Terapie ARV orali e Long Acting nei PWH: organizzazione, gestione e somministrazione.

WORKING GROUP

Le nuove frontiere della TARV: la terapia iniettiva Long Acting.

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Disclosures:

Grant from Gilead Fellowship Program 2023

Evoluzione della terapia antiretrovirale (ART)

1987

Zidovudina (AZT): Approvazione del primo farmaco antiretrovirale, che segna l'inizio del trattamento farmacologico contro l'HIV.

Inizio anni '90 (1991-1994)

Espansione degli NRTI: Introduzione di altri nucleoside reverse transcriptase inhibitors (NRTI) come didanosina, stavudina e lamivudina, che ampliano le opzioni terapeutiche.

1995

Inibitori della proteasi (PI): Arrivo dei primi inibitori della proteasi, come saquinavir e ritonavir, che rivoluzionano il trattamento riducendo drasticamente la carica virale.

1996

HAART (Terapia Antiretrovirale Altamente Attiva): Introduzione della terapia combinata, che unisce più classi di farmaci per bloccare efficacemente la replicazione dell'HIV e prevenire lo sviluppo di resistenze.

2003

Regimi a dose fissa: Sviluppo di pillole combinate che semplificano la terapia e migliorano l'aderenza dei pazienti.

2007

Inibitori dell'integrasi: Approvazione del primo inibitore dell'integrasi, Raltegravir, che introduce una nuova classe di farmaci con meccanismi d'azione differenti.

2012-2013

Nuovi inibitori dell'integrasi: Introduzione di farmaci come Dolutegravir, caratterizzati da maggiore efficacia e tollerabilità, che consolidano ulteriormente il ruolo degli integrasi nella terapia antiretrovirale.

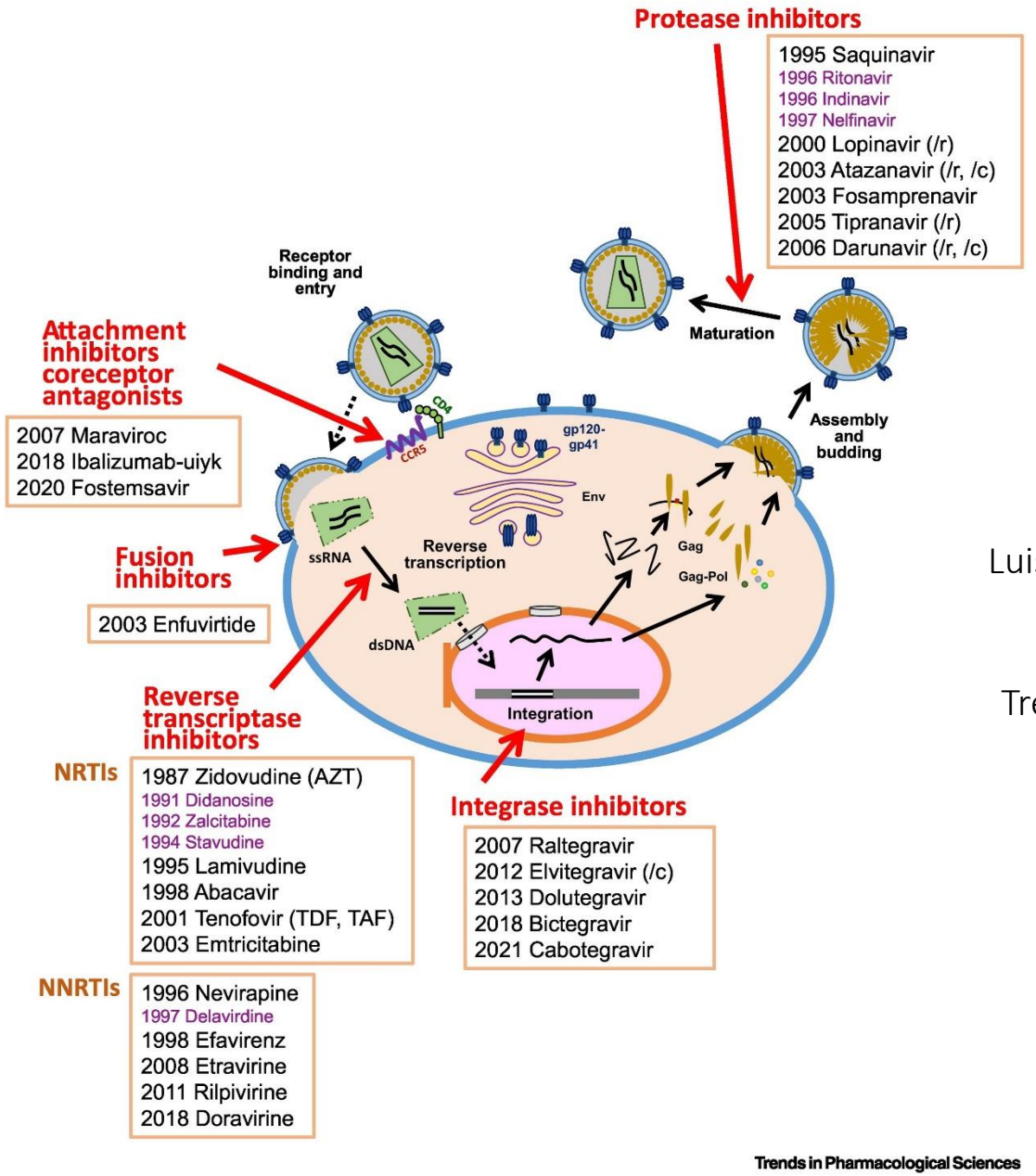
2017-2021

Terapie a lunga durata d'azione: Sperimentazione e approvazione della formulazione iniettabile mensile di Cabotegravir e Rilpivirine (CAB-RPV), offrendo una valida alternativa ai regimi orali per pazienti virologicamente soppressi.

2022 e oltre

Innovazioni con nuove classi di farmaci: Introduzione di Lenacapavir, il primo inibitore della capside, disponibile in formulazione orale e iniettabile sottocutanea con rilascio estremamente lento (possibilità di dosing ogni sei mesi). Questo rappresenta un ulteriore passo avanti, soprattutto per i pazienti con esperienza terapeutica estesa che non hanno ottenuto la soppressione virale con le terapie precedenti.

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

Importanza della ottimizzazione e semplificazione terapeutica

- Tollerabilità al regime terapeutico corrente
- Rischio di complicazioni a lungo termine
- Valutazione della barriera genetica
- Valutazione delle comorbidità (insufficienza renale, osteopenia/osteoporosi, infezione da HBV, dislipidemia)
- Ridurre il Pill Burden
- Migliorare l'aderenza al trattamento
- Ridurre le interazioni tra farmaci e con il cibo

Single Tablet Regimens – Two Drugs Regimens – Booster Sparing Regimens – Long Acting Injectable

Terapia Long Acting Iniettabile

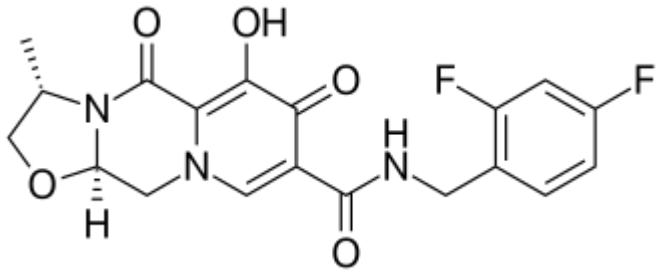
Una buona opzione per sostituire i regimi orali in pazienti con:
- difficoltà a deglutire le compresse
- difficoltà a conservare il farmaco al domicilio per questioni di riservatezza
- stigma

Attenzione all'aderenza

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

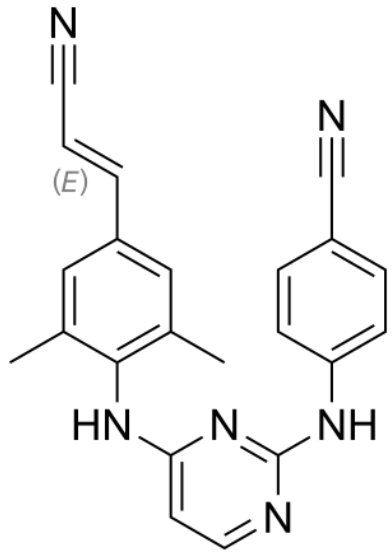
www.readfiles.it
ReAdfiles
Trimestrale di aggiornamento medico
Fondata da Mauro Moroni

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



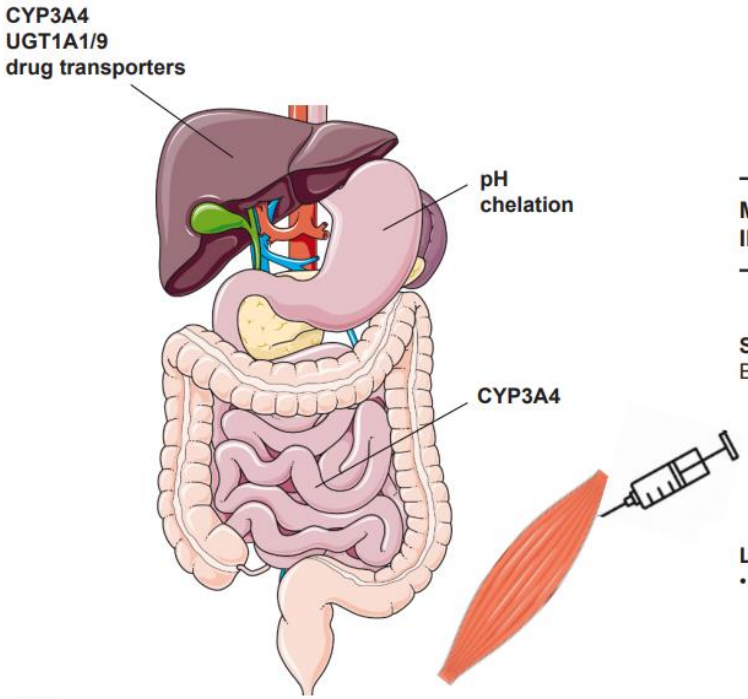
- NNRTI
- Formulazione orale (25 mg cp) e iniettabile (900 mg 3 mL)
- Non dovrebbe essere somministrato con rifampicina, rifapentina, carbamazepina, oxacarbazepina, fenitoina o fenobarbital per induzione dell'enzima CYP3A4

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

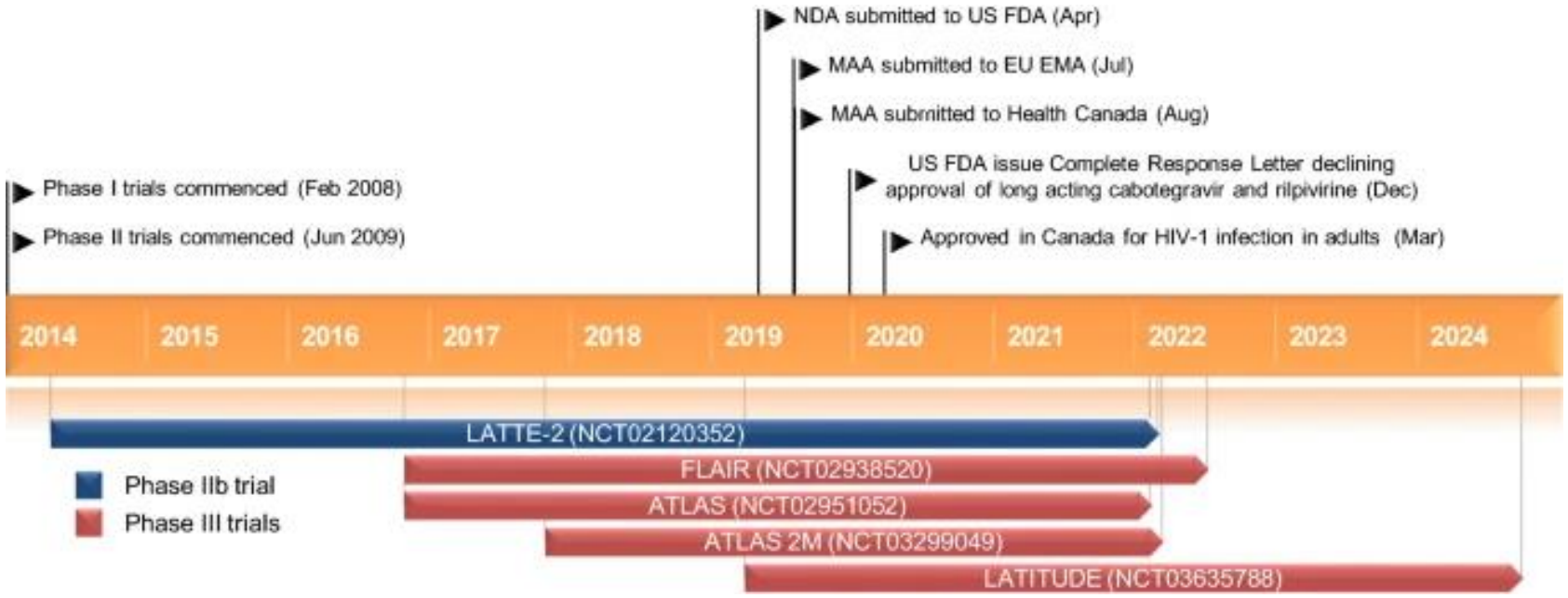
- Antacids
- famotidine
- lansoprazole
- liraglutide
- omeprazole
- orlistat
- pantoprazole
- rabeprazole
- ranitidine

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

Studi principali Cabotegravir Rilpivirina

ATLAS: efficacia e sicurezza rispetto alla terapia orale
ATLAS-2M: confronto tra somministrazione mensile e bimestrale
FLAIR: switch da ART orale a cabotegravir/rilpivirina



Risultati di efficacia - Studio ATLAS

Studio di fase III, open-label, multicentrico di non -inferiorità

Confronto tra cabotegravir/rilpivirina 4 wks e terapia orale PI, NNRTI, INSTI in switch di pz in soppressione virologica da 6 mesi

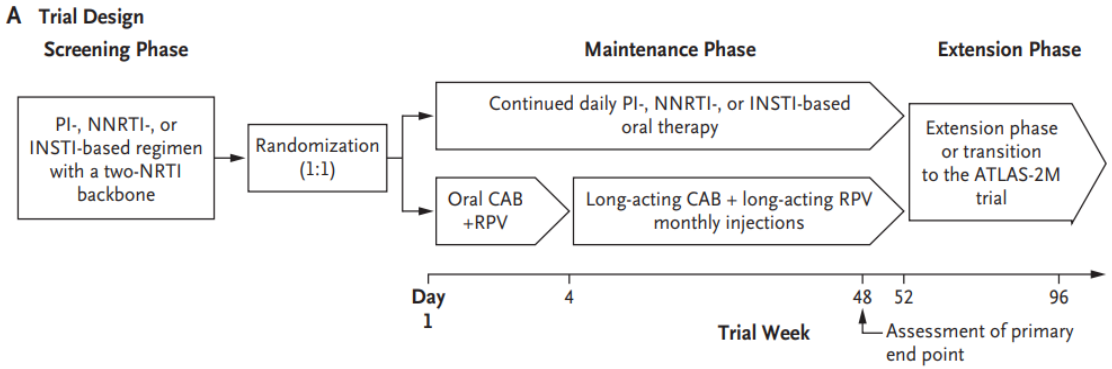
Risultati di mantenimento della soppressione virologica a 48 settimane

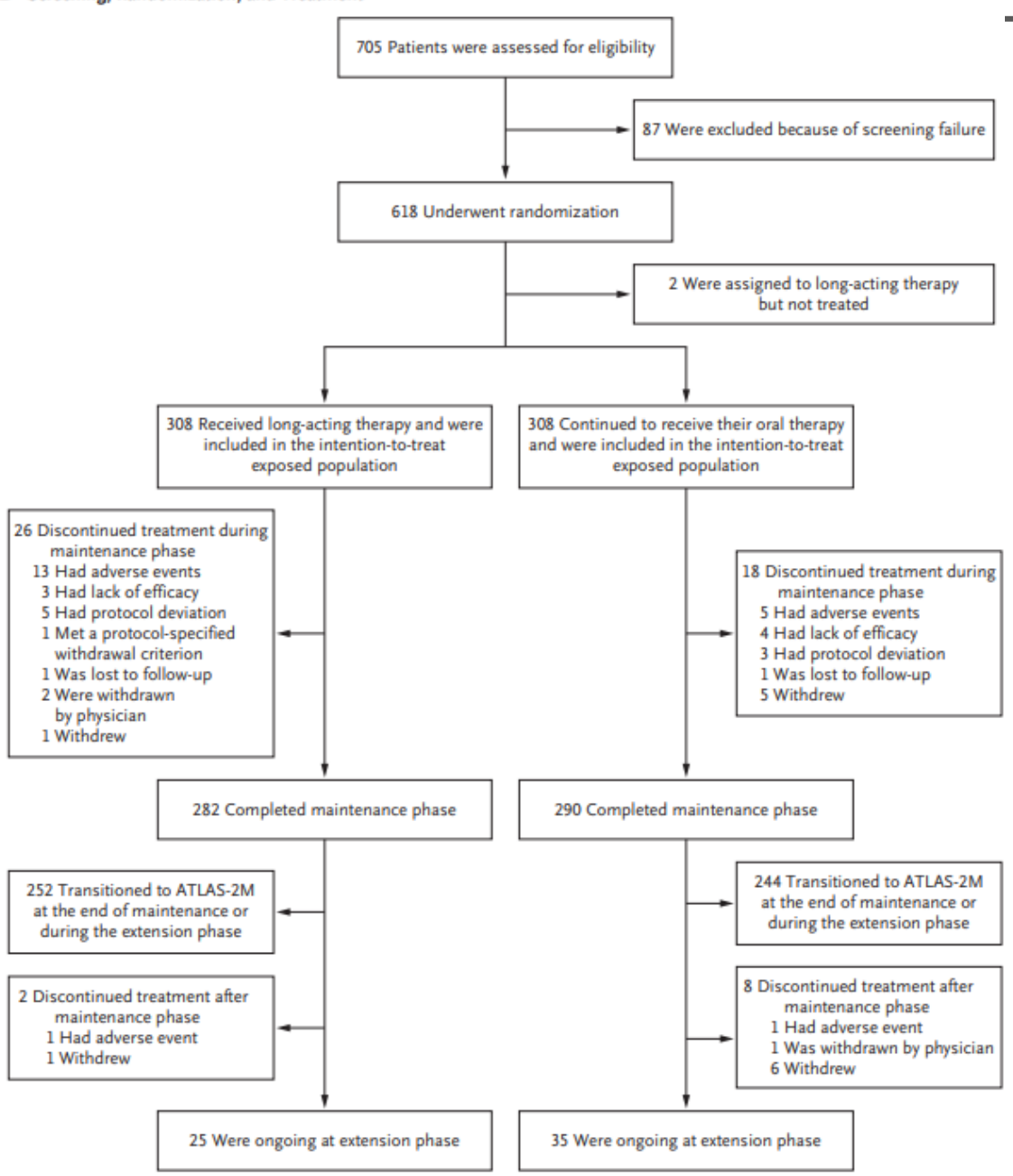
Outcome favorevoli nel 93% dei pazienti

5/308(1,6%) CVF nel gruppo LA – RAMs E138A, E138K+ V108I, E138E/K **+ N155H** , 2 **polimorfismi L74I**

3/308 (1%) CVF nel gruppo terapia orale

83% reazioni avverse prevalentemente per inieizione



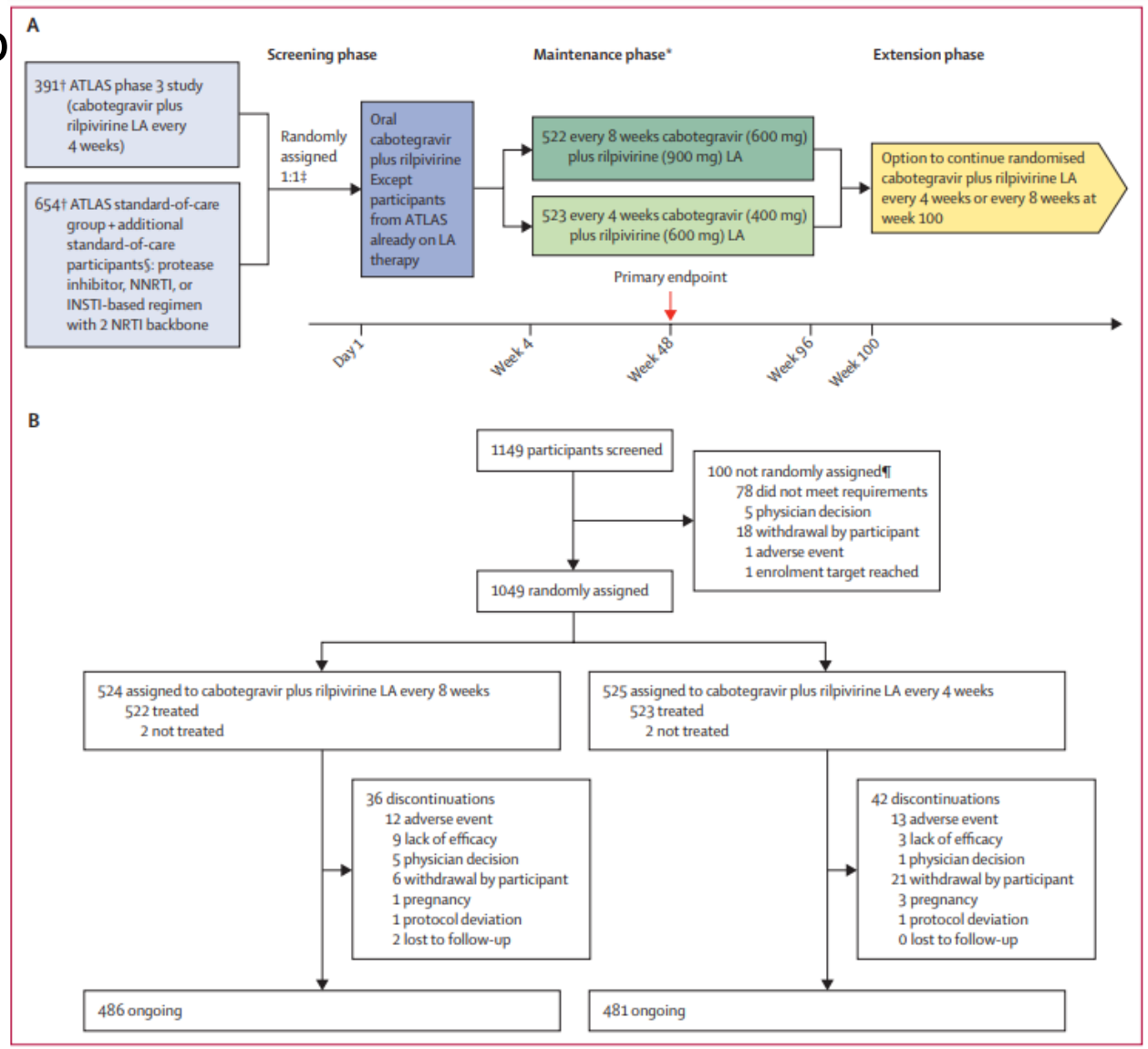


Studio ATLAS-2M, studio di fase III, randomizzato multicentrico, open-label – analisi alla 152 settimana

Confronto tra somministrazione ogni 4 wks e ogni 8 wks
Maggiore preferenza per la somministrazione bimestrale
1045 pazienti arruolati; randomizzazione 1:1
regime bimestrale è stato non inferiore rispetto a quello mensile in termini di mantenimento della soppressione virologica, con un profilo di sicurezza favorevole e una buona accettabilità da parte dei pazienti

Virologic Failure

Overall, there were numerically more virologic failures in the Q8W arm (2% [n = 12/522]), including 2 participants since week 96 [18], than in the Q4W arm (<1% [n = 2/523]; no new CVFs since week 48). An additional participant in the Q8W arm experienced a non–protocol-defined virologic failure at week 48 and is included in the total (Supplementary Table 1). This participant was classified as having virologic failure after the week 96 publication based on an exploratory viral load assay. Excluding the participant with non–protocol-defined virologic failure, 5 (45%) of the 11 participants with CVF through week 96 developed RPV resistance-associated mutations (RAMs) (Y188L, K101E, K101E + E138A, E138E/K, K101E + M230L) in combination with INSTI RAMs (Q148Q/R + N155N/H, Q148R, N155H, Q148R + E138E/K). Both participants with CVF since week 96 had treatment-emergent RAMs to RPV (E138A + M230M/L, E138A + Y181Y/C) and INSTIs (Q148R) at suspected virologic failure (SVF) (Supplementary



Studio FLAIR- studio fase III, randommizzato, open-label, multicentrico, di non-inferiorità

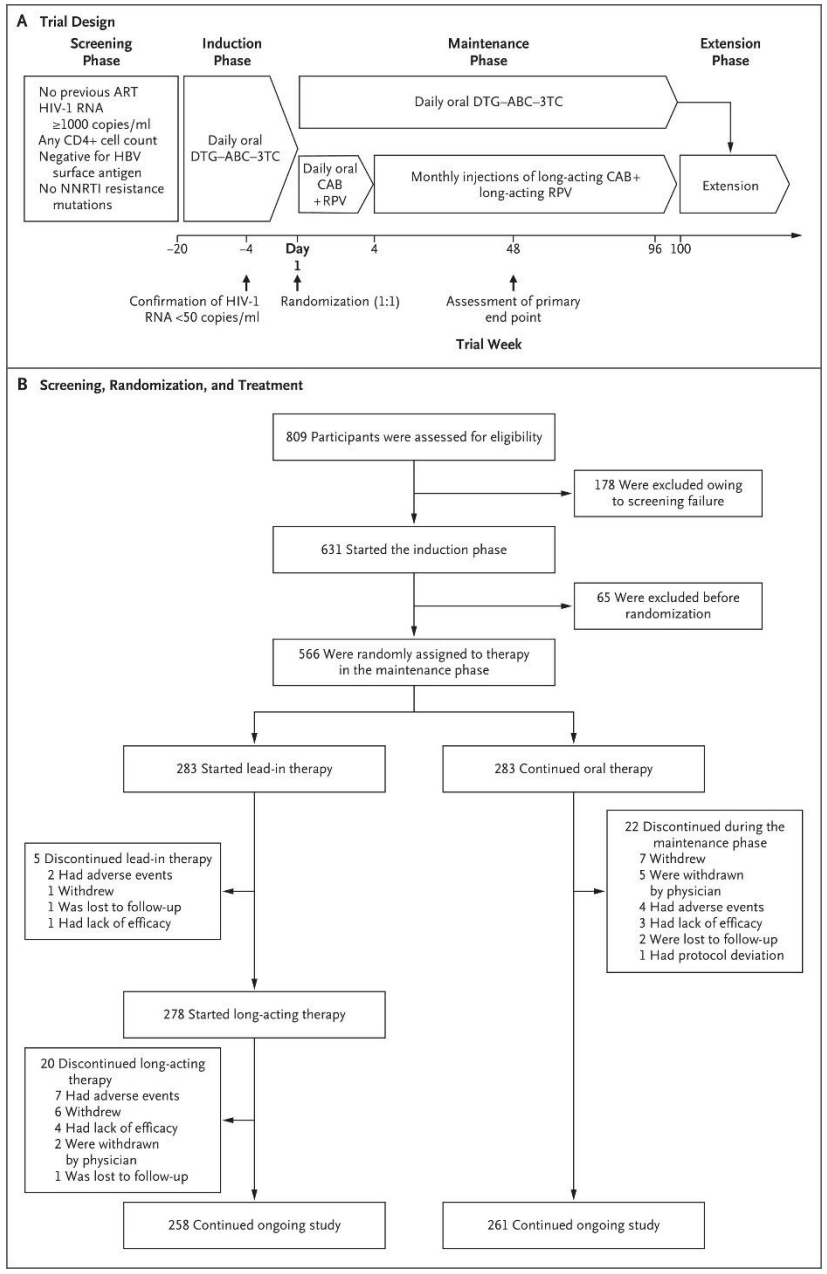
Passaggio da Standard of care con terapia orale DTG/ABC/3TC a iniettiva ogni 4 wks

Risultati a 48 settimane e 96 settimane

Tasso di soppressione virologica stabile

Feedback positivo da parte dei pazienti

	Long-acting group (n=283)	Standard care group (n=283)	Difference, percentage points (95% CI)*†	Adjusted difference, percentage points (95% CI)*‡
Snapshot outcomes (intention-to-treat population)				
HIV-1 RNA <50 copies per mL§	245 (87%)	253 (89%)	-2·8 (-8·2 to 2·5)	-2·8 (-8·2 to 2·5)
HIV-1 RNA ≥50 copies per mL§	9 (3%)	9 (3%)	0·0 (-2·9 to 2·9)	0·0 (-2·9 to 2·9)
Data in window not below threshold	3 (1%)	2 (<1%)	..	..
Discontinued for absence of efficacy	6 (2%)	5 (2%)	..	..
Discontinued for other reason while not below threshold	0	2 (<1%)¶	..	..
No virological data in week 96 window	29 (10%)	21 (7%)	..	..
Discontinued due to adverse event‖	12 (4%)	4 (1%)	..	..
Discontinued for other reason	16 (6%)**	17 (6%)††	..	..
On study but missing data in window	1 (<1%)	0	..	..
Snapshot outcomes (per-protocol population)				
HIV-1 RNA <50 copies per mL§	241/278 (87%)	252/281 (90%)	-3·0 (-8·3 to 2·4)	-3·0 (-8·3 to 2·4)
HIV-1 RNA ≥50 copies per mL§	9/278 (3%)	9/281 (3%)	0·0 (-2·9 to 3·0)	0·1 (-2·9 to 2·9)
Confirmed virological failure (intention-to-treat population)				
Confirmed virological failure between week 48 and 96	0	1 (<1%)‡‡	..	..
Total confirmed virological failures at week 96	4 (1%)§§	4 (1%)	..	..
Total treatment-emergent resistance	3 (1%)	0	..	..



Efficacy, safety, and tolerability of switching to long-acting cabotegravir plus rilpivirine versus continuing fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with HIV, 12-month results (SOLAR): a randomised, open-label, phase 3b, non-inferiority trial

Moti N Ramgopal, Antonella Castagna, Charles Cazanave, Vicens Diaz-Brito, Robin Dretler, Shinichi Oka, Olayemi Osiyemi, Sharon Walmsley, James Sims, Giovanni Di Perri, Kenneth Sutton, Denise Sutherland-Phillips, Alessandro Berni, Christine L Latham, Feifan Zhang, Ronald D'Amico, Miguel Pascual Bernáldez, Rodica Van Solingen-Ristea, Veerle Van Eygen, Parul Patel, Vasiliki Chounta, William R Spreen, Harmony P Garges, Kimberly Smith, Jean van Wyk

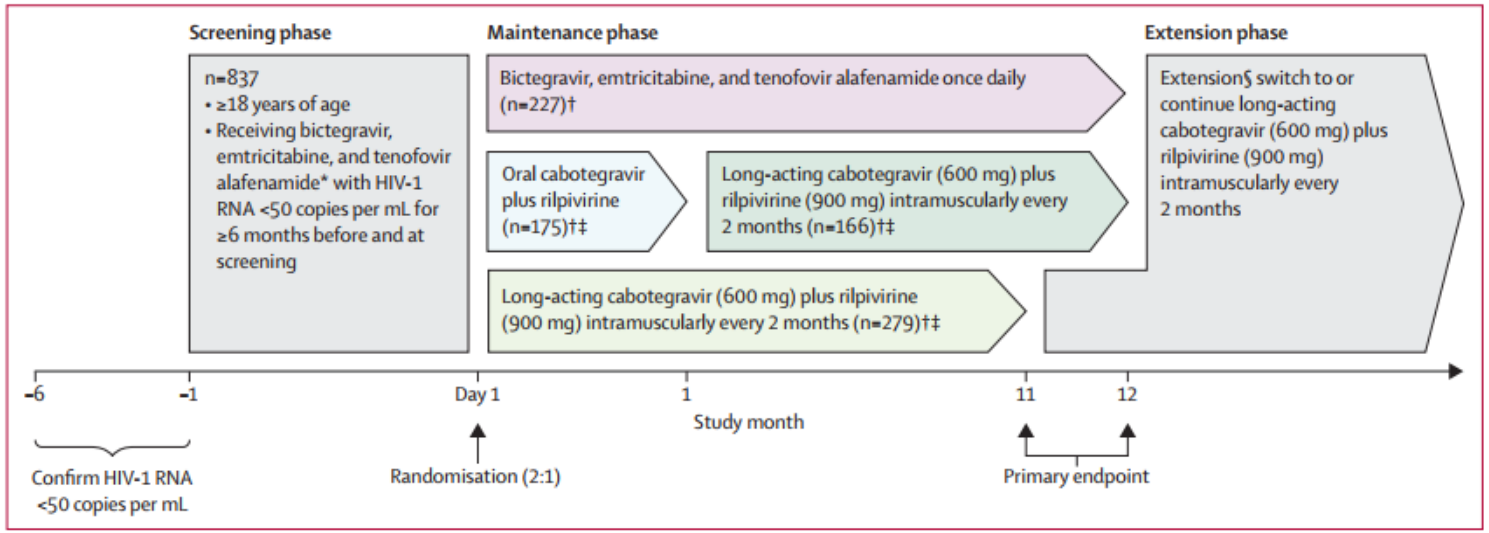


Figure 1: **Trial design**

Oral Lead In

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

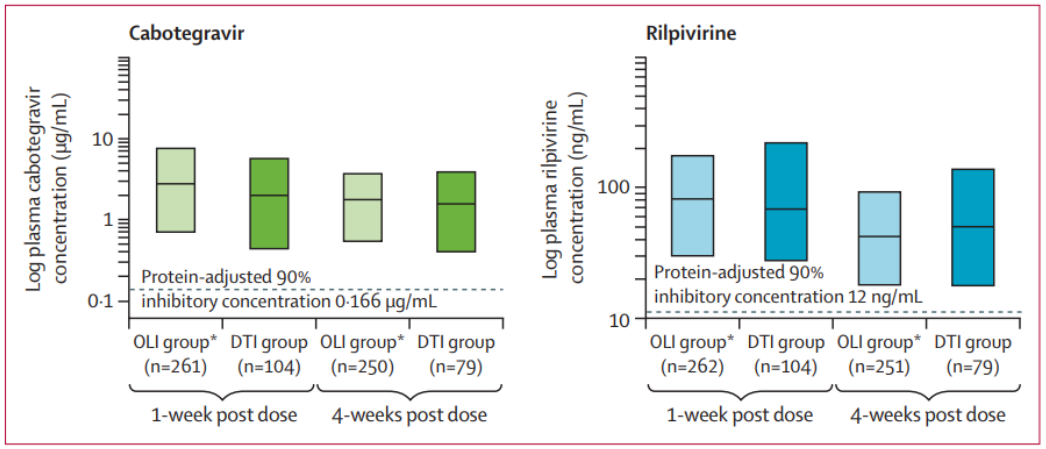


Figure 2: **Initial plasma cabotegravir and rilpivirine concentrations following first injections as DTI and after OLI**

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, Harold Katner, 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

	DTI group (after 24 weeks of CAB plus RPV; n=111)	OLI group (after 24 weeks of CAB plus RPV; n=121)	Randomly assigned long-acting arm (after 124 weeks of CAB plus RPV; n=283)
Any adverse event	102 (92%)	100 (83%)	276 (98%)
Excluding ISRs	88 (79%)	85 (70%)	271 (96%)
Any grade 3–4 adverse events	5 (5%)	9 (7%)	49 (17%)
Excluding ISRs	4 (4%)	5 (4%)	38 (13%)
Drug-related adverse events	2 (2%)	4 (3%)	17 (6%)
Drug-related adverse events excluding ISRs	1 (1%)*	0	5 (2%)
Drug-related adverse events	86 (77%)	79 (65%)	248 (88%)
Excluding ISRs	22 (20%)	23 (19%)	102 (36%)
Adverse events leading to withdrawal	1 (1%)*	2 (2%)†	15 (5%)
Any serious adverse events	4 (4%)	5 (4%)	33 (12%)
Drug-related serious adverse events	1 (1%)*	0	1 (<1%)‡
Fatal serious adverse events	0	0	0
Common adverse events§			
Nasopharyngitis	20 (18%)	13 (11%)	98 (35%)
Headache	7 (6%)	3 (2%)	55 (19%)
Upper respiratory tract infection	10 (9%)	7 (6%)	53 (19%)
Diarrhoea	2 (2%)	10 (8%)	49 (17%)
Back pain	3 (3%)	3 (2%)	47 (17%)
Influenza	3 (3%)	3 (2%)	42 (15%)
Pyrexia	9 (8%)	4 (3%)	35 (12%)
Gastroenteritis	7 (6%)	3 (2%)	29 (10%)
Syphilis	4 (4%)	6 (5%)	29 (10%)
Dizziness	8 (7%)	4 (3%)	20 (7%)
Common drug-related adverse events¶			
Pyrexia	6 (5%)	2 (2%)	18 (6%)
Fatigue	0	2 (2%)	10 (4%)
Headache	1 (1%)	1 (1%)	15 (5%)
Dizziness	3 (3%)	2 (2%)	6 (2%)

Data are n (%). CAB=cabotegravir. DTI=direct-to-injection. ISR=injection site reaction. OLI=oral lead-in. RPV=rilpivirine. *Grade 4 drug-related serious adverse event (Hodgkin lymphoma) led to withdrawal from the DTI group. †One (1%) discontinued due to injection site pain and one (1%) due to weight gain. ‡One drug-related serious adverse event, right knee monoarthritis, was reported in the week 48 analysis. §Common adverse events that occurred in 5% or more of the extension switch population or 10% or more of the randomly assigned long-acting group, excluding ISRs. ¶Common drug-related adverse events that were reported by 3% or more of the extension switch population or the randomly assigned long-acting group, excluding ISRs.

Table 3: **Summary of adverse events**

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

Eleggibilità Cabotegravir Rilpivirina

- Soppressione virologica e aderenti ad un regime orale da almeno 6 mesi

- Assenza di mutazioni documentate o sospette che potrebbero compromettere l'attività di cabotegravir e rilpivirina

- Possibilità e comodità a recarsi in ospedale per le iniezioni – farmaco non autorizzato per la self-administration

- no protesi glutee e filler – il farmaco al momento è approvato solo per l'iniezione intramuscolare glutea

- assenza di coinfezione HBV

Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis

Amy G. Cutrell[a], Jonathan M. Schapiro[b], Carlo F. Perno[c], Daniel R. Kuritzkes[d], Romina Quercia[e], Parul Patel[a], Joseph W. Polli[a], David Dorey[f], Yongwei Wang[g], Sterling Wu[h], Veerle Van Eygen[i], Herta Crauwels[i], Susan L. Ford[j], Mark Baker[k], Christine L. Talarico[a], Marty St Clair[a], Jerry Jeffrey[a], C. Thomas White[a], Simon Vanveggel[i], Kati Vandermeulen[i], David A. Margolis[a,*], Michael Aboud[e], William R. Spreen[a] and Ian van Lunzen[l]

AIDS

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eISSN: 1473-5571

Design and methods: Data from 1039 adults naive to long-acting CAB+RPV were pooled in a multivariable analysis to examine the influence of baseline viral and participant factors, dosing regimen and drug concentrations on confirmed virologic failure (CVF) occurrence using a logistic regression model. In a separate model, baseline factors statistically associated with CVF were further evaluated to understand CVF risk when present alone or in combination.

Results: Overall, 1.25% ($n = 13/1039$) of participants experienced CVF. Proviral RPV resistance-associated mutations (RAMs), HIV-1 subtype A6/A1, higher BMI (associated with Week 8 CAB trough concentration) and lower Week 8 RPV trough concentrations were significantly associated ($P < 0.05$) with increased odds of CVF (all except RPV trough are knowable at baseline). Few participants (0.4%) with zero or one baseline factor had CVF. Only a combination of at least two baseline factors (observed in 3.4%; $n = 35/1039$) was associated with increased CVF risk (25.7%, $n = 9/35$).

Conclusion: CVF is an infrequent multifactorial event, with a rate of approximately 1% in the long-acting CAB+RPV arms across Phase 3 studies (FLAIR, ATLAS and ATLAS-2M) through Week 48. Presence of at least two of proviral RPV RAMs, HIV-1 subtype A6/A1 and/or BMI at least 30 kg/m^2 was associated with increased CVF risk. These findings support the use of long-acting CAB+RPV in routine clinical practice.

Table 1 Full population characteristic at baseline

Variables	N = 74
Age, years, median, (IQR)	54 (44.7–61)
Gender n (%)	59 (79.7)
Cis-gender man	12 (16.2)
Cis-gender woman	3 (4.1)
Transgender woman	
Ethnicity, n (%)	65 (87.8)
Caucasian	3 (4.1)
African	5 (6.8)
Latino-American	
Risk Factor n (%)	35 (47.3)
MSM	28 (37.8)
Heterosexual	9 (12.2)
PWID	
Zenith HIV-RNA as log10 copies/mL, median (IQR)	5.22 (4.48–5.72)
Nadir CD4, cells/mm3, median (IQR)	234.5 (62.5-484.2)
Time since HIV diagnosis, years, median (IQR)	11.8 (6.6–18.2)
Time on ART, years, median (IQR)	11 (8–18)
Antiretroviral regimen before BL, n (%)	27 (36.5)
- 2NRTI + INSTI	2 (2.7)
- 2NRTI + NNRTI	3 (4.1)
- 2NRTI + PI	36 (48.6)
- 2DR (3TC/DTG, RPV/DTG)	3 (4.1)
- Other 2DR	3 (4.1)
- Other ARV regimen	
CDC Stage C, n (%)	27 (36.5)
HIV VL ≤ 30 copies/ml at BL, n (%)	53 (71.6)
HIV VL ≥ 30 copies/ml at BL, n (%)	21 (28.4)
TCD4 + cells/mm3, median (IQR) at BL	651 (431–1014)
BMI, Kg/m2, median (IQR)	25.4 (22.6–30.2)
Oral lead in, n (%)	7 (9.5)
PWH with NNRTI resistance-associated mutations (RAMs) at BL, n (%)	12 (16%)
Comorbidities, n (%)	23 (31.1)
Cardiovascular disease	27 (36.5)
Endocrinological disorders	27 (36.5)
Hepatology disease	18 (24.3)
Psychiatric disease	12 (16.2)
Neurological disease	2 (2.7)
Pulmonary disease	5 (6.8)
Oncological disease	
PWH with ≤2 comorbidities, n (%)	35 (47.3)
PWH with ≥2 comorbidities, n(%)	39 (52.7)

Iannone *et al. BMC Infectious Diseases* (2025) 25:105
https://doi.org/10.1186/s12879-025-10499-0

BMC Infectious Diseases

RESEARCH Open Access

Unconventional use of injectable long-acting cabotegravir and rilpivirine against HIV-1 in PWH in clinical need: 52 weeks real-world data

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Methods Retrospective observational study in two Italian outpatient settings enrolling PWH who switched to LA CAB + RPV from February 2021 to January 2024 in presence of exclusion criteria enlisted in registrational trials or with other worrisome clinical risks. Kaplan-Meier (KM) was used to assess the probability of CAB/RPV discontinuation. Cox regression analysis was used to evaluate potential predictors of discontinuation.

Results We enrolled 74 PWH, with a median of 7 injections (IQR 5–9), a median age of 53 years (IQR 45–61), median time of exposure to antiretrovirals of 11 years (IQR 8–18) and median time from HIV diagnosis of 11.8 years (IQR 6.6–18.2). Eleven (14.9%) discontinued LA CAB + RPV mainly for injection-site pain. Of 53 PWH who were undetectable before switch, 37 maintained viral suppression at week 52. We registered only one virological failure at week 12. Twenty-one started injections with unsuppressed viral loads (median 66 cps/ml, IQR 40–215) and 10 (47.6%) achieved viral suppression. Overall probability of discontinuation was 14.9% at week 52. Younger age was protective against discontinuation (HR 0.93, 95%CI 0.88–0.99, $p = 0.048$).

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

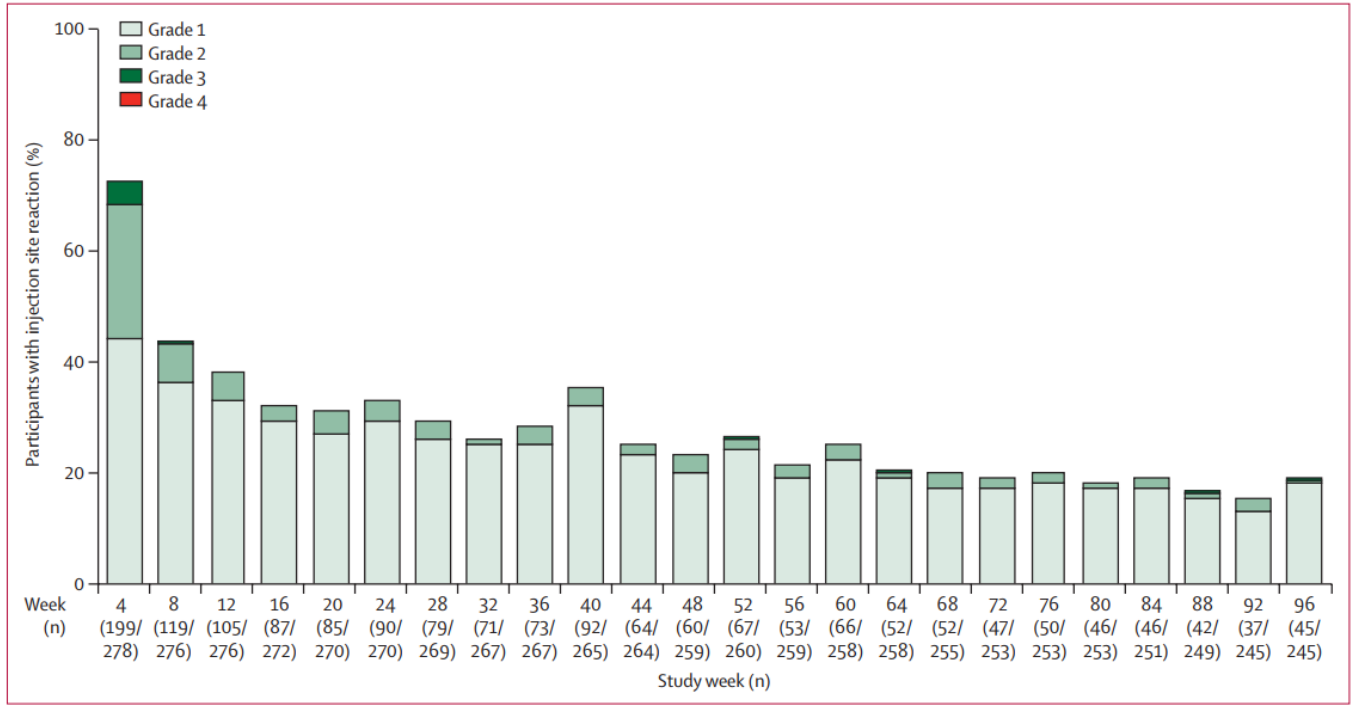

Figure 2: **Injection site reaction incidence over time through week 96**
Incidence is derived relative to the number of participants who received injections at each respective study visit. There were no grade 4 injection site reactions.

Impatto sulla qualità di vita

Improvements in Patient-Reported Outcomes After 12 Months of Maintenance Therapy With Cabotegravir + Rilpivirine Long-Acting Compared With Bictegravir/Emtricitabine/Tenofovir Alafenamide in the Phase 3b SOLAR Study

Cristina Mussini[1] · Charles Cazanave[2] · Eisuke Adachi[3] · Beng Eu[4,5] · Marta Montero Alonso[6] · Gordon Crofoot[7] · Vasiliki Chounta[8] · Irina Kolobova[8] · Kenneth Sutton[8] · Denise Sutherland-Phillips[8] · Rimgaile Urbaityte[9] · Alice Ehmann[10] · Jenny Scherzer[11] · Patricia de los Rios[8] · Ronald D'Amico[8] · William Spreen[8] · Jean van Wyk[12]

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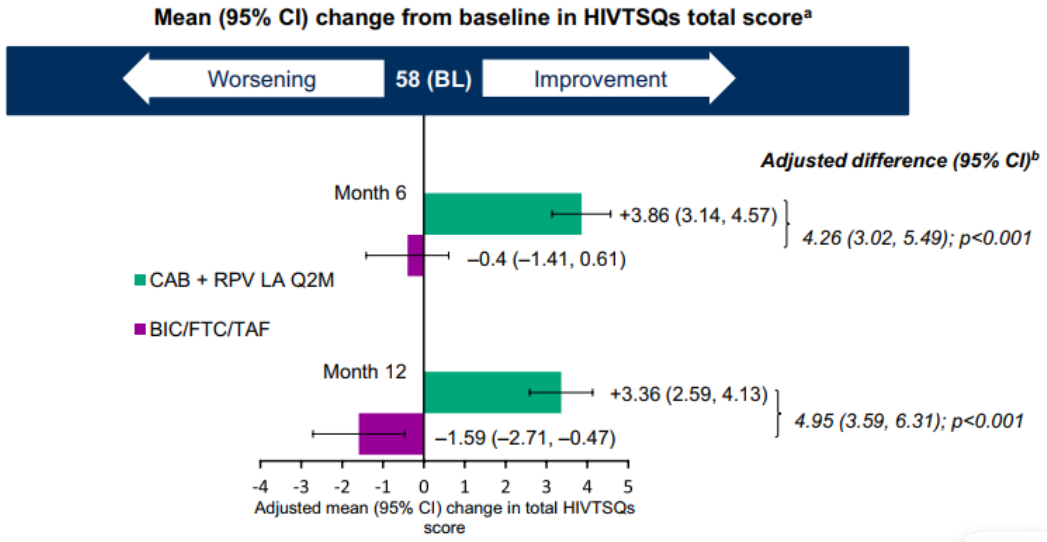


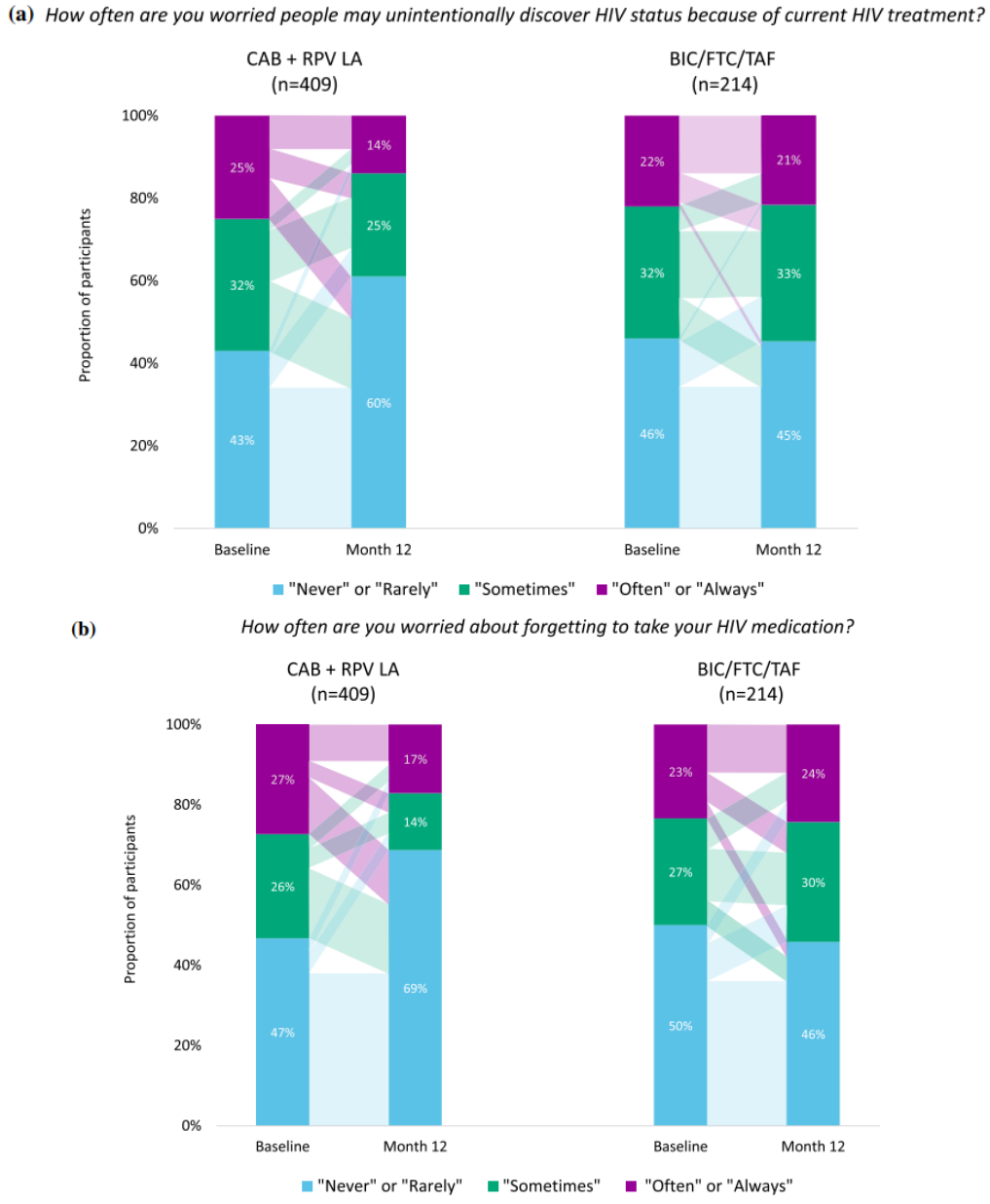


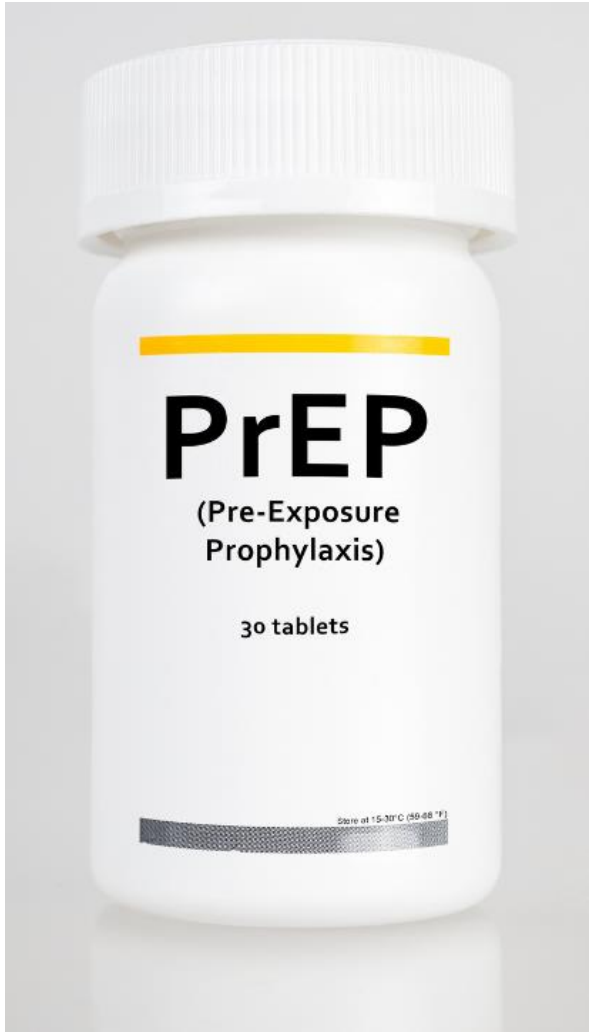
Fig. 2 Shifts in fear of disclosure (a), adherence anxiety (b) and reminder of HIV status (c) from baseline to Month 12[a]. [a]Participants with missing data at Month 12: CAB + RPV LA, n = 38; BIC/FTC/TAF, n = 9. BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB, cabotegravir; LA, long-acting; RPV, rilpivirine

Profilassi Pre-Esposizione

Definizione: è una strategia preventiva che consiste nell'assunzione di farmaci antiretrovirali da parte di persone non infette, ma a rischio di esposizione all'HIV, per ridurne significativamente il rischio di contrarre il virus.

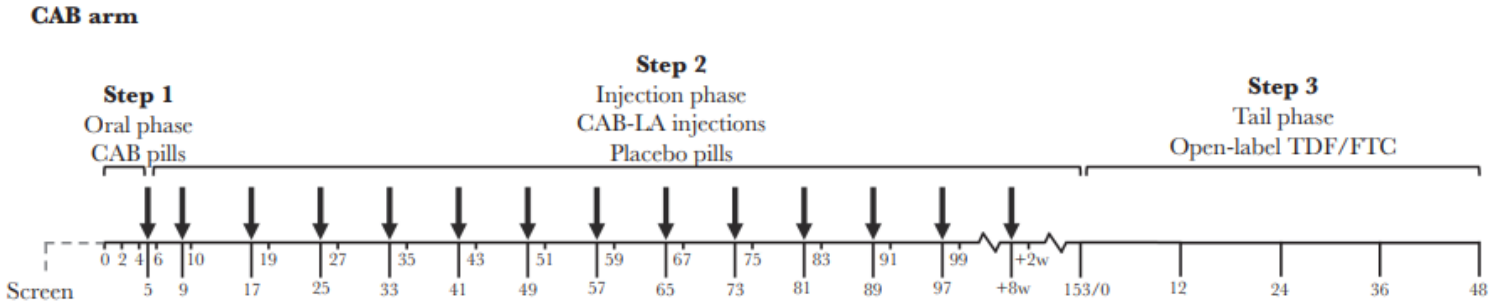
PrEP orale con TDF/ FTC continuativa o on demand

PrEP iniettiva



Risultati dello studio HPTN 083 – Trial multicentrico fase II b/III

Confronto in tra cabotegravir e TDF/FTC in PrEP in
maschi cisgender e transgender MSM – doppio cieco e doppio placebo
Eleggibili 4566 – 58 nuove diagnosi di HIV
CAB LA: riduzione dell'incidenza di nuove infezioni del 66%



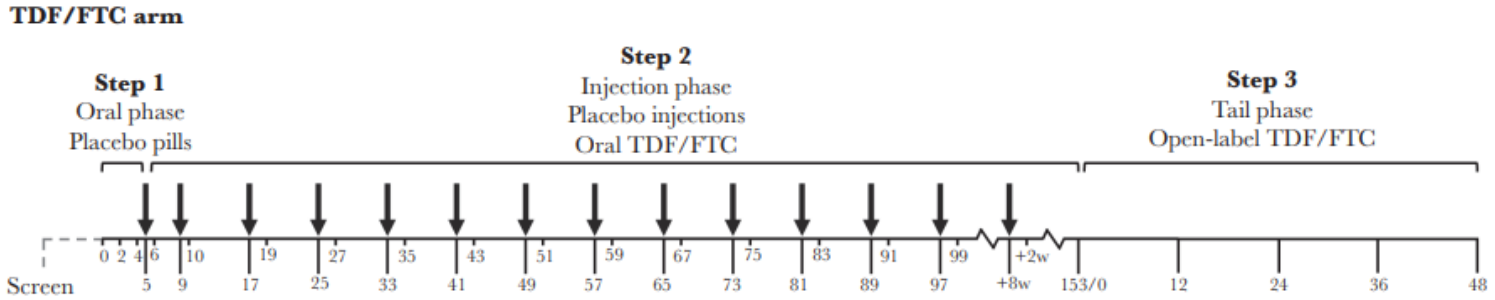


Table 1. Classification of Human Immunodeficiency Virus Infections[a]

Infection Type and Study Arm	Infections, No.	Classification Group
Baseline		
CAB arm	4 (A1–A4)	HIV positive at study enrollment
TDF/FTC arm	3 (E40–42)	HIV positive at study enrollment
Incident		
CAB arm	5 (B1–B5)	No recent CAB exposure[c]
	3 (C1–C3)	Infected during the CAB oral lead-in period
	4 (D1–D4)	Infected in the setting of on-time CAB-LA injections
TDF/FTC arm	39 (E1–E39)	Infected after enrollment

- Lo studio sottolinea l'efficacia di TDF/FTC e CAB LA in PrEP
- Resistenze per INSTI riscontrate 5 pz nel CAB LA senza resistenza fenotipica DTB e BIC
- Ritardo nella diagnosi di HIV maggiore di 1 visita >50%

Risultati dello studio HPTN 084

Trial di valutazione della superiorità di Cabotegravir su TDF/FTC in PrEP
Studio Multicentrico in donne africane: 3224 randomizzazioni (1614 nel gruppo cabotegravir e 1610 nel gruppo TDF-FTC). 40 infezioni (4 CAB LA; 36 in TDF/FTC)
Riduzione stimata delle infezioni da HIV del 91% tra Cabotegravir e TDF/FTC

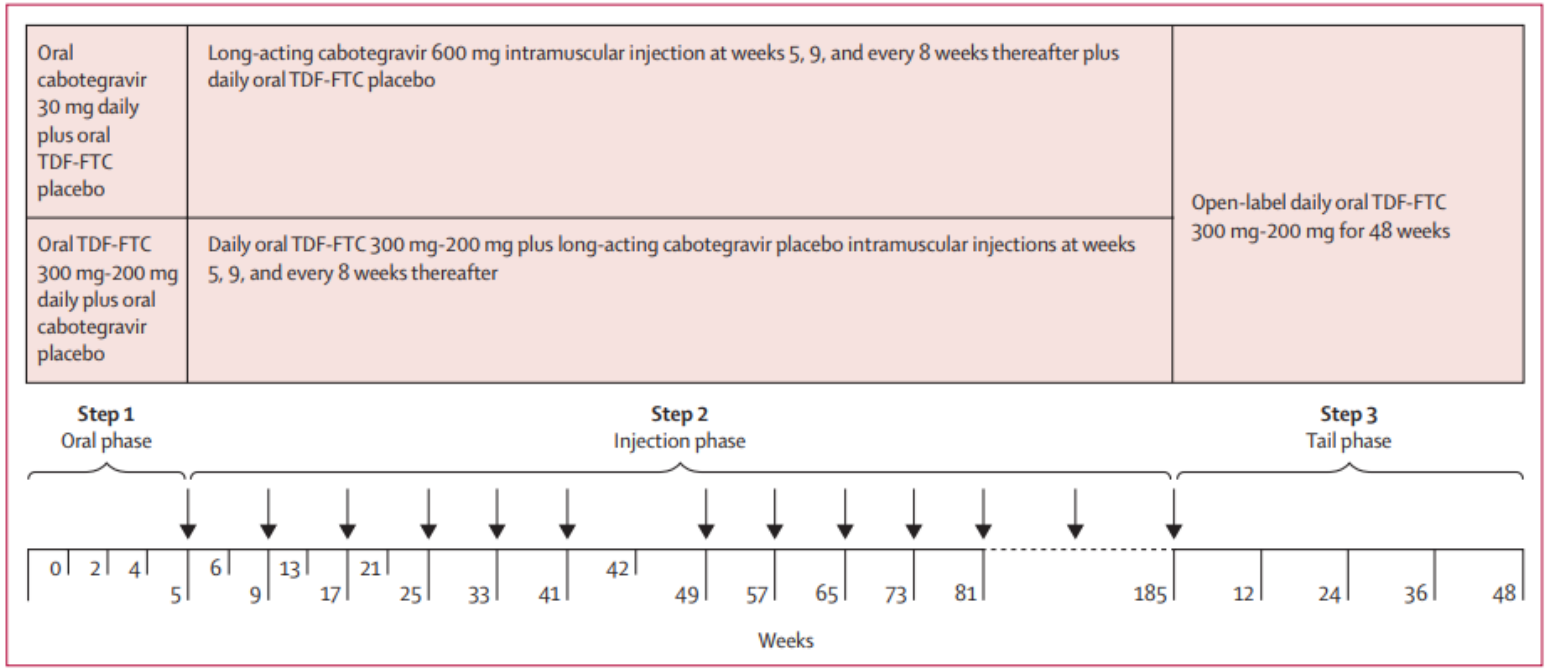
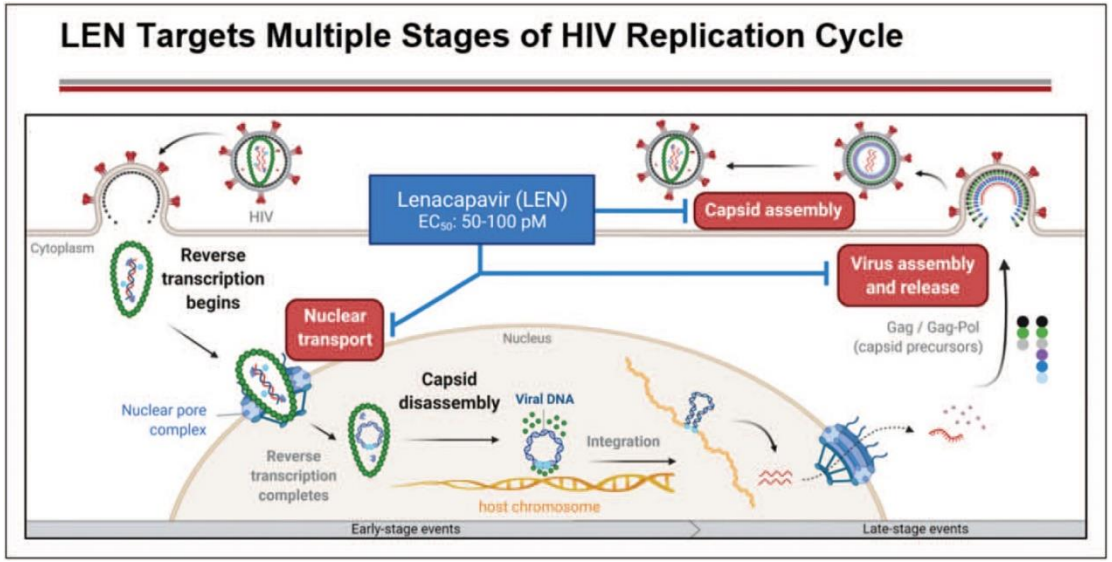


Figure 1: **Trial design**
TDF-FTC=tenofovir disoproxil fumarate plus emtricitabine.

- Garanzia di aderenza
- Iniezione ogni 8 settimane risulta conveniente e discreto
- Abbattimento delle difficoltà di assunzione delle pillole (cambio di abitudini, difficoltà nella deglutizione, HIV stigma e discriminazione, violenza del partner)

LENACAPAVIR - un nuovo approccio

Lenacapavir (LEN) è il primo inibitore della capside della sua classe, disponibile sia in formulazione orale che in formulazione iniettabile sottocutanea. Quest'ultima ha un rilascio estremamente lento, che ne consente la somministrazione ogni sei mesi.



A differenza di CAB-RPV, LEN è stato approvato per l'uso in combinazione con altri farmaci antiretrovirali (ARV) nei pazienti con HIV (PLWH) con esperienza terapeutica estesa (HTE) che non riuscivano altrimenti a raggiungere la soppressione virale nell'Unione Europea.

Studi su Lenacapavir: CAPELLA. Studio fase III, randommizzato.

HTE – HIV RNA > 400 cp/mL da 8 wks, resistenza > 2 farmaci antiretrovirali di 3-4 classi ARV, <2 farmaci attivi. 2 coorti. OBR: optimized background therapy

Riduzione viremica di 0,5 log10 in 88% dei pazienti in monoterapia funzionale.

Oral Lead in: giorno 1-2 e 8 (600 mg cp)- sottocute in addome (927 mg 1,5 mL)

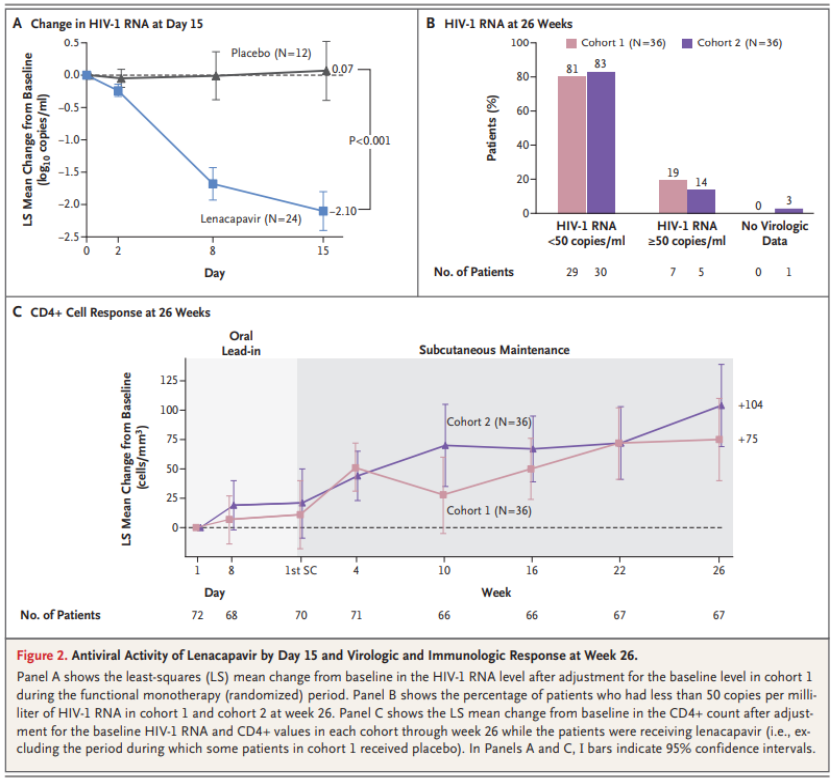
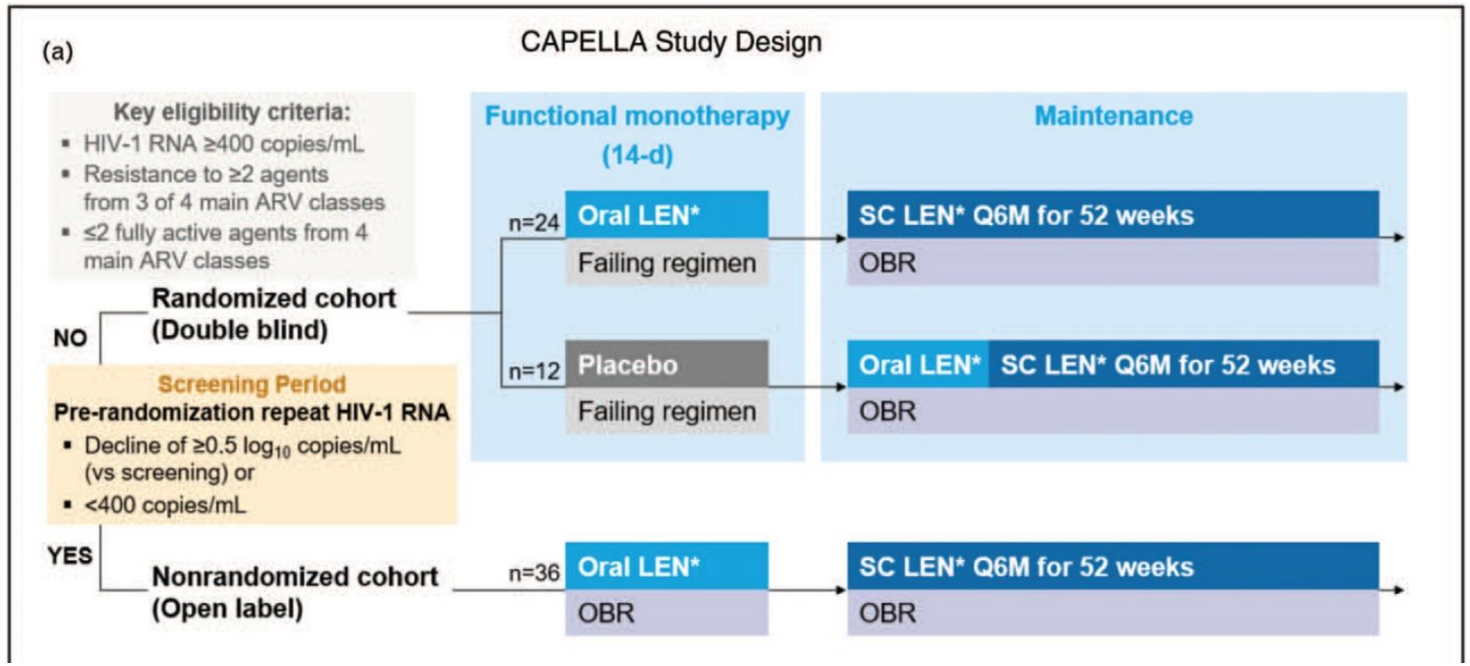
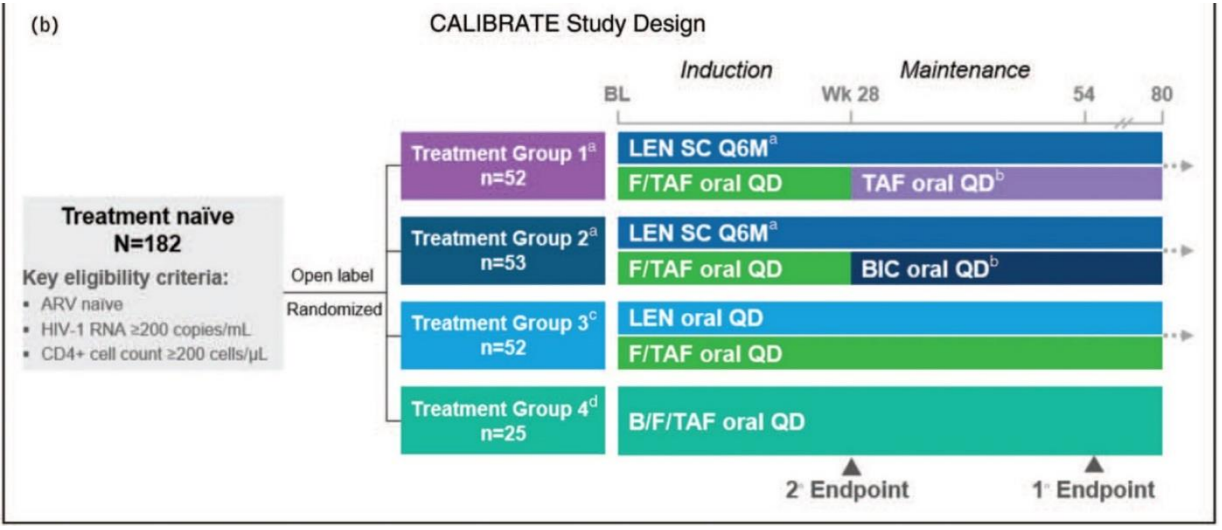


Figure 2. Antiviral Activity of Lenacapavir by Day 15 and Virologic and Immunologic Response at Week 26.

Panel A shows the least-squares (LS) mean change from baseline in the HIV-1 RNA level after adjustment for the baseline level in cohort 1 during the functional monotherapy (randomized) period. Panel B shows the percentage of patients who had less than 50 copies per milliliter of HIV-1 RNA in cohort 1 and cohort 2 at week 26. Panel C shows the LS mean change from baseline in the CD4+ count after adjustment for the baseline HIV-1 RNA and CD4+ values in each cohort through week 26 while the patients were receiving lenacapavir (i.e., excluding the period during which some patients in cohort 1 received placebo). In Panels A and C, I bars indicate 95% confidence intervals.



CALIBRATE: studio fase II, valutazione di Lenacavavir in combinazione con altre terapie TAF, BIC, TAF/FTC – ART NAIVE
Risultati promettenti e sicurezza a lungo termine



Lenacapavir administered every 26 weeks or daily in combination with oral daily antiretroviral therapy for initial treatment of HIV: a randomised, open-label, active-controlled, phase 2 trial

Samir K Gupta, Mezgebe Berhe, Gordon Crofoot, Paul Benson, Moti Ramgopal, James Sims, Cheryl McDonald, Peter Ruane, William E Sanchez, Anita Scribner, Shan-Yu Liu, Laurie A VanderVeen, Hadas Dvory-Sobol, Martin S Rhee, Jared M Baeten, Ellen Koenig

Summary

Background Antiretroviral agents with novel mechanisms and dosing intervals could expand treatment options for people with HIV. Lenacapavir, an inhibitor of capsid protein that makes use of a unique mechanism, can be administered orally or subcutaneously. We sought to explore the efficacy of lenacapavir in various combination regimens as initial and maintenance therapy for HIV.

Methods In a phase 2, randomised, open-label, ongoing study at 41 investigational sites in the USA and Dominican Republic, we randomly assigned adults with HIV who had not previously received antiretrovirals to four groups (2:2:2:1). Randomisation was stratified by plasma HIV-1 RNA load (≤100 000 or >100 000 copies per mL) at screening. Groups 1 and 2 both received lenacapavir (927 mg) subcutaneously every 26 weeks (after 2 weeks of oral loading [600 mg on days 1 and 2, followed by 300 mg on day 8]) with oral daily emtricitabine (200 mg) and tenofovir alafenamide (25 mg) for 28 weeks followed by subcutaneous lenacapavir (927 mg) plus oral daily tenofovir alafenamide (25 mg, group 1) or bictegravir (75 mg, group 2). Group 3 received oral daily lenacapavir (600 mg on days 1 and 2, followed by 50 mg daily) with emtricitabine (200 mg) and tenofovir alafenamide (25 mg). Group 4 received oral daily bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg). Participants and investigators were not masked to group assignment. The primary endpoint was the percentage of participants with virological suppression (HIV-1 RNA <50 copies per mL) at week 54, analysed in the full analysis set (all randomly assigned participants who received at least one dose of study drug) using only on-treatment data. The safety outcome measures were incidences of treatment-emergent adverse events and graded laboratory abnormalities, analysed in the full analysis set. This study is registered at ClinicalTrials.gov, NCT04143594.

Findings Between Nov 22, 2019, and Aug 27, 2020, 249 people with HIV were screened, 183 participants were randomly assigned and 182 received a dose of antiretroviral drugs (52 in group 1, 53 in group 2, 52 in group 3, and 25 in group 4). 22 participants did not complete the full study course (five in group 1, 12 in group 2, four in group 3, and one in group 4). At week 54, virological suppression was 90% (47 of 52 patients) for group 1 (difference *vs* group 4: –2·6%, 95% CI –18·4 to 13·2), 85% (45 of 53) for group 2 (–7·1%, –23·4 to 9·3), 85% (44 of 52) for group 3 (–7·2%, –23·5 to 9·1), and 92% (23 of 25) for group 4. The most frequent non-injection-site adverse events with lenacapavir (subcutaneous or oral) were headache (13%, 21 of 157) and nausea (13%, 21 of 157). The most common lenacapavir-related injection-site reactions were erythema (27%, 28 of 105), swelling (23%, 24 of 105), and pain (19%, 20 of 105), which were generally mild or moderate. No serious adverse event related to study treatment occurred. Three participants discontinued subcutaneous lenacapavir because of grade 1 injection-site reactions (two for induration and one for erythema or swelling).

LENACAPAVIR IN PrEP
Studi PURPOSE 1 E 2

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 3, 2024 VOL. 391 NO. 13

Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women

L.-G. Bekker, M. Das, Q. Abdool Karim, K. Ahmed, J. Batting, W. Brumskine, K. Gill, I. Harkoo, M. Jaggernath, G. Kigozi, N. Kiwanuka, P. Kotze, L. Lebina, C.E. Louw, M. Malahleha, M. Manentsa, L.E. Mansoor, D. Moodley, V. Naicker, L. Naidoo, M. Naidoo, G. Nair, N. Ndlovu, T. Palanee-Phillips, R. Panchia, S. Pillay, D. Potloane, P. Selepe, N. Singh, Y. Singh, E. Spooner, A.M. Ward, Z. Zwane, R. Ebrahimi, Y. Zhao, A. Kintu, C. Deaton, C.C. Carter, J.M. Baeten, and F. Matovu Kiweewa, for the PURPOSE 1 Study Team*

ABSTRACT

BACKGROUND

There are gaps in uptake of, adherence to, and persistence in the use of preexposure prophylaxis for human immunodeficiency virus (HIV) prevention among cisgender women.

METHODS

We conducted a phase 3, double-blind, randomized, controlled trial involving adolescent girls and young women in South Africa and Uganda. Participants were assigned in a 2:2:1 ratio to receive subcutaneous lenacapavir every 26 weeks, daily oral emtricitabine–tenofovir alafenamide (F/TAF), or daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF; active control); all participants also received the alternate subcutaneous or oral placebo. We assessed the efficacy of lenacapavir and F/TAF by comparing the incidence of HIV infection with the estimated background incidence in the screened population and evaluated relative efficacy as compared with F/TDF.

RESULTS

Among 5338 participants who were initially HIV-negative, 55 incident HIV infections were observed: 0 infections among 2134 participants in the lenacapavir group (0 per 100 person-years; 95% confidence interval [CI], 0.00 to 0.19), 39 infections among 2136 participants in the F/TAF group (2.02 per 100 person-years; 95% CI, 1.44 to 2.76), and 16 infections among 1068 participants in the F/TDF group (1.69 per 100 person-years; 95% CI, 0.96 to 2.74). Background HIV incidence in the screened population (8094 participants) was 2.41 per 100 person-years (95% CI, 1.82 to 3.19). HIV incidence with lenacapavir was significantly lower than background HIV incidence (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.04; P<0.001) and than HIV incidence with F/TDF (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.10; P<0.001). HIV incidence with F/TAF did not differ significantly from background HIV incidence (incidence rate ratio, 0.84; 95% CI, 0.55 to 1.28; P=0.21), and no evidence of a meaningful difference in HIV incidence was observed between F/TAF and F/TDF (incidence rate ratio, 1.20; 95% CI, 0.67 to 2.14). Adherence to F/TAF and F/TDF was low. No safety concerns were found. Injection-site reactions were more common in the lenacapavir group (68.8%) than in the placebo injection group (F/TAF and F/TDF combined) (34.9%); 4 participants in the lenacapavir group (0.2%) discontinued the trial regimen owing to injection-site reactions.

CONCLUSIONS

No participants receiving twice-yearly lenacapavir acquired HIV infection. HIV incidence with lenacapavir was significantly lower than background HIV incidence and HIV incidence with F/TDF. (Funded by Gilead Sciences; PURPOSE 1 ClinicalTrials.gov number, NCT04994509.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Das can be contacted at moupali.das@gilead.com or at Gilead Sciences, 333 Lakeside Dr., Foster City, CA 94404.

*The members of the PURPOSE 1 Study Team are listed in the Supplementary Appendix, available at NEJM.org.

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DOI: 10.1056/NEJMoa2407001

CME

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons

C.F. Kelley, M. Acevedo-Quiñones, A.L. Agwu, A. Avihingsanon, P. Benson, J. Blumenthal, C. Brinson, C. Brites, P. Cahn, V.D. Cantos, J. Clark, M. Clement, C. Creticos, G. Crofoot, R.S. Diaz, S. Doblecki-Lewis, J.A. Gallardo-Cartagena, A. Gaur, B. Grinsztejn, S. Hassler, J.C. Hinojosa, T. Hodge, R. Kaplan, M. Lacerda, A. LaMarca, M.H. Losso, J. Valdez Madruga, K.H. Mayer, A. Mills, K. Mounzer, N. Ndlovu, R.M. Novak, A. Perez Rios, N. Phanuphak, M. Ramgopal, P.J. Ruane, J. Sánchez, B. Santos, P. Schine, T. Schreibman, L.S.Y. Spencer, O.T. Van Gerwen, R. Vasconcelos, J.G. Vasquez, Z. Zwane, S. Cox, C. Deaton, R. Ebrahimi, P. Wong, R. Singh, L.B. Brown, C.C. Carter, M. Das, J.M. Baeten, and O. Ogbuagu, for the PURPOSE 2 Study Team*

ABSTRACT

BACKGROUND

Twice-yearly subcutaneous lenacapavir has been shown to be efficacious for prevention of HIV infection in cisgender women. The efficacy of lenacapavir for preexposure prophylaxis (PrEP) in cisgender men, transgender women, transgender men, and gender-nonbinary persons is unclear.

METHODS

In this phase 3, double-blind, randomized, active-controlled trial, we randomly assigned participants in a 2:1 ratio to receive subcutaneous lenacapavir every 26 weeks or daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF). The primary efficacy analysis compared the incidence of HIV infection in the lenacapavir group with the background HIV incidence in the screened population. The secondary efficacy analysis compared the incidence of HIV infection in the lenacapavir group with that in the F/TDF group.

RESULTS

Among 3265 participants who were included in the modified intention-to-treat analysis, HIV infections occurred in 2 participants in the lenacapavir group (0.10 per 100 person-years; 95% confidence interval [CI], 0.01 to 0.37) and in 9 participants in the F/TDF group (0.93 per 100 person-years; 95% CI, 0.43 to 1.77). The background HIV incidence in the screened population (4634 participants) was 2.37 per 100 person-years (95% CI, 1.65 to 3.42). The incidence of HIV infection in the lenacapavir group was significantly lower than both the background incidence (incidence rate ratio, 0.04; 95% CI, 0.01 to 0.18; P<0.001) and the incidence in the F/TDF group (incidence rate ratio, 0.11; 95% CI, 0.02 to 0.51; P=0.002). No safety concerns were identified. A total of 26 of 2183 participants (1.2%) in the lenacapavir group and 3 of 1088 (0.3%) in the F/TDF group discontinued the trial regimen because of injection-site reactions.

Considerazioni per il futuro

Integrazione delle terapie iniettive nei protocolli clinici

Possibilità di combinazioni terapeutiche innovative

Ruolo degli infermieri nella gestione delle terapie long-acting

Grazie per l’attenzione.