DeMoor, Sandy Griffith, Shanker Thiagarajah, Rodica Van Solingen-Ristea, Susan L Ford, Herta Crauwels, Parul Patel, Amy Cutrell, Kimberly Y Smith, Kati Vandermeulen, Eileen Birmingham, Marty St Clair, William R Spreen, Ronald D'Amico

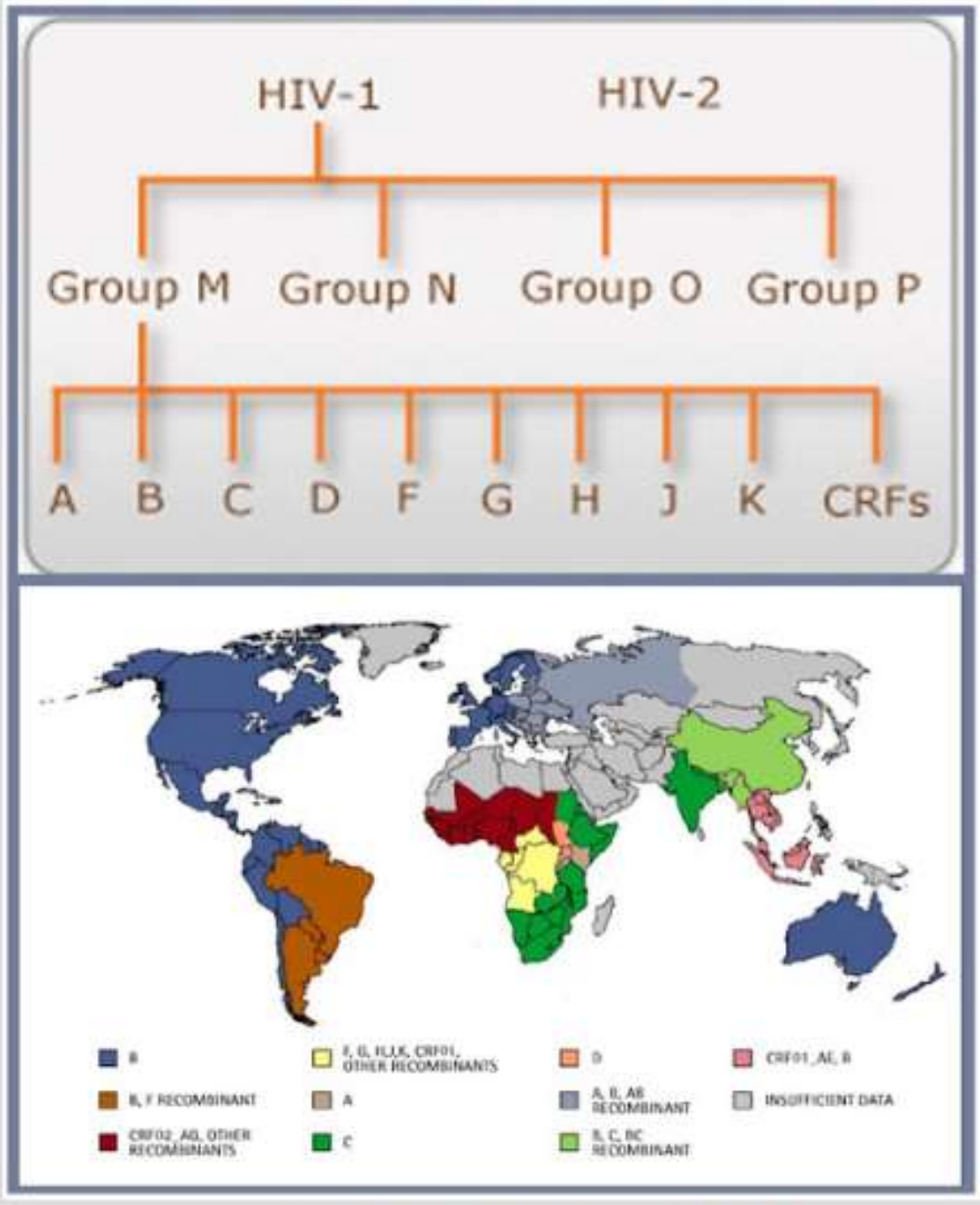
There were no drug-related hypersensitivity reactions and no significant creatinine changes from baseline for the extension switch or randomly assigned long-acting groups since the week 96 analysis. There were no clinically significant changes in lipase concentration in the extension switch population (from extension baseline) or the randomly assigned long-acting group; no lipase abnormalities were associated with clinical pancreatitis diagnoses. One (1%) participant in the direct-to-injection group, one (1%) in the oral lead-in group, and two (1%) in the randomly assigned long-acting group (since the week 96 analysis) had alanine aminotransferase concentrations three or more times higher than the upper limit of normal (single episodes each). No participants in the oral lead-in or direct-to-injection groups and only one (<1%) participant in the randomly assigned long-acting group met protocol-defined liver stopping criteria. This participant met liver stopping criteria at week 124 due to secondary syphilis

Chi può andare a tale terapia ?

- Soppressione (HIV – RNA < 50 copie / ml) per almeno 6 mesi …. (quindi non può essere la prima terapia)
- Avere il proprio virus HIV che non presenti una farmacoresistenza ai farmaci (o alla classe di farmaci) che andremo a utilizzare
- non avere evidenziato una intolleranza / tossicità alla rilpivirina
- Volerlo …….

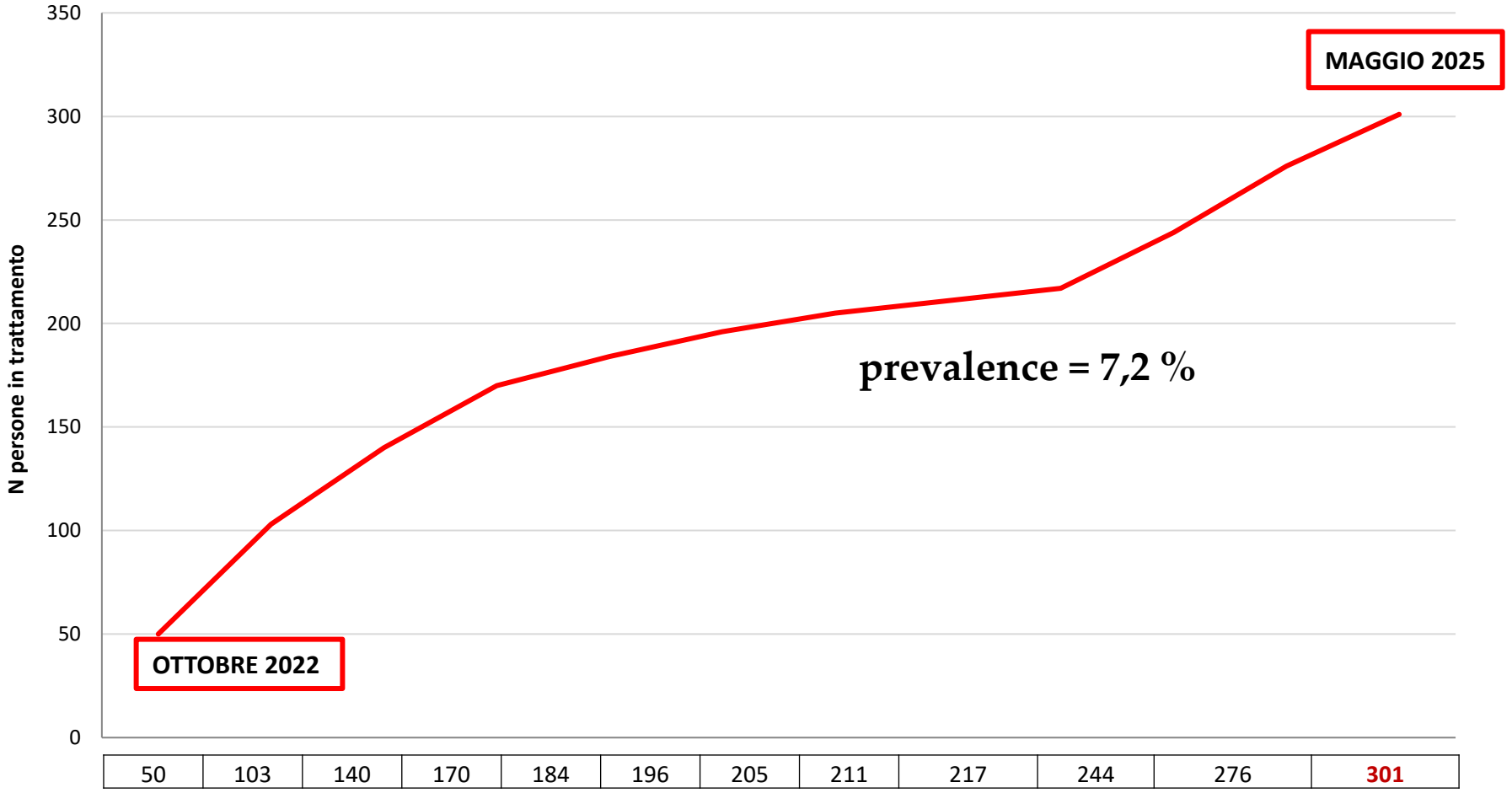
Chi non può / potrebbe andare a tale terapia ?

- Se donna, non essere in gravidanza o in un progetto di gravidanza
- Avere la coinfezione HBV (epatite B)
- Essere eccessivamente sovrappeso
- Avere protesi glutee
- Difficoltà a recarsi ogni 2 mesi in ospedale per le iniezioni (non si possono fare da soli)
- Avere un sottotipo HIV A1 / A6
- Avere un BMI $\geq$ 30 kg/m 2

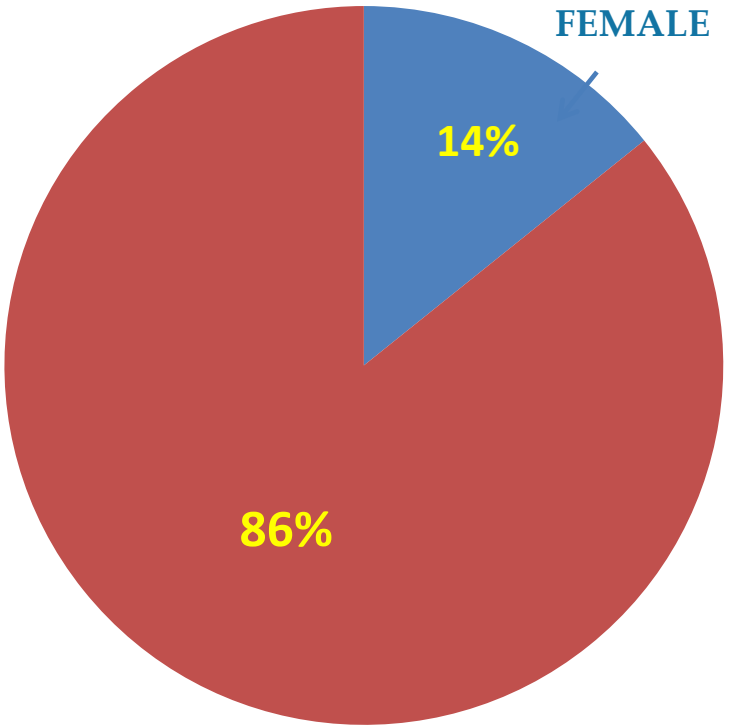


Albero filogenetico e distribuzione dei vari sottotipi di HIV

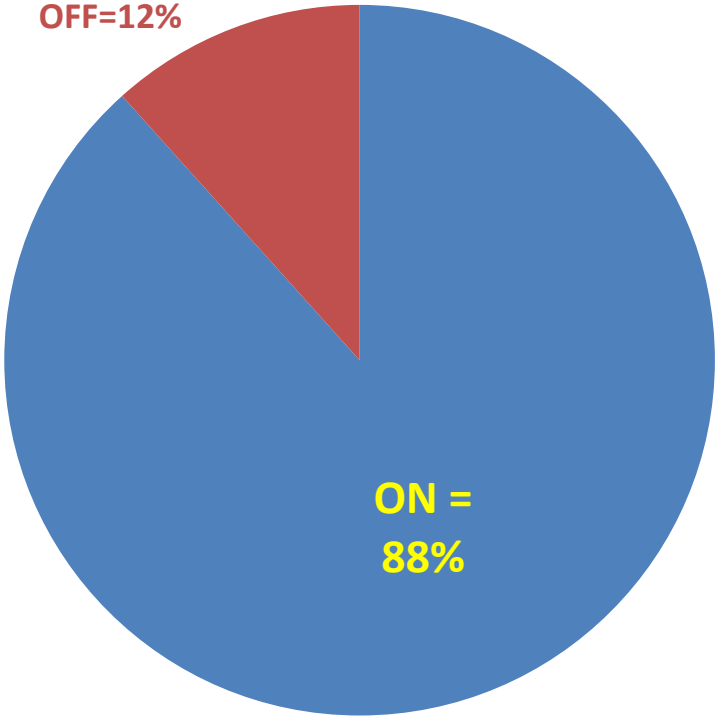
Starting L.A. - Cumulative trend



Sex at birth



Treatment OFF/ON

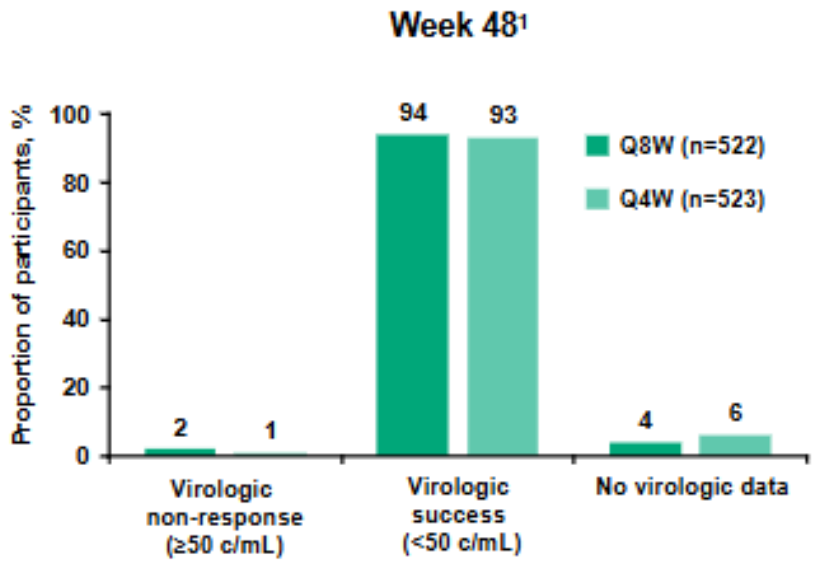


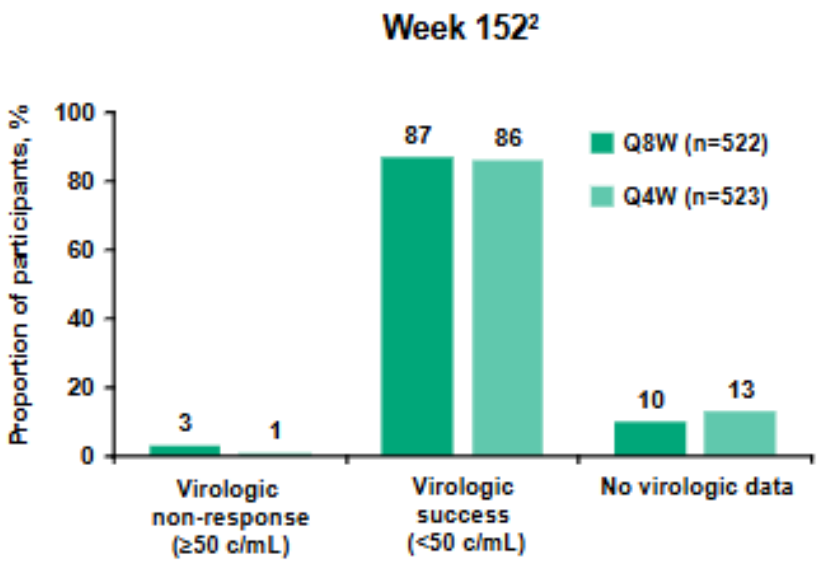
Situazione attuale

- **338 trattamenti avviati**
- **53 sospensioni , per tutte le cause (15,6 %)**

Efficacia / durabilità

ATLAS-2M: Virologic outcomes at Weeks 48 and 152

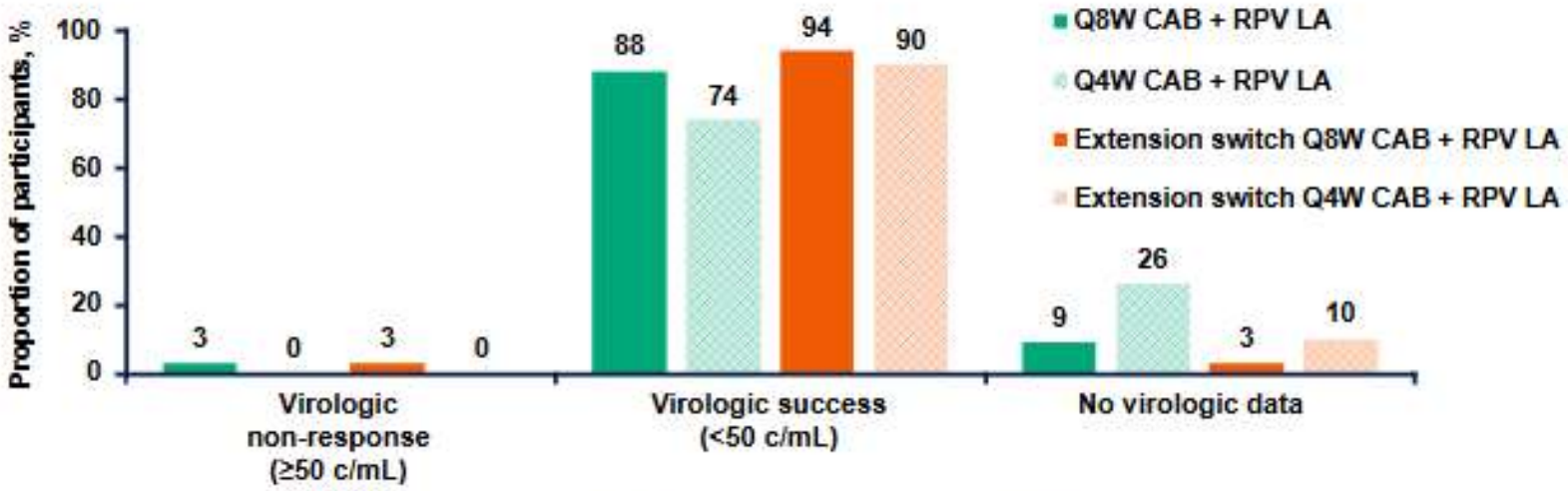




CAB + RPV LA dosed Q8W or Q4W achieved a high rate of virologic suppression through to Week 152

1. Overton ET, et al. Lancet 2021;396:1994–2005
2. Overton ET, et al. Clin Infect Dis 2023;76:1668–54

LATTE-2: Virologic Snapshot outcomes at Week 256



- 81% of participants randomized to CAB + RPV LA at Day 1, and 93% of participants who switched from oral CAB + ABC/3TC at Week 100 maintained virologic suppression at Week 256
- No participants met the PDVF criterion after Week 48

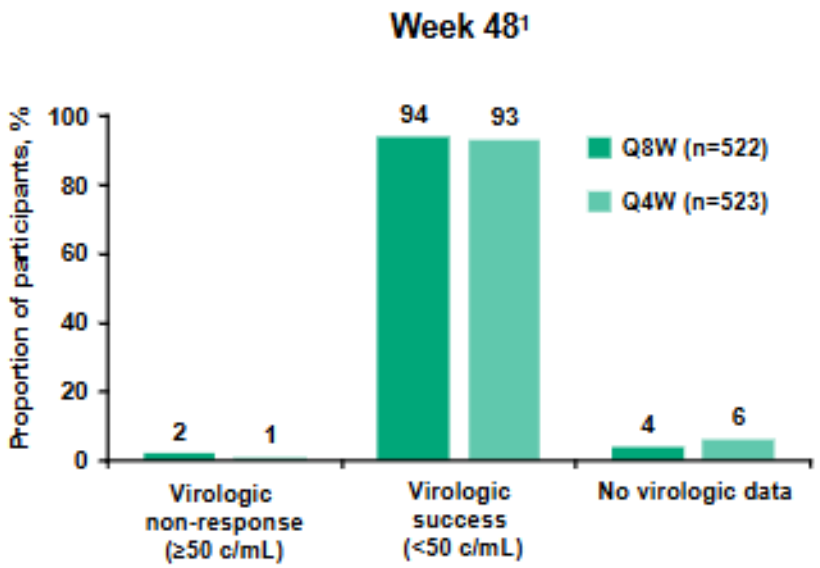
Smith GHR, et al. Open Forum Infect Dis 2021;8:ofab439

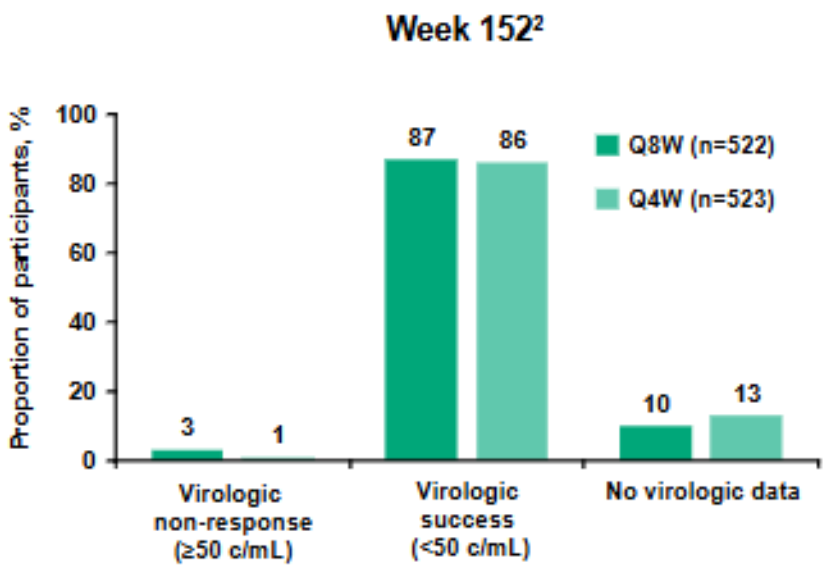
LATTE-2 Week 256 conclusions

- CAB + RPV LA, dosed both Q4W and Q8W, demonstrated durable antiviral activity through ~5 years of treatment in virologically suppressed participants randomized to LA therapy[1]
  - At Week 256, 81% of participants randomized to LA therapy at Day 1 and 93% of participants who switched from oral CAB + ABC/3TC at Week 100 maintained virologic suppression (HIV-1 RNA <50 c/mL)[1]
  - No participants had PDVF after Week 48 in any treatment arm, demonstrating the durability of CAB + RPV LA as maintenance therapy[1]
- CAB + RPV LA continues to be well tolerated through 5 years of treatment for both dosing regimens[1]
- ISRs, whilst frequent, were mostly mild or moderate in severity and resolved within a median of 2–3 days[1]
- CAB + RPV LA is therefore a potential therapeutic alternative to daily oral ART that may help address challenges such as stigma, drug/food interactions, pill burden, and adherence[1,2]

1. Smith GHR, et al. Open Forum Infect Dis 2021;8:ofab439
2. Smith G, et al. IDWeek 2020. Poster 636

ATLAS-2M: Virologic outcomes at Weeks 48 and 152





CAB + RPV LA dosed Q8W or Q4W achieved a high rate of virologic suppression through to Week 152

1. Overton ET, et al. Lancet 2021;396:1994–2005
2. Overton ET, et al. Clin Infect Dis 2023;76:1646–54

De-stigmatizzante

CARISEL: Participants perceive CAB + RPV LA to be less stigmatising than daily oral BIC/FTC/TAF

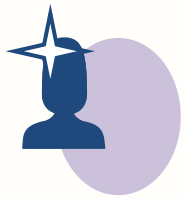
'agreed' or 'completely agreed' that CAB + RPV LA is **less stigmatising** than oral medication*

'agreed' or 'completely agreed' that they would **recommend** CAB + RPV LA to other people living with HIV†

*Proportion of participant responses are as follows (n=376): Completely agree, 36.5%; agree, 24.5%; neutral, 13.0%; disagree, 1.1%; completely disagree, 1.3%; missing, 1.1%
†Proportion of participant responses are as follows (n=375): Completely agree, 71.7%; agree, 19.8%; neutral, 4.0%; disagree, 0.3% completely disagree, 0.3%; missing, 1.1%

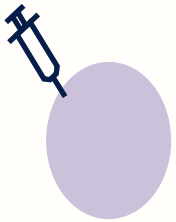
Tollerabilità, il vero problema

ATLAS, FLAIR, and ATLAS-2M: Frequently reported AEs* at Week 48



Headache[1,2]

Pyrexia[1,2]



ISRs[1,2]

<2%
(n=23/1,636†) of participants discontinued due to injection-related reasons[3,4]

98%
(n=9,196/9,322) of ISRs were mild-to-moderate and declined over time[3,4]

3 days median duration[3,4]

*Very common, ≥10%; please refer to the SmPCs for the full list of adverse reactions
†ATLAS n=308; FLAIR n=283; ATLAS-2M n=1,045
ISR, injection site reaction; **SmPC,** Summary of Product Characteristics

1. Vocabria EU SmPC. Sep 2022; **2.** Rekambys EU SmPC. Sep 2022
3. Rizzardini G, et al. J Acquir Immune Defic Syndr 2020;85:498–506 (and suppl. appendix)
4. Overton ET, et al. Lancet 2021;396:1994–2005

Effetti collaterali più comuni di Cabotegravir Rilpivirina:

- generalmente ben tollerato
- reazioni nel sito di iniezione (dolore nel sito di iniezione, arrossamento e gonfiore; ma anche noduli, indurimento, lividi, prurito)
- addestramento dei pazienti ad applicare ghiaccio sul sito di iniezione, o impacchi caldi, assunzione di antidolorifici
- la reazione si risolve in alcuni giorni (durata mediana di 3 gg)
- cefalea, disturbi del sonno, vertigini, febbre, astenia, rash cutaneo

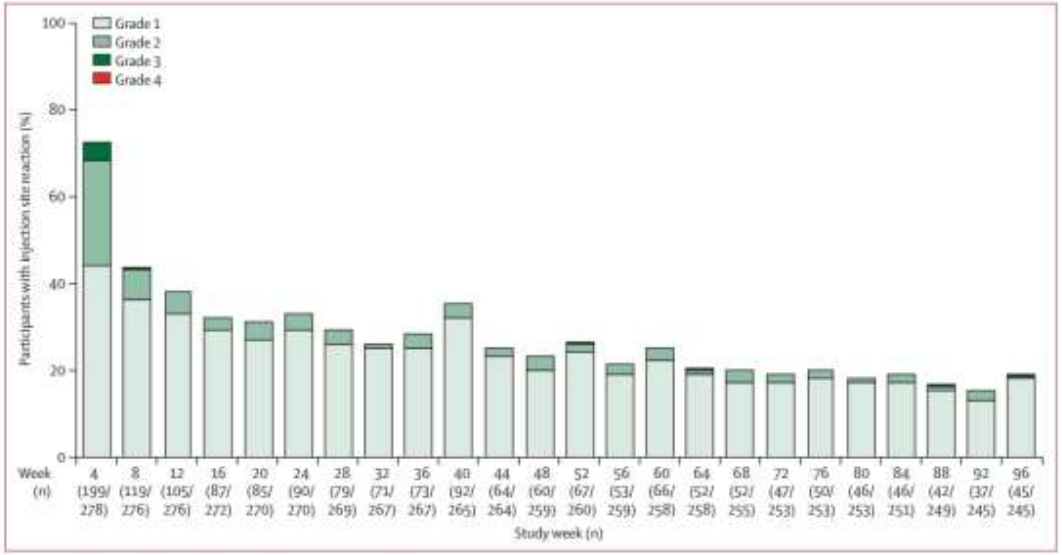


Figure 2: **Injection site reaction incidence over time through week 96**
Incidence is derived relative to the number of participants who received injections at each respective study visit. There were no grade 4 injection site reactions.

P 066

Causes of discontinuation of long acting cabotegravir and rilpivirine in clinical practice. Results from the prospective multicenter SCOLTA cohort.

Lucia Taramasso (1), Nicola Squillace (2), Elena Ricci (3), Sergio Ferrara (4), Giancarlo Orofino (5), Eleonora Sarchi (6), Emanuele Pontali (7), Giovanni Cenderello (8), Giovanni Francesco Pellicanò (9), Filippo Lagi (10), Elena Salomoni (11), Olivia Bargiacchi (12), Maria Aurora Carleo (13), Luigi Pusterla (14), Salvatore Martini (15), Rita Bellagamba (16), Giordano Madeddu (17), Giuseppe Vittorio De Socio (18), Barbara Menzaghi (19), Goffredo Angioni (20), Katia Falasca (21), Antonio Cascio (22), Antonio Di Biagio (1,23) and Paolo Bonfanti (2) for the CISAI study group.

1 Infectious Disease Clinic, IRCCS Ospedale Policlinico San Martino di Genova, Italy; 2 Infectious Disease Unit, Fondazione IRCCS San Gerardo dei Tintori, Monza - University of Milano-Bicocca, Monza, Italy; 3 Fondazione ASIA, Milan, Italy; 4 Unit of Infectious Diseases, Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy; 5 Unit of Infectious Diseases, "Divisione A", Amedeo di Savoia Hospital, Torino, Italy; 6 Infectious Diseases Unit, S.Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy; 7 Department of Infectious Diseases, Galliera Hospital, Genoa, Italy; 8 Infectious Diseases Department, Sanremo Hospital, Sanremo, Italy; 9 Unit of Infectious Diseases, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; 10 AOU Infectious and Tropical Diseases, Careggi Hospital, Florence, Italy; 11 SOC I USL CENTRO FIRENZE, Unit of Infectious Diseases, Santa Maria Annunziata Hospital, Florence, Italy; 12 Unit of Infectious Diseases, Ospedale Maggiore della Carità, Novara, Italy; 13 Infectious Diseases and Gender Medicine Unit, Cotugno Hospital, AO dei Colli, Naples, Italy; 14 Infectious Diseases Unit, Ospedale S. Anna, Como, Italy; 15 Department of Infectious Disease, University of Campania Luigi Vanvitelli, Naples, Italy; 16 Clinical and Research Infectious Diseases Department, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy; 17 Unit of Infectious Diseases, Department of Medicine, Surgery and Pharmacy, University of Sassari, Italy; 18 Unit of Infectious Diseases, Santa Maria Hospital, Perugia, Italy; 19 Unit of Infectious Diseases, ASST della Valle Olona – Busto Arsizio (VA), Italy; 20 Infectious Diseases Unit, SS Trinità Hospital, Cagliari, Italy; 21 Clinic of Infectious Diseases, Department of Medicine and Science of Aging, G. D'Annunzio University, Chieti-Pescara, Chieti, Italy; 22 Unit of Infectious Diseases, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy; 23 Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy.

Periodo di osservazione media di 10 mesi,

34 persone (9 %) su 377 interrompono (

24 per eventi avversi)

Table 2. Adverse events leading to discontinuation of long-acting therapy with cabotegravir/rilpivirine in SCOLTA cohort.

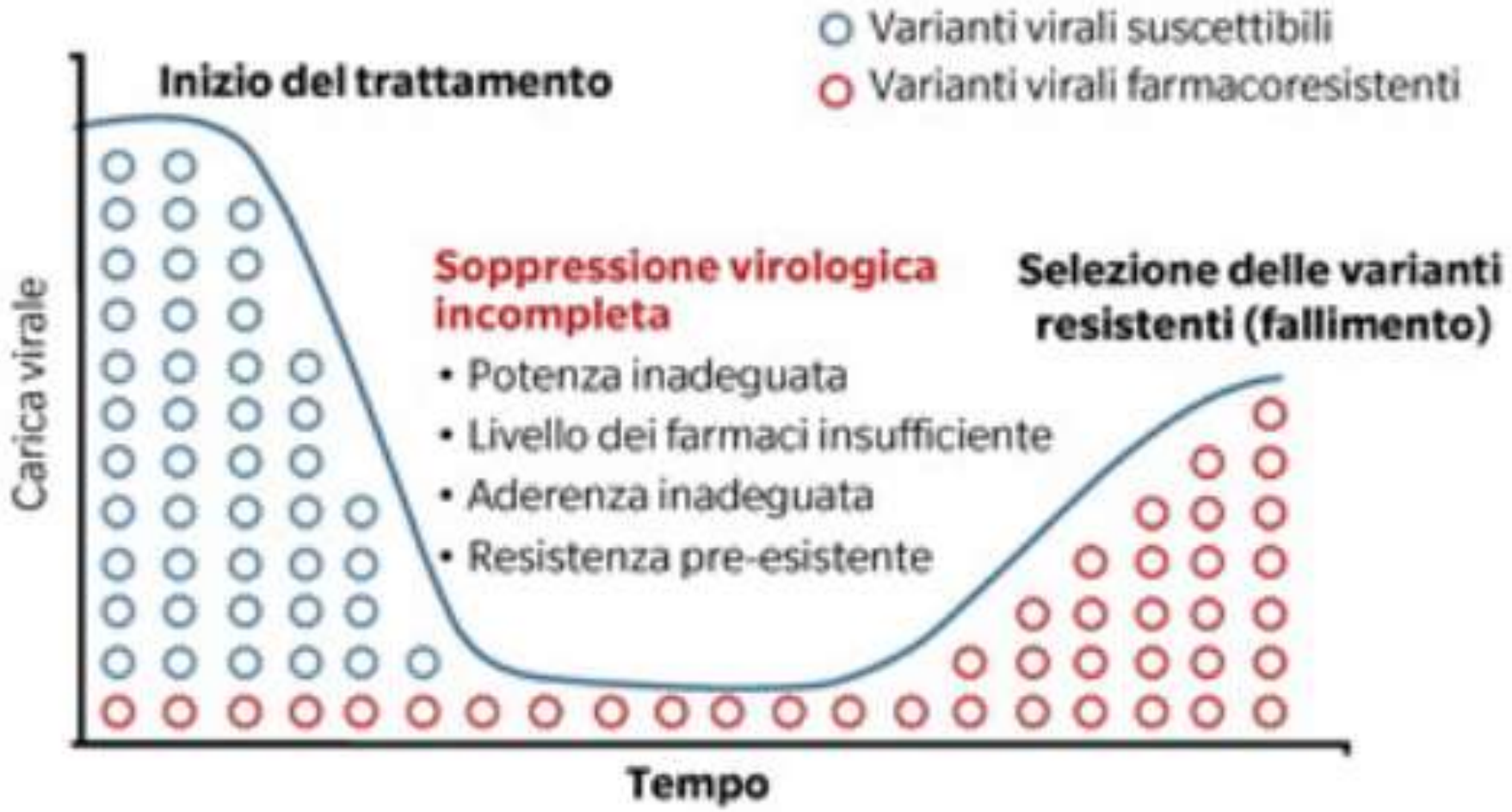
	Sex at birth, Age	Previous regimen	Pain/local reaction	Fever	Other	Causal correlation with therapy	Days since first injection
1	F, 59	3TC/DTG	Yes, G 3	No	No	Certain	132
2	M, 67	3TC/DTG	Yes, G 2	Yes, G 2	No	Certain	56
3	M, 55	RPV/DTG	Yes, G 2	No	No	Certain	29
4	M, 40	RPV/DTG	Yes, G 2	No	No	Certain	28
5	M, 61	RPV/DTG	Yes, G 2	No	No	Certain	56
6	F, 54	FTC/TAF/BIC	Yes, G 2	No	No	Certain	445
7	M, 55	FTC/TAF/RPV	Yes, G 1	No	No	Certain	64
8	M, 35	FTC/TAF/BIC	No	Yes, G 3	No	Certain	112
9	M, 44	RPV/DTG	No	Yes, G 2	Arthromyalgia, G 2	Possibile	87
10	M, 49	3TC/DTG	No	Yes, G 2	No	Probable	1
11	M, 32	3TC/DTG	No	Yes, G 1	No	Unlikely	94
12	F, 65	RPV/DTG	No	Yes, G 1	No	Possible	181
13	M, 56	3TC/ABC/RPV	No	No	difficulty walking, G 3 ; weight gain, G 1	Unlikely for both	87
14	M, 46	RPV/DTG	No	No	Arthromyalgia, G NA	Certain	30
15	M, 59	FTC/TAF/BIC	No	No	Arthromyalgia, G 1	Probable	19
16	M, 51	RPV/DTG	No	No	Rash, G 2	Possible	140
17	M, 31	FTC/TAF/BIC	No	No	Arthromyalgia, G 4	Certain	63
18	M, 54	FTC/TAF/RPV	No	No	Acute pancreatitis, G 4	Probable	67
19	M, 66	FTC/TAF/RPV	No	No	Glycaemic decompensation, G 3	Possible	98
20	F, 41	FTC/TAF/BIC	No	No	Migraine, G 2	Certain	31
21	M, 62	FTC/TAF/BIC	No	No	Hepatitis, G 3	Probable	92
22	F, 62	3TC/DTG	No	No	Rash, G 3	Possible	143
23	M, 50	FTC/TAF/BIC	No	No	Altered emotionality, G 3	Probable	339
24	F, 58	RPV/DTG	NA	NA	NA	NA	283

La resistenza,il vero dramma

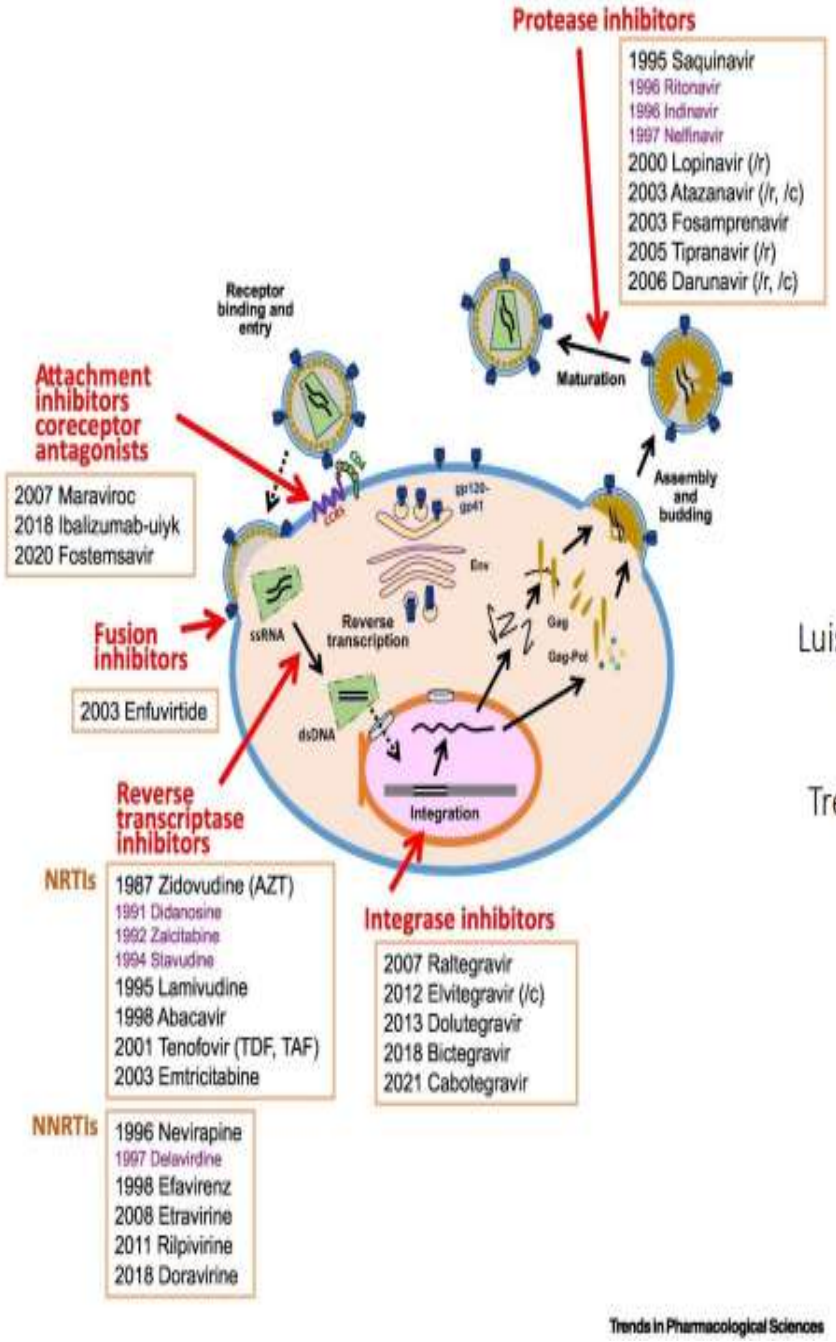
Qual è il vero dramma che dobbiamo evitare ?

- **Indurre farmacoresistenze !!**
- **A causa di un regime che non riesce a mantenere la soppressione**
- **Se compaiono resistenze a cabotegravir, c'è il rischio di rendere inutilizzabili tutti gli altri farmaci della stessa classe , ossia quella importantissima degli INSTI**

FIG. 2 Sviluppo della farmacoresistenza di HIV



CICLO DI REPLICAZIONE VIRALE E TARGET TERAPEUTICI



Luis Menéndez-Arias, Rafael Delgado,
Update and latest advances in antiretroviral therapy,
Trends in Pharmacological Sciences,
Volume 43, Issue 1,
2022

COMBINE-2 C2C: High effectiveness, persistence and adherence to CAB + RPV LA in a large pan-European cohort

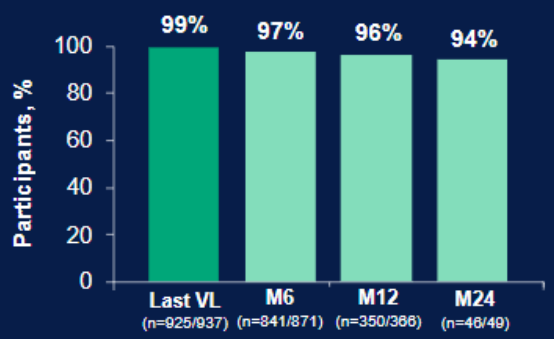
Study population and design

CAB + RPV LA in virologically suppressed* people with HIV (N=956)

- **Median (IQR) age:** 45 (37–53) years
- **≥50 years:** 36%
- **Male:** 85%
- **BMI ≥30 kg/m²:** 10%

Effectiveness

Participants with HIV-RNA <50 c/mL



0.3% (3/956)

on CAB + RPV LA experienced CVF† with NNRTI and/or INSTI resistance

0.5% (5/956) experienced CVF overall;
4/5 resuppressed on PI or INSTI-based regimens‡

- **Virologic suppression and CVF rates were consistent across BMI categories (<30 vs ≥30 kg/m²)**
  Virologic suppression: 99% vs 99%; CVF: 0.5% vs 0%

Persistence and adherence

- **High persistence**

92% (882/956)

of participants remained on CAB + RPV LA with a median (IQR) follow-up of 10.2 (7.1–16.6) months

- **High adherence**

96% (919/956)

of participants had **on-time** injections, 3% had delayed injections and 1% missed injections

*HIV VL <50 c/mL; †Defined as two VL ≥200 c/mL or one VL ≥200 c/mL plus discontinuation; ‡Data unavailable for one individual

13th IAS Conference on HIV Science; July 13-17, 2025; Kigali, Rwanda

Pozniak et al. IAS 2025; Kigali, Rwanda. Poster EP0171

NX-IT-DLL-PPT-250009

CAB+RPV LA: High effectiveness, good tolerability and safety profile among older people with high prevalence of comorbidities and polypharmacy

IAS 2025

Kuretski et al[1]

Follow-up (FU) time NR

181 aged ≥50 years,
including 42 (23%) with ≥65 years

- 68% multimorbidity*
- 68% polypharmacy†
- Mean 20 years since diagnosis

Key results through M11

- → 97% virologically suppressed
- → 3 Virological failures
- → 99% adherence to injections (n=1,998)
- → 4% discontinued due to ISRs§

RELATIVITY[2]

Month 11

154 aged >60 years

- 70% comorbidities
- Median 22 years since diagnosis

Key results

- → ≥ 90% virologically suppressed
- → 0 Virological failures
- → 1.3% discontinued due to ISRs§

GEPPO[3]

Median FU: 17.3 months
(CI 95%: 16.7-17.6)

78 aged >65 years

- 62% multimorbidity*
- 32% polypharmacy†
- Median 20 years since diagnosis

Key results

- → 100% virologically suppressed
- → 0 Virological failures
- → 92% remained on CAB+RPV LA, 13% with >5 years on treatment

*Multimorbidity defined as ≥2 conditions in Kuretski, ≥3 comorbidities in GEPPO
†Polypharmacy defined as ≥5 medications in Kuretski and GEPPO
§In Kuretski, 45% discontinued CAB+RPV LA, mostly due to relocation (19%) and loss to follow-up (4.4%); in RELATIVITY, 5.2% discontinued CAB+RPV LA, mostly due to other reasons not specified (2.6%)

1. Kuretski J et al. IAS 2025. Poster EP0076
2. Troya J, et al. IDWeek 2024. Poster P561
3. Calcagno A, et al. CROI 2025. Poster 877

Di cosa parliamo

- Vocabria © + Rekambys ©
- Sunlenca ©

Farmaco di “ nicchia”

4.1 Indicazioni terapeutiche

Sunlenca iniettabile, in associazione con altri antiretrovirali, è indicato per il trattamento degli adulti con infezione da HIV-1 multifarmaco-resistente per i quali non è possibile instaurare un regime antivirale soppressivo alternativo (vedere paragrafi 4.2 e 5.1).

Non può essere somministrato da solo, ma bisogna trovare almeno un altro farmaco antiretrovirale efficace

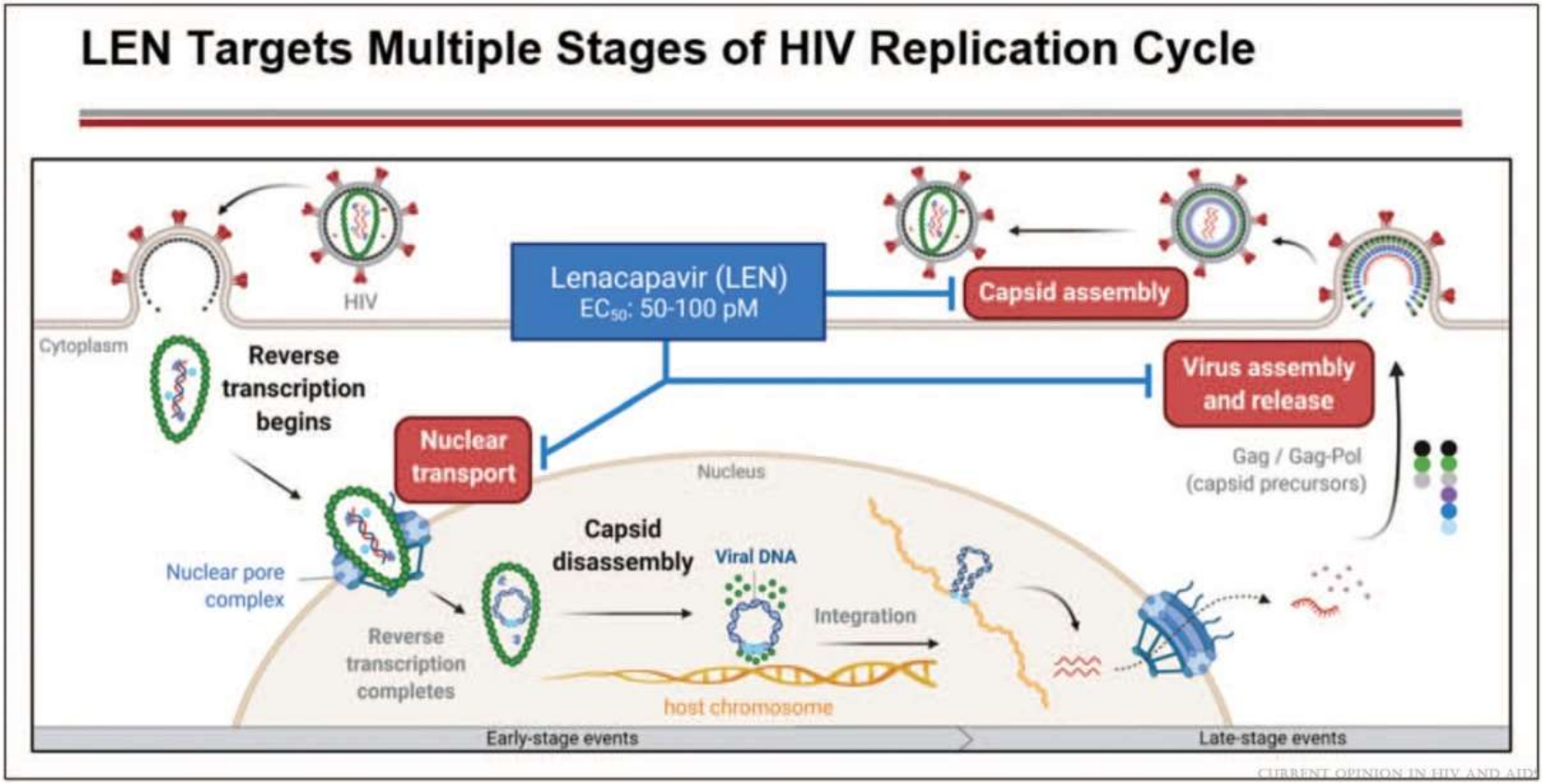
FIGURE 1

Lenacapavir: a first-in-class HIV-1 capsid inhibitor

Dvory-Sobol, Hadas; Shaik, Naveed; Callebaut, Christian; Rhee, Martin S.

Current Opinion in HIV and AIDS17(1):15-21, January 2022.

doi: 10.1097/COH.0000000000000713



Lenacapavir targets multiple stages of the HIV replication cycle. Adapted from [4▪▪,5].

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Serum Half-Life	Elimination/ Metabolic Pathway	Adverse Events
Lenacapavir (LEN) *Sunlenca*	• 300-mg tablet • Single-dose 463.5-mg/1.5-mL vial for injection	**Initiation Option 1** • Day 1: 927 mg SQ x 1 dose + 600 mg PO x 1 dose • Day 2: 600 mg PO x 1 dose **Initiation Option 2** • Day 1: 600 mg PO x 1 dose • Day 2: 600 mg PO x 1 dose • Day 8: 300 mg PO x 1 dose • Day 15: 927 mg SQ x 1 dose **Maintenance Dosing** • 927 mg by SQ injection every 6 months from the date of the last injection (+/-2 weeks) • **Note:** Each SQ dose requires two injections.	PO: 10–12 days SQ: 8–12 weeks	Substrate of P-glycoprotein, CYP3A (minor), UGT1A1 (minor) CYP3A4 inhibitor (moderate)	Injection site reactions, including nodules and induration Nausea, diarrhea, headache