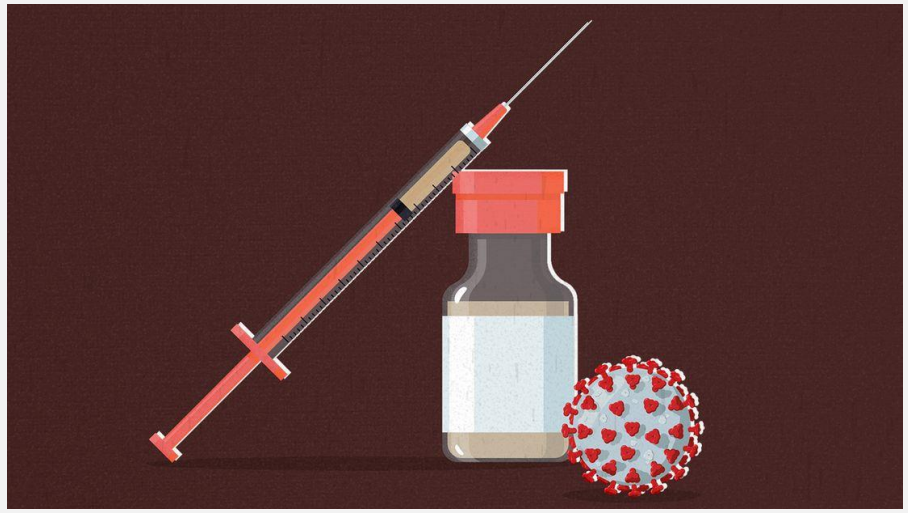


XV Workshop Nazionale
Innovazione e Ricerca per la Pratica Clinica
TERAPIE INNOVATIVE DELLE EPATITI CRONICHE VIRALI E DELLE INFEZIONI VIRALI
Firenze, 9-10 Gennaio 2023
Centro Congressi Hotel Albani

HIV- TERAPIA LONG-ACTING

Sergio Lo Caputo
Malattie Infettive
Università di Foggia

Disclosure of potential conflicts of interest

- Has been advisor for Gilead, ViiV, Janssen-Cilag, GSK, MSD and Astra Zeneca
- Had received speakers' honoraria from Gilead, ViiV, MSD, Astra Zeneca, GSK and Janssen-Cilag
- Had received support for travel meetings from Gilead, Janssen-Cilag, and ViiV
- Had received grant for research from Gilead

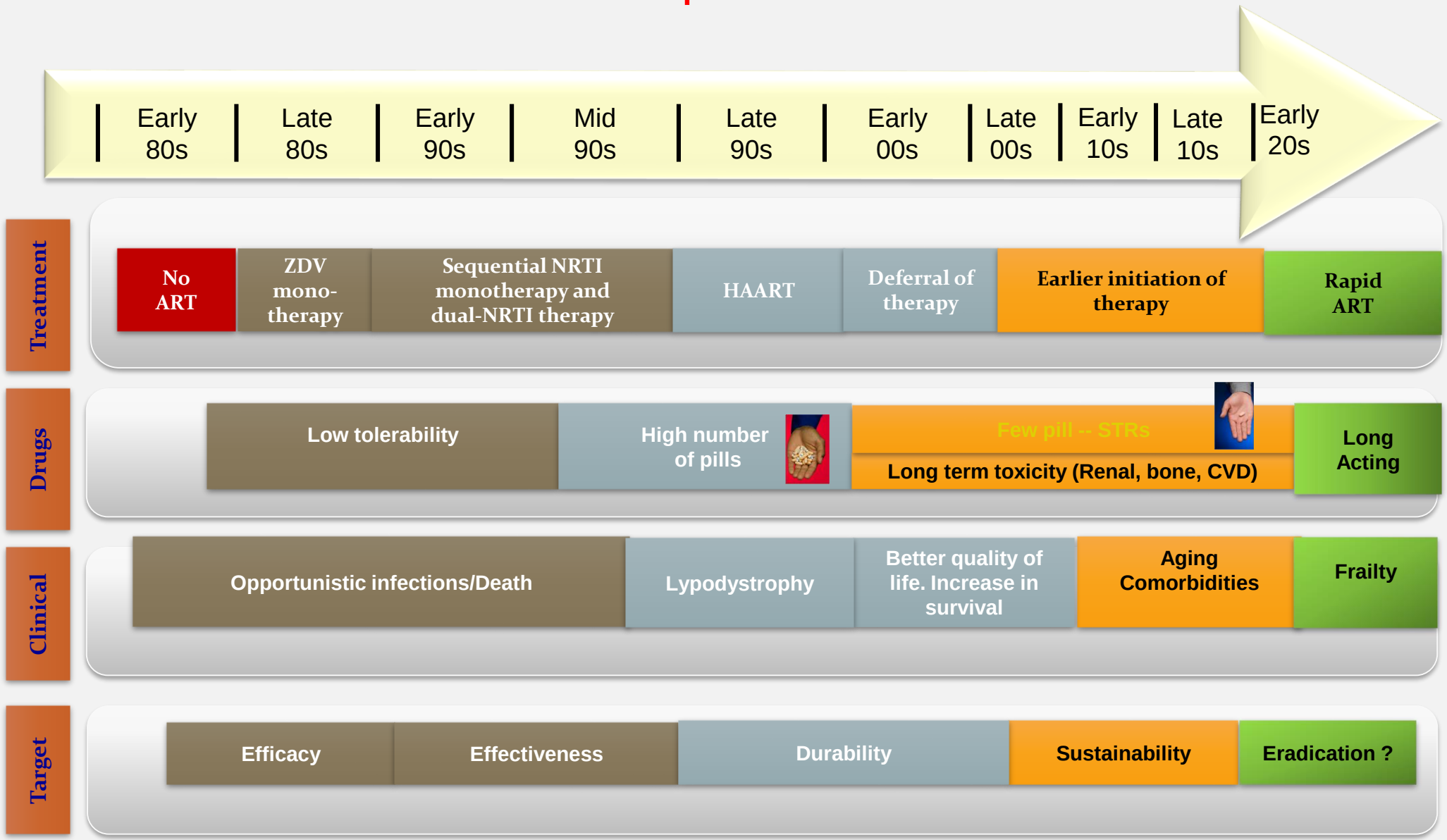
SIMPLIFYING TREATMENT IMPROVED ADHERENCE…

1995

2006

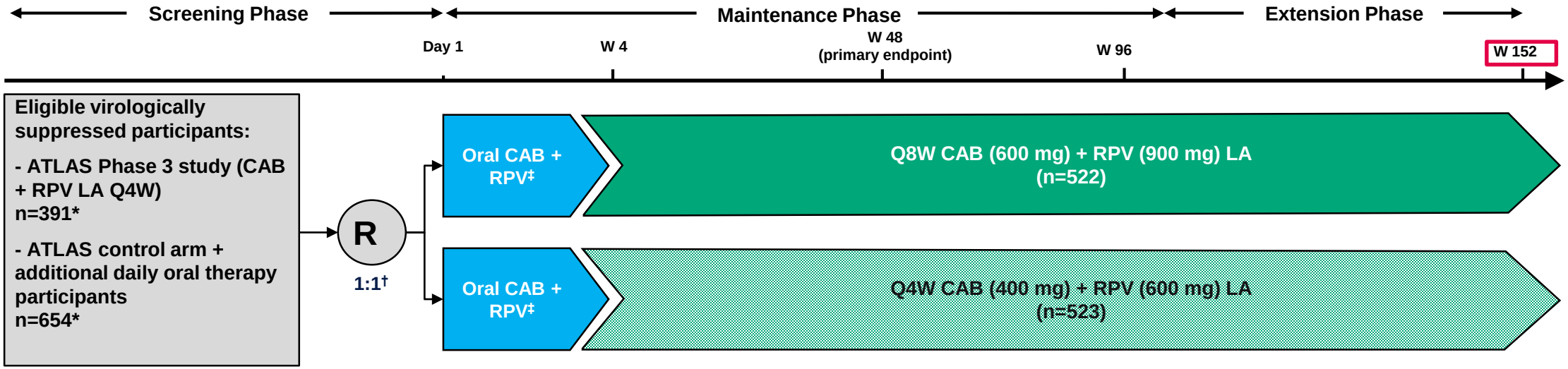
2022

Evoluzione della Terapia Antiretrovirale



ATLAS-2M Study Design

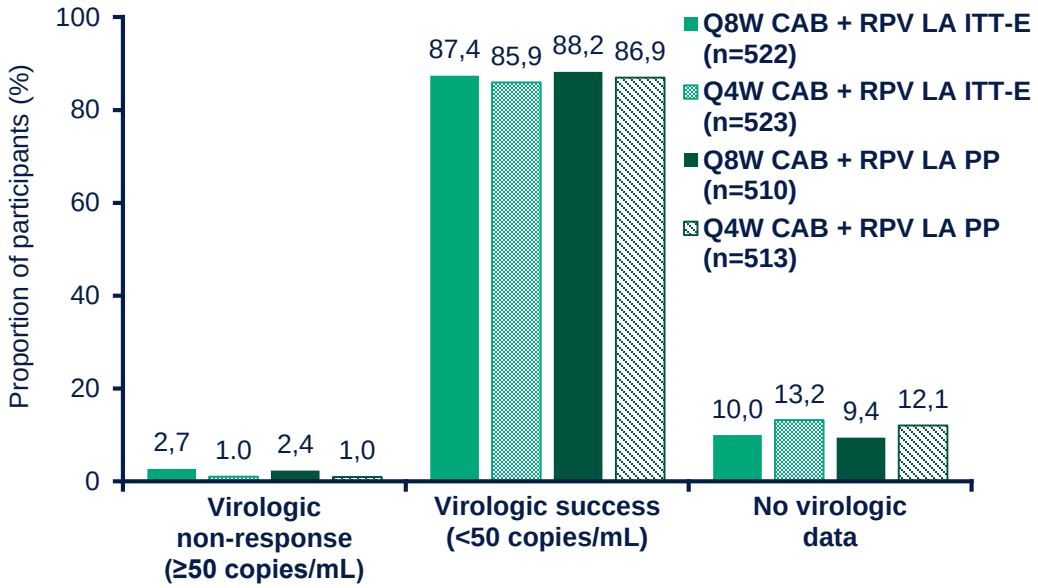
Phase 3b, randomized, multicenter, parallel-group, noninferiority, open-label study

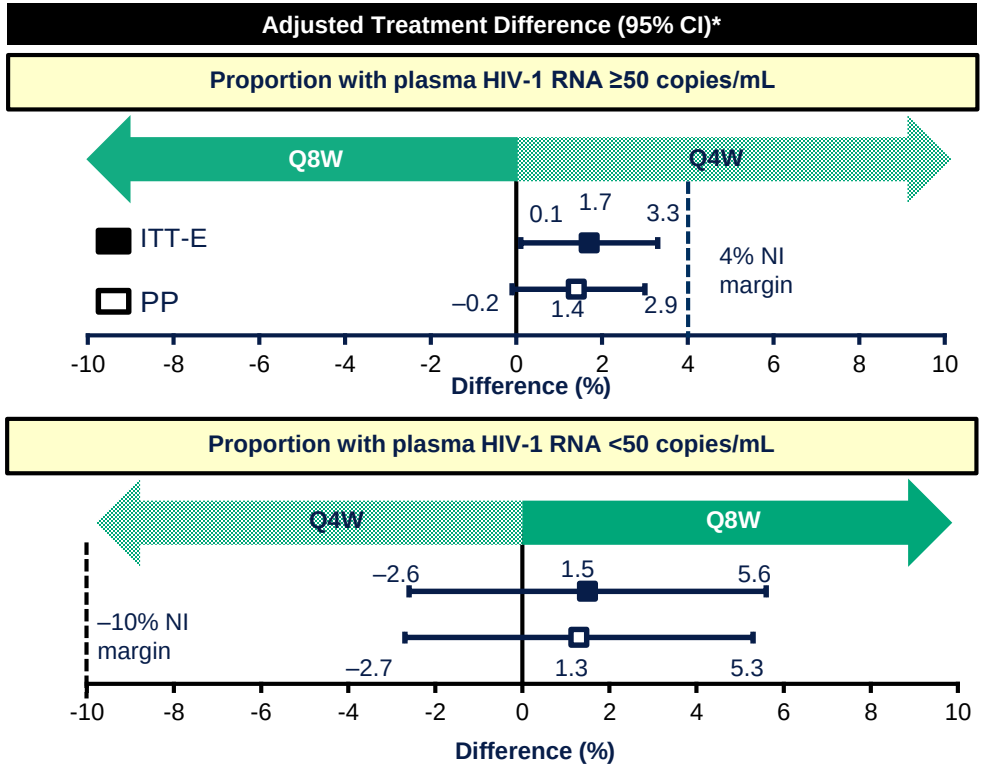


- The primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (FDA Snapshot, ITT-E)
- Secondary endpoints included the proportion of participants with plasma HIV-1 RNA ≥50 or <50 copies/mL at Week 152 (FDA Snapshot, ITT-E)
  - Per-protocol analyses were carried out at specific time points, including Week 48, Week 96, and Week 152
- Other endpoints assessed at Week 152 included the incidence of confirmed virologic failure (CVF; two consecutive plasma HIV-1 RNA levels ≥200 copies/mL), incidence of viral resistance in participants with CVF, safety and tolerability, and treatment satisfaction

*ITT-E population. †Randomization was stratified by prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks). ‡Excluding participants with prior CAB + RPV exposure in ATLAS (n=391). For further study design details, please see Overton et al. *Lancet*. 2020;396:1994-2005. CAB, cabotegravir; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomized; RPV, rilpivirine; W, week.

Virologic Outcomes at Week 152





- Baseline characteristics were similar between arms; 27% (n=280) of participants were female at birth, median (range) age was 42 (19–83), 20% (n=211) had a BMI ≥30 kg/m^2, and 37% (n=391) had prior CAB + RPV exposure[1]
- Noninferiority between Q8W and Q4W was confirmed for pre-specified analyses of HIV-1 RNA ≥50 and <50 copies/mL
- Results for the pre-specified per-protocol population were consistent with those for the ITT-E population

*Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks).
CAB, cabotegravir; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; PP, per protocol; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

1. Overton et al. *Lancet*. 2020;396:1994-2005.

Snapshot Outcomes at Week 152 (ITT-E Population)

ITT-E Population, n (%)	Q8W (n=522)	Q4W (n=523)
HIV-1 RNA <50 copies/mL	456 (87)	449 (86)
HIV-1 RNA ≥50 copies/mL	14 (3)	5 (1)
Data in window not below threshold	1 (<1)	0 (0)
Discontinued for lack of efficacy	12 (2)	4 (1)
Discontinued for other reason while not below threshold	1 (<1)	1 (<1)
No virologic data	52 (10)	69 (13)
Discontinued study due to AE or death*	23 (4)	24 (5)
Discontinued study for other reason†	28 (5)	44 (8)†
On study but missing data in window	1 (<1)‡	1 (<1)

*There were five deaths between the Week 96 and Week 152 analyses: suicide (n=1) and pancreatic cancer (n=1) in the Q8W arm; cardiac arrest (n=1), chronic obstructive pulmonary disease and chronic renal failure (n=1), and angina pectoris (n=1) in the Q4W arm. †Two participants discontinued due to COVID-19–related reasons. ‡COVID-19 related.
AE, adverse event; ITT-E, intention-to-treat exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

Snapshot "Discontinued Study for Other Reason" Through Week 152 (ITT-E Population)

ITT-E Population, n (%)	Q8W (n=522)	Q4W (n=523)
Discontinued study for other reason	28 (5)	44 (8)
Withdrawal by participant	16 (2)*	33 (6)
Physician decision†	5 (1)	3 (<1)
Protocol deviation	2 (<1)	4 (<1)
Protocol-specified withdrawal criterion met‡	2 (<1)	3 (<1)
Lost to follow-up	2 (<1)	1 (1)
Lack of efficacy	1 (<1)	0 (0)

- Withdrawal by participant was more common in the Q4W arm than the Q8W arm
  - The most common reasons for withdrawal by participant included frequency of visits (Q8W, n=4; Q4W, n=10), participant relocated (Q8W, n=1; Q4W, n=6), and intolerability of injections (Q8W, n=1; Q4W, n=8)
- Prohibited medication use (Q8W, n=0; Q4W, n=3) was the most common reason for protocol deviation

*Three participants completed the Maintenance Phase but decided not to continue to the Extension Phase, citing no specific reason for discontinuation beyond the completion of their study commitment. †Q8W, pulmonary tuberculosis (n=1), increased memory loss caused concerns about ability to consent (n=1), false-positive pregnancy test (n=1), participant was randomized in error (n=1), participant required long-term anticoagulant treatment (n=1); Q4W, other medical needs (n=1), participant relocated and communicated desire to withdraw to site staff (n=1), significant cardiovascular history (n=1). ‡The protocol-specified withdrawal criterion met for the five participants was pregnancy.
ITT-E, intention-to-treat exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

Participants With CVF Since the Week 96 Analysis

Participants With CVF Since Week 96					
#, arm	**Sex at birth, BMI (kg/m^2), country**	**HIV-1 subtype at baseline**	**Viral load at failure (copies/mL)**	**RPV RAMs observed at failure**	**INI RAMs observed at failure**
1, Q8W	Male, <30, Germany	B	24,221	E138A+M230M/L	Q148R
2, Q8W	Male, <30, Russia	A6*	59,467	E138A+Y181Y/C	Q148R

- The characteristics of the two participants (Q8W arm) who met the CVF criterion between Week 96 and 152 (Week 112 and Week 120) are shown
  - Neither had RAMs at baseline; however, the participant with subtype A6 had L74I integrase (IN) polymorphism at baseline
  - Both had treatment-emergent RAMs to CAB (Q148R) and RPV (E138A+Y181Y/C; E138A+M230M/L)

*This participant was originally classified as subtype A1 but, upon reanalysis, was later reclassified as subtype A6.
BMI, body mass index; CVF, confirmed virologic failure; INI, integrase inhibitor; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

Summary of CVFs Through Week 152

- **In total, through Week 152, 13 participants had CVF (Q8W, n=11 [2%]; Q4W, n=2 [<1%])**
  - Most CVFs occurred by Week 48 (77%, n=10/13), with 6/10 (60%) having ≥2 baseline factors (proviral RPV RAMs, HIV-1 subtype A6/A1, BMI ≥30 kg/m^2), which have been reported to be associated with increased risk of failure[1]
  - No participants with CVF through Week 152 had injection visits >7 days later than the scheduled visit date
  - Overall, 12/13 CVFs resuppressed on alternative regimens (one participant was non-adherent to protease inhibitor [PI]-based ART)
- An additional participant had a non-protocol-defined virologic failure at Week 48 (Q8W)
  - The participant had subtype A1, with RPV RAM E138K and IN mutation S230S/R observed at withdrawal; no RAMs to RPV or INIs were present at baseline; the participant resuppressed on an alternate regimen

1. Cutrell et al. *AIDS*. 2021;35:1333-1342.

Safety Summary (Excluding ISRs) Through Week 152

Parameter, n (%)	Q8W (n=522)	Q4W (n=523)
Any AE	469 (90)	490 (94)
Drug-related AEs	142 (27)	167 (32)
Any Grade ≥3 AE	66 (13)	63 (12)
Drug related*	10 (2)	10 (2)
Leading to withdrawal	17 (3)	20 (4)
Drug related	6 (1)	13 (2)
Any serious AE	48 (9)	44 (8)
Drug related	3 (<1)	3 (<1)

- Safety profiles at Week 152 were consistent with the previous analyses, with no new significant safety information observed
- Since Week 96, excluding ISRs, there were two participants with drug-related AEs leading to withdrawal (both Q4W, lipoatrophy and pyrexia) and no drug-related serious AEs

*One drug-related AE in each arm was Grade 4 (Q8W, acute pancreatitis [n=1]; Q4W, increased blood creatine phosphokinase [n=1]); none were Grade 5.
AE, adverse event; ISR, injection site reaction; Q4W, every 4 weeks; Q8W, every 8 weeks.

Common Adverse Events (Excluding ISRs) Through Week 152

Parameter, n (%)	Q8W (n=522)	Q4W (n=523)
AEs occurring in ≥10% of participants		
Nasopharyngitis	97 (19)	105 (20)
URTI	80 (15)	98 (19)
Headache	66 (13)	82 (16)
Back pain	64 (12)	77 (15)
Arthralgia	62 (12)	65 (12)
Diarrhea	56 (11)	66 (13)
Pyrexia	48 (9)	73 (14)
Drug-related AEs occurring in ≥3% of participants		
Pyrexia	23 (4)	33 (6)
Fatigue	11 (2)	23 (4)

AE, adverse event; ISR, injection site reaction; Q4W, every 4 weeks; Q8W, every 8 weeks; URTI, upper respiratory tract infection.

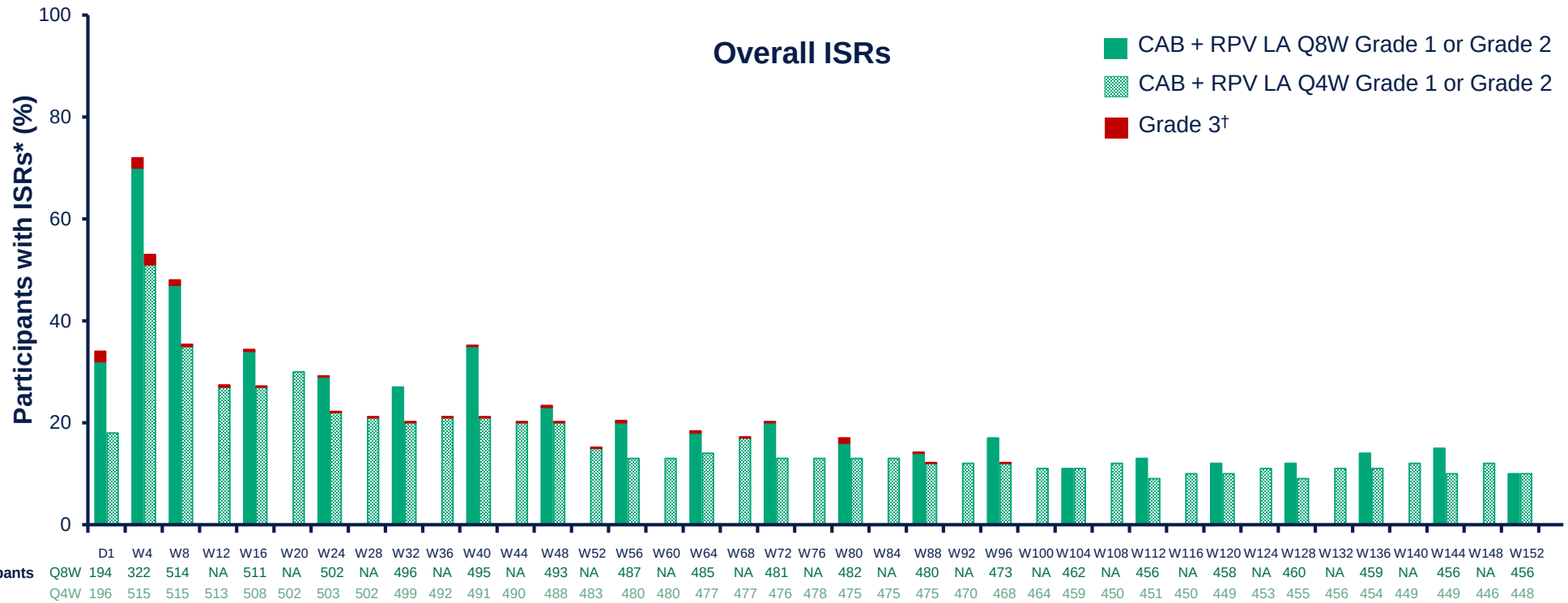
ISR Summary Through Week 152

	Q8W (n=522)	Q4W (n=523)
Participants who received ≥1 injection, n (%)	516 (99)	517 (99)
Number of injections	20,563	39,478
ISR events, n*	4168	5494
Injection site pain, n (% of injections)†	3189 (16)	4180 (11)
Injection site nodule, n (% of injections)†	259 (1)	457 (1)
Grade 3, n (% of ISR events)‡	54 (1)	50 (1)
Median duration, days (IQR)	3 (2, 5)	3 (2, 5)
Participants withdrawing for injection-related reasons, n (% of participants with injections)	8 (2)	13 (3)

- ISRs were the most common AEs; most were mild to moderate in severity (99%, n=9555/9662), short-lived (median duration 3 days), with few participants discontinuing due to injection-related reasons
- Three participants withdrew due to injection-related reasons between Week 96 and Week 152 (Q8W, n=1; Q4W, n=2)

*Each ISR event was counted separately. A participant may have had multiple ISR events following a single injection. †Those occurring with ≥1% of injections in either treatment arm are shown.
‡There were no Grade 4 or Grade 5 ISRs. AE, adverse event; IQR, interquartile range; ISR, injection site reaction; Q4W, every 4 weeks; Q8W, every 8 weeks.

ISRs Through Week 152



		D1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	W100	W104	W108	W112	W116	W120	W124	W128	W132	W136	W140	W144	W148	W152
Participants at visit	Q8W	194	322	514	NA	511	NA	502	NA	496	NA	495	NA	493	NA	487	NA	485	NA	481	NA	482	NA	480	NA	473	NA	462	NA	456	NA	458	NA	460	NA	459	NA	456	NA	456
	Q4W	196	515	515	513	508	502	503	502	499	492	491	490	488	483	480	480	477	477	476	478	475	475	475	470	468	464	459	450	451	450	449	453	455	456	454	449	449	446	448

- The number of participants reporting ISRs at each visit decreased over the first 48 weeks and remained consistent thereafter

*AE grade is the maximum grade reported by the participant at each visit. †There were no Grade 4 or 5 ISRs.
AE, adverse event; CAB, cabotegravir; D, day; ISR, injection site reaction; LA, long-acting; NA, not applicable; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; W, week.

Treatment Satisfaction

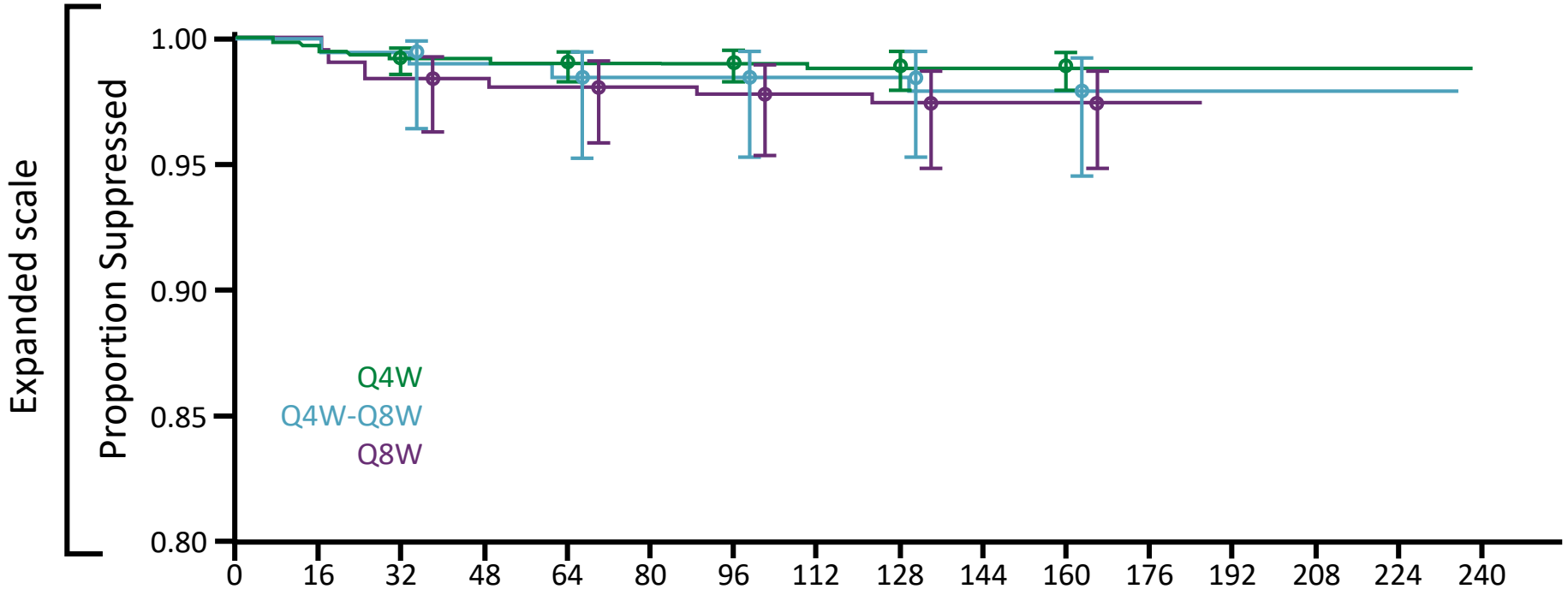
- In participants without prior CAB exposure, HIV treatment satisfaction questionnaire total mean scores significantly improved* (Q8W, 4.98; Q4W, 3.23) from baseline (Q8W, 57.73; Q4W, 56.72) to Week 152 for both treatment groups
- The adjusted mean change* from baseline significantly favored Q8W dosing at all three timepoints (Week 24, 1.07 [p=0.036]; Week 48, 1.73 [p=0.004]; Week 152, 1.75 [p=0.004])

*Adjusted for baseline score, sex at birth, age (<50, ≥50 years), race (White, non-White), and third agent class (INI, PI, non-nucleoside reverse transcriptase inhibitor).

ATLAS, ATLAS-2M + FLAIR Pooled Analysis: Study Design

- Pooled data from ATLAS through Wk 96, ATLAS-2M through Wk 152, and FLAIR through Wk 124 for participants exposed to only Q4W or Q8W for 2 separate model analyses:
  - MVA: covariates present at baseline and post-baseline (N = 1224)
  - BFA: covariates present at baseline only (N = 1363)
- After significant factors identified, virologic outcomes summarized for patients according to combinations of these factors in the total population (N = 1651): N = 1292 for MVA and N = 1431 for BFA
  - Factors explored as potential predictors of CVF: Q4W or Q8W dosing, sex at birth, baseline BMI, HIV-1 subtype A6/A1, baseline viral factors, predicted trough plasma concentrations

ATLAS, ATLAS-2M + FLAIR Pooled Analysis: Virologic Suppression by Regimen



Participants at each week																
Q4W	1128	1077	1029	849	781	759	745	717	694	523	408	166	115	113	62	0
Q4W-Q8W	195	195	194	193	190	189	188	183	182	181	180	146	116	112	53	0
Q8W	327	318	307	306	301	299	295	287	285	282	226	16	0	0	0	0

Orkin. HIV Glasgow 2022. Abstr 044. Reproduced with permission.

Slide credit: clinicaloptions.com

ATLAS, ATLAS-2M + FLAIR Pooled Analysis: Virologic Response[4]

Parameter	Q4W (n = 1129)*	Q8W (n = 327)	Q4W to Q8W (n = 195)	Overall (n = 1651)*
Number of CVFs, n (%)	11 (1.0)	8 (2.4)	4 (2.0)	23 (1.4)
Person-yr	2621	936	734	4291
Incidence rate (per 100 person-yr	0.42	0.85	0.54	0.54
95% CI for incidence rate	0.21-0.75	0.37-1.68	0.15-1.40	0.34-0.80

*1 participant lost to follow-up and unable to have exposure calculated; not included in graph.

- Majority of participants maintained HIV-1 RNA suppression up to 3 yr[1-3]; overall CVF rate was 1.4%
- Unadjusted incidence rate of CVF: 0.54/100 person-yr; similar across dosing arms
- Absolute difference between Q4W and Q8W regimens signifies ~1 additional CVF on Q8W over 200 person-yr

1. Swindells. AIDS. 2022;36:185. 2. Orkin. Lancet HIV. 2021;8:e668. 3. Overton. CROI 2022. Abstr H03.
4. Orkin. HIV Glasgow 2022. Abstr 044. Reproduced with permission.

ATLAS, ATLAS-2M + FLAIR Pooled Analysis: Predictors of CVF Using Baseline Factors Analysis

Covariate	Expanded BFA adjusted IRR (95% CI) (n = 1363)	*P* Value
RPV RAMs: yes/no	21.7 (5.80-80.8)	<.0001
HIV-1 subtype A6/A1: yes/no	12.9 (4.42-37.5)	<.0001
Baseline BMI, kg/m^2*	1.09 (1.00-1.19)	.0447
Regimen: Q8W/Q4W Integrase L74I†: yes/no Sex at birth: female/male Other NNRTI RAMs: yes/no CAB RAMs: yes/no Other INSTI RAMs: yes/no	Eliminated from model	

*BMI evaluated on a continuous scale; IRR is per one unit increase in kg/m^2. The IRR for BMI ≥30 kg/m^2 was 3.97, *P* = .01. †Included mixtures except L74I/M.

- With expanded dataset, baseline factors that remained significantly predictive of CVF risk included:
  - **Pre-existing RPV RAMs**
  - **HIV-1 subtype A6/A1**
  - **BMI**
- Dosing regimen and integrase L74I were not predictive of CVF risk

Combined Clinical Trials of LA CAB + RPV: Efficacy Through Wk 48

Parameter, n (%)	BMI <30 kg/m² (n = 1032)		BMI ≥30 kg/m² (n = 213)	
	Q8W (n = 268)	Q4W (n = 764)	Q8W (n = 59)	Q4W (n = 154)
HIV-1 RNA <50 copies/mL	252 (94)	708 (92.7)	54 (91.5)	142 (92.2)
HIV-1 RNA ≥50 copies/mL	1 (0.4)	9 (1.2)	4 (6.8)	7 (4.5)
▪ Data in window not below threshold	1 (0.4)	1 (0.1)	0	4 (2.6)
▪ Discontinued for lack of efficacy	0	6 (0.8)	4 (6.8)	3 (1.9)
▪ Discontinued for other reason while not below threshold	0	2 (0.3)	0	0
No virologic data in Wk 48 window	15 (5.6)	47 (6.2)	1 (1.7)	5 (3.2)
▪ Discontinued due to AE or death	6 (2.2)	29 (3.8)	0	1 (0.6)
▪ Discontinued for other reasons	9 (3.4)	18 (2.4)	1 (1.7)	4 (2.6)

Elliot. EACS 2021. Abstr BPD1/8.

Slide credit: clinicaloptions.com

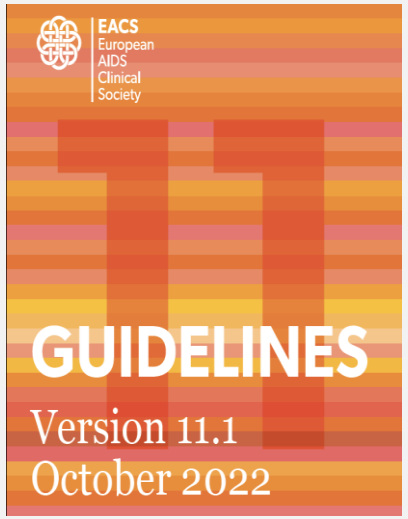
Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

(Last updated June 3, 2021; last reviewed June 3, 2021)

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

Key Considerations and Panel's Recommendations

- Advances in antiretroviral (ARV) treatment and a better understanding of HIV drug resistance have made it possible to consider switching a person with HIV from an effective regimen to an alternative regimen in some situations.
- The fundamental principle of regimen optimization is to maintain viral suppression without jeopardizing future treatment options.
- Adverse events, drug-drug or drug-food interactions, pill burden, pregnancy, cost, or the desire to simplify a regimen may prompt a regimen switch.
- It is critical to review a patient's full ARV history, including virologic responses, past ARV-associated toxicities and intolerances, and cumulative resistance test results before selecting a new ARV regimen **(AI)**.
- A long-acting ARV regimen, such as the combination of injectable cabotegravir and rilpivirine, is an optimization option for patients who are engaged with their health care, virologically suppressed on oral therapy for 3 to 6 months, and who agree to make the frequent clinic visits needed to receive the injectable drugs **(AI)**.
- Monotherapy with either a boosted protease inhibitor or an integrase strand transfer inhibitor has been associated with unacceptable rates of virologic failure and the development of resistance; therefore, monotherapy as a switch strategy **is not recommended (AI)**.
- When switching an ARV regimen in a person with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV should be continued **(AII)**. Using lamivudine or emtricitabine as the only drug in a regimen with HBV activity **is not recommended (AII)**, because HBV resistance to these drugs can emerge. Discontinuation of HBV drugs may lead to reactivation of HBV, which may result in serious hepatocellular damage.
- Consultation with an HIV specialist is recommended when planning a regimen switch for a patient with a history of resistance to one or more drug classes **(AIII)**.
- Close monitoring to assess tolerability, viral suppression, adherence, and safety is recommended during the first 3 months after a regimen switch **(AIII)**.



Dual therapies

In persons with suppression of HIV-VL < 50 copies/mL for the past 6 months these dual therapy strategies should only be given if there is

a) no historical resistance and

b) HBV immunity or if non-immune concomitant HBV Vaccination

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

DTG + RPV
XTC + DTG
XTC + DRV/b
Long-acting CAB + RPV bi-monthly injections

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

Dual therapy options supported only by small trials:
These regimens should be indicated only in persons not eligible for other treatment combinations due to intolerance or resistance to other drugs

DRV/b + RPV
DRV/b + DTG

Switch Strategies for Virologically Suppressed Persons

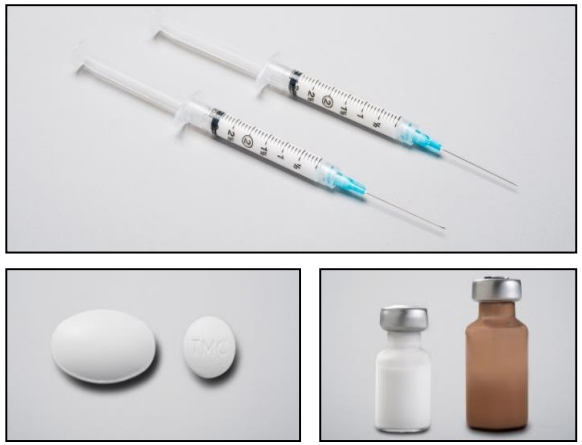
GUIDANCE ON USE OF LA CAB + RPV

- **Optimal candidates**
  - Virologically suppressed (HIV-1 RNA <50 c/mL) for past 6 mo
- **Contraindications**
  - Prior INSTI or NNRTI resistance (except K103N)
  - Chronic HBV infection or no HBV immunity

EACS Guidelines. October 2022.

CAB + RPV Therapy – oral lead-in

- HIV therapy has been simplified to once-daily, oral regimens containing 2 or 3 antiretrovirals
- Despite the success of daily oral therapy, considerable interest exists in LA injection treatment options



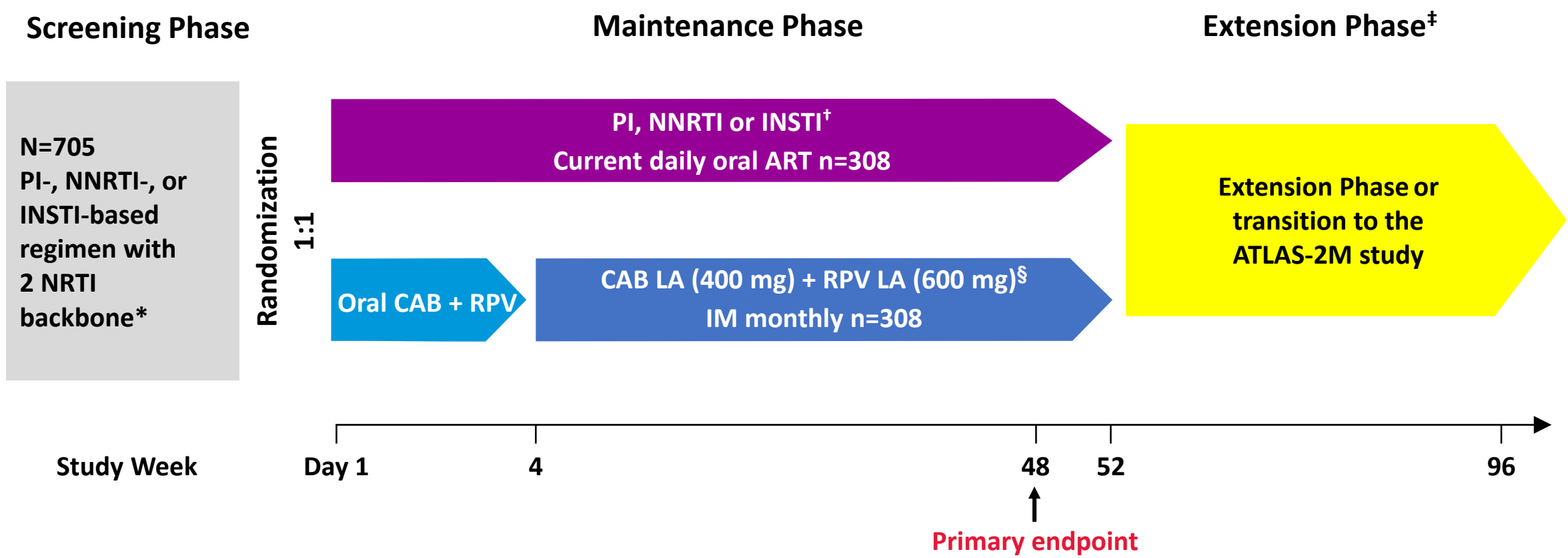
- Cabotegravir (CAB) is an HIV-1 integrase strand transfer inhibitor
  - **Oral 30 mg tablet: $t_{½}$ ~40 hours**
  - LA IM injection, 200 mg/mL: $t_{½}$ ~40 days
- Rilpivirine (RPV) is an HIV-1 non-nucleoside reverse transcriptase inhibitor
  - **Oral 25 mg tablet: $t_{½}$ ~50 hours**
  - LA IM injection, 300 mg/mL: $t_{½}$ ~90 days

CAB, cabotegravir; IM, intramuscular; LA, long-acting; RPV, rilpivirine; t½, half-life.

1. Margolis D, et al. HIV Glasgow 2018; UK. Poster 118; 2. Orkin C, et al. CROI 2019; Seattle, WA. Abstract 3947.

Swindells S, et al. CROI 2019; Seattle, WA. Abstract 1475.

ATLAS Study Design: Randomized, Multicenter, International, Open-Label, Noninferiority Study in Virologically Suppressed Adults (Ongoing)



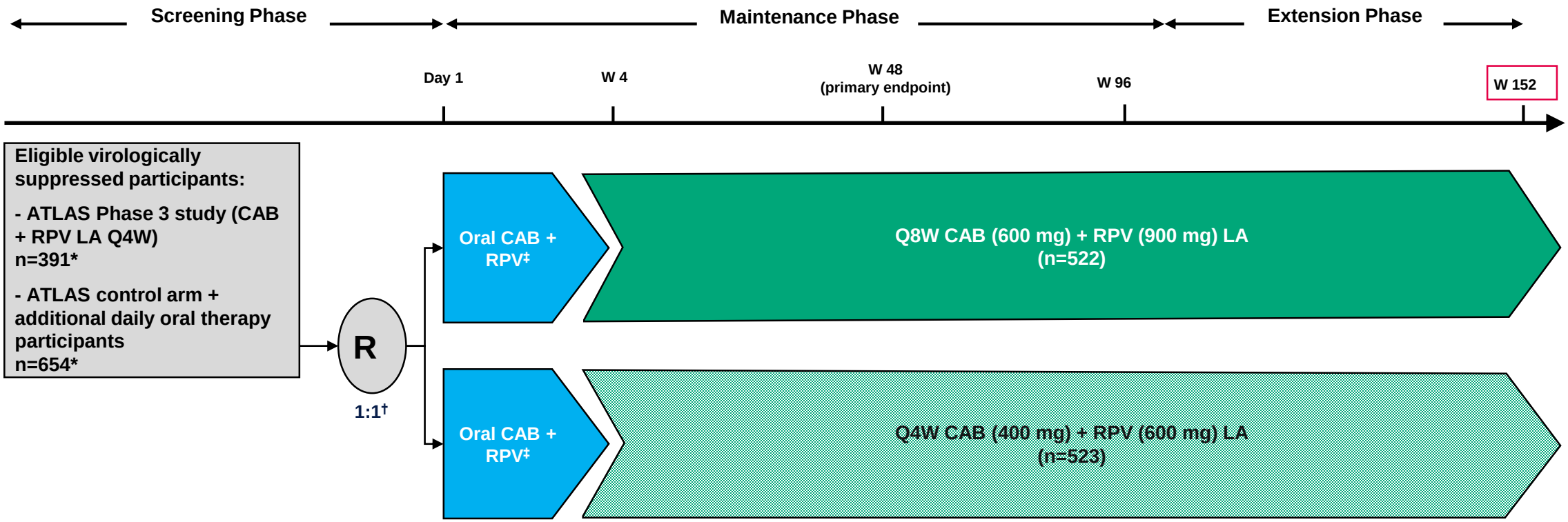
ART, antiretroviral therapy; CAB, cabotegravir; CAR, current ART; IM, intramuscular; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside RTI; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine; VL, viral load.

*Uninterrupted ART 6 months and VL <50 c/mL at Screening. 2× VL <50 c/mL ≤12 months; †INSTI-based regimen capped at 40% of enrolment, excluding Triumeq; ‡Optional switch to CAB LA + RPV LA at Week 52 for those on CAR; §Participants who withdraw/complete IM CAB LA + RPV LA must complete 52 weeks of follow-up.

Swindells S, et al. *CROI 2019*; Seattle, WA. Abstract 1475.

ATLAS-2M Study Design

Phase 3b, randomized, multicenter, parallel-group, noninferiority, open-label study



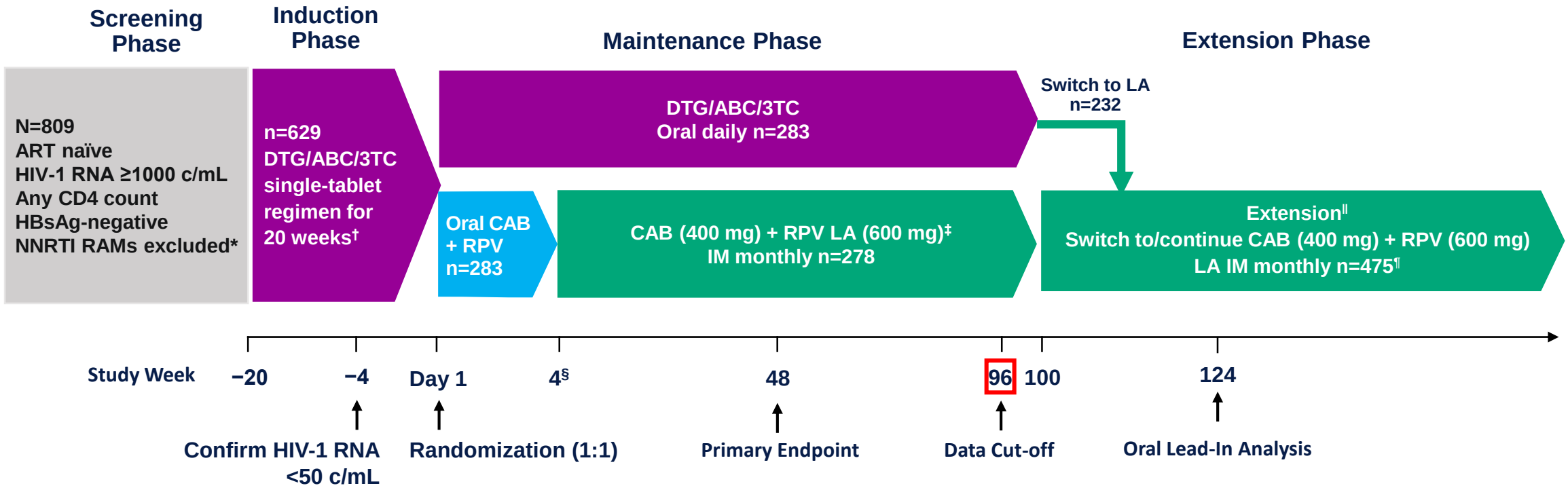
NP-IT-CBR-PPT-220005

*ITT-E population. †Randomization was stratified by prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks). ‡Excluding participants with prior CAB + RPV exposure in ATLAS (n=391). For further study design details, please see Overton et al. *Lancet*. 2020;396:1994-2005. CAB, cabotegravir; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomized; RPV, rilpivirine; W, week.

Overton et al. CROI 2022; Virtual. Poster H03.

FLAIR Study Design

Phase 3, randomized, multicenter, parallel-group, noninferiority, open-label study

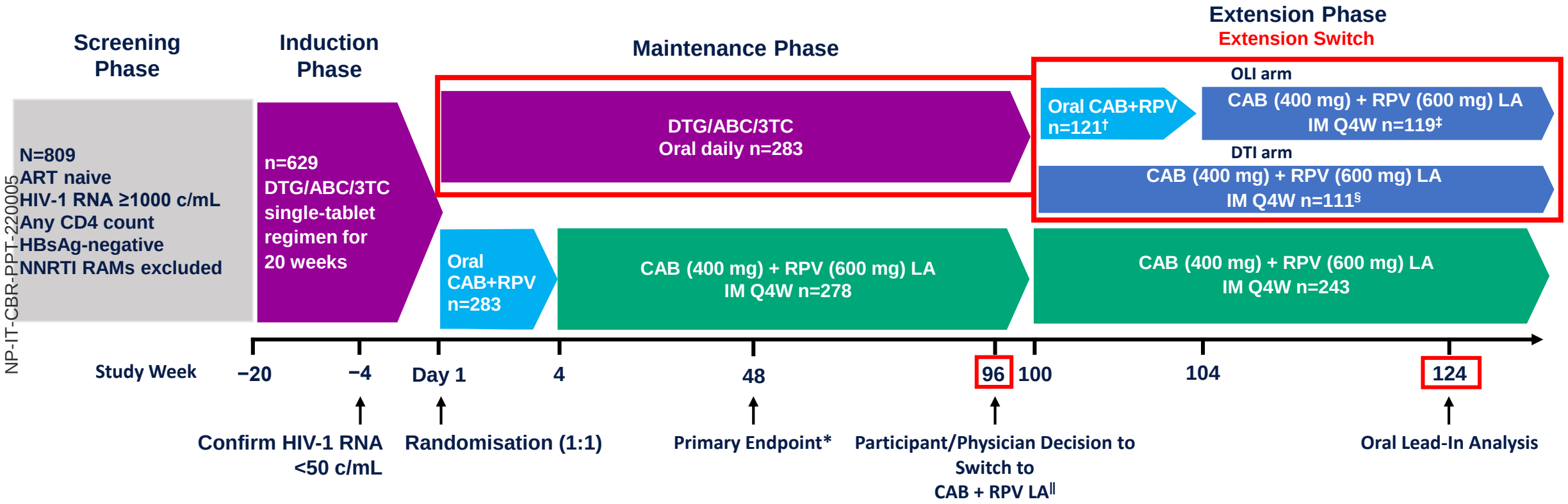


*NNRTI RAMs but not K103N were exclusionary or any known resistance to INIs. †If the participant had toxicity or intolerability in association with DTG/ABC/3TC, one switch to an approved alternative background NRTI was permitted. Participants who were positive for HLA-B*5701 received DTG plus two alternative non-ABC NRTIs instead of DTG/ABC/3TC (n=30).‡Participants who withdraw/complete CAB + RPV LA enter 52-week long-term follow-up. §Participants received initial loading doses of CAB 600 mg and RPV LA 900 mg at Week 4. Beginning at Week 8, participants received CAB 400 mg + RPV 600 mg LA injections every 4 weeks. ‖The extension phase will continue indefinitely until CAB + RPV LA is either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation, or until development of either CAB or RPV LA is terminated. ¶Estimate based on Maintenance Phase Conclusion Form – data on file.

Orkin et al. CROI 2020; Boston, MA. Poster 482LB.

FLAIR OLI: Study Design

Phase III, Randomised, Multicentre, Parallel-Group, Noninferiority, Open-Label Study

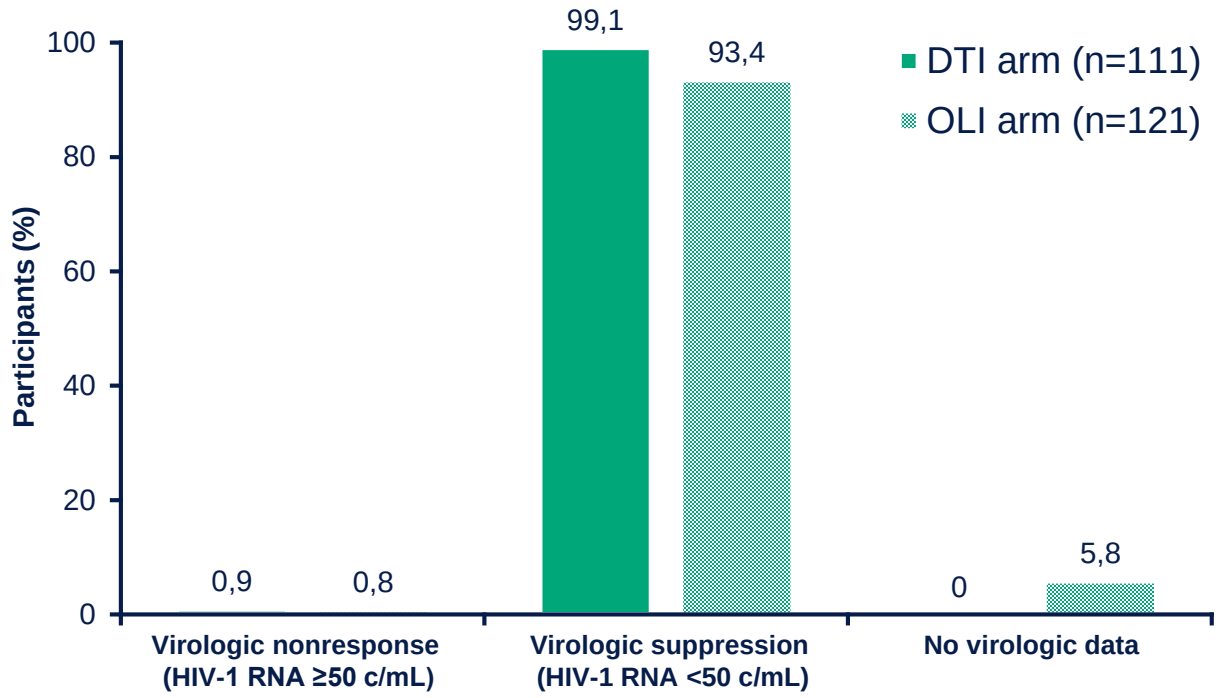


NP-IT-CBR-PPT-220005

*Proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 48 as per the Food and Drug Administration (FDA) Snapshot algorithm.
†Two discontinuations during OLI: 1 participant relocation, 1 pregnancy.
‡For participants in the OLI arm, daily oral CAB (30 mg) + RPV (25 mg) was initiated at Week 100 and continued for ≥4 weeks. Participants received their last dose of oral CAB + RPV and their first loading injections of CAB (600 mg) + RPV (900 mg) LA at Week 104. This was followed by CAB 400 mg + RPV 600 mg LA Q4W.
§For participants in the DTI arm, the last dose of CAR and first loading injections of CAB (600 mg) + RPV (900 mg) LA were administered at Week 100. This was followed by CAB 400 mg + RPV 600 mg LA Q4W.
‖Participants, in consultation with their physician, elected to receive CAB + RPV LA either with an OLI or DTI at Week 96. The new treatment regimen began at Week 100.
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; CAR, current antiretroviral therapy; DTI, direct to inject; DTG, dolutegravir; HBsAg, hepatitis B surface antigen; IM, intramuscular; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; OLI, oral lead-in; Q4W, every 4 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

D'Amico et al. HIV Glasgow 2020; Virtual. Slides O414.

FLAIR OLI: Snapshot Virologic Outcomes at Week 124 (Extension Switch)



Outcome, n (%)	DTI arm n=111	OLI arm n=121
HIV-1 RNA <50 copies/mL	110 (99.1)	113 (93.4)
HIV-1 RNA ≥50 copies/mL	1 (0.9)	1 (0.8)
Data in window not below threshold	0	1 (0.8)*
Discontinued for lack of efficacy	1 (0.9)†	0
Discontinued for other reason while not below threshold	0	0
Change in background therapy	0	0
No virologic data	0	7 (5.8)
Discontinued due to AE	0	2 (1.7)‡
Discontinued due to death	0	0
Discontinued study for other reason	0	5 (4.1)§
On study but missing data in window	0	0

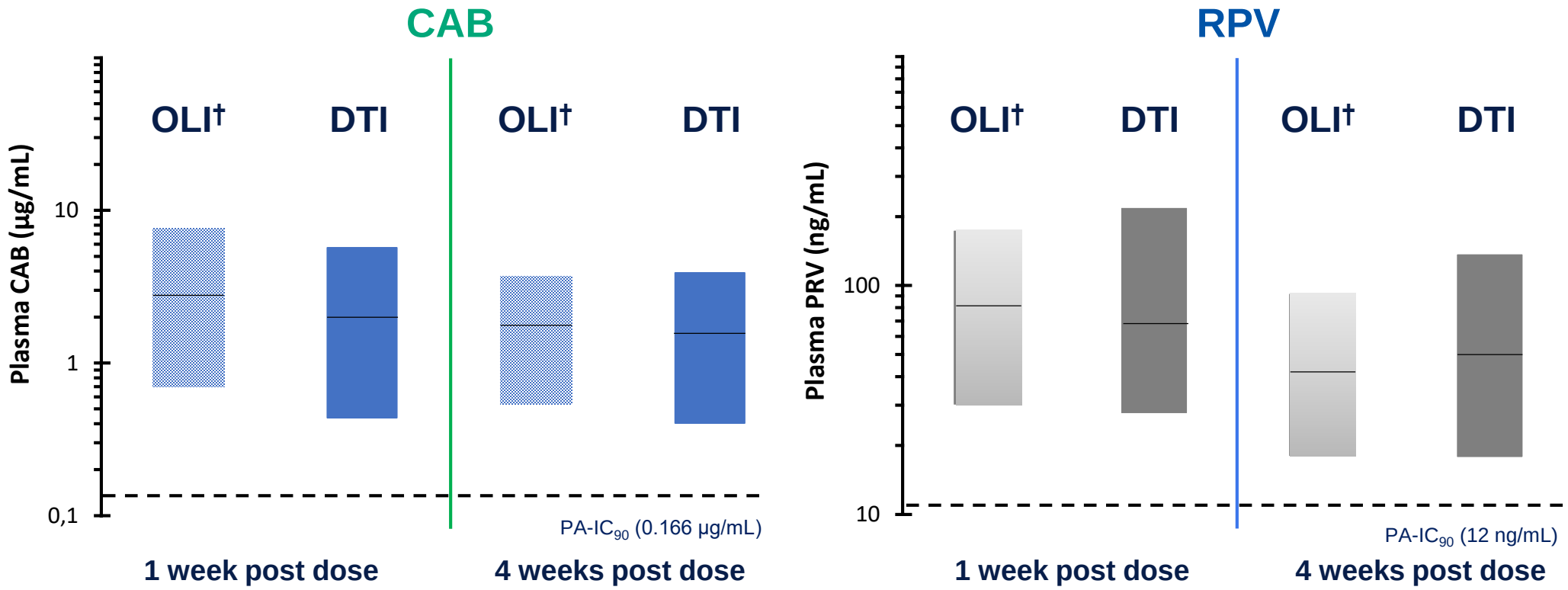
*Participant had HIV-1 RNA of 57 copies/mL at Week 124.
†Participant met the CVF criterion at Week 112.
‡Two participants discontinued due to AEs of injection site pain and weight gain.
§Five participants discontinued due to other reasons, which included burden of travel, prohibited medication use, participant relocation, burden of procedures/intolerability of injections and pregnancy.

- Only 1 participant (0.4%) met the CVF criterion in the Extension Switch population
  - The participant was in the DTI arm and met the CVF criterion on the 12th week of LA therapy. No INSTI or NNRTI resistance-associated mutations were detected at baseline and no INSTI resistance-associated mutations were detected at the timepoint of suspected virologic failure (NNRTI mutations could not be generated as the assay failed)

AE, adverse event; CVF, confirmed virologic failure; DTI, direct to inject; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; OLI, oral lead-in.

D'Amico et al. HIV Glasgow 2020; Virtual. Slides O414.

FLAIR OLI: Pharmacokinetics*
No Impact on Early CAB + RPV LA Concentrations in Absence of OLI



*5th percentile, median and 95th percentile values 1 week and 4 weeks after LA administration (OLI, LA arm: Week 5, n=262[CAB]/263[RPV]; Week 8, n=250[CAB]/251[RPV]; no OLI, DTI arm: Week 101, n=104; Week 104, n=79).
†Historical data: participants who were randomised to CAB + RPV LA in the Maintenance Phase.

- CAB and RPV concentrations were assessed 1 week and 4 weeks post loading dose injections
- No clinically meaningful differences in median CAB and RPV concentrations were observed between the DTI vs. OLI participants

CAB, cabotegravir; DTI, direct to inject; LA, long-acting; OLI, oral lead-in; PA-IC_{90}, protein-adjusted concentration required for 90% inhibition; RPV, rilpivirine.

D'Amico et al. HIV Glasgow 2020; Virtual. Slides O414.

FLAIR OLI: Extension Phase Common AEs and Drug-Related AEs (Excluding ISRs, Extension Switch)

Common (≥5% in either arm) AEs, n (%)	DTI arm n=111	OLI arm n=121
Nasopharyngitis	20 (18)	13 (11)
Upper respiratory tract infection	10 (9)	7 (6)
Pyrexia	9 (8)	4 (3)
Diarrhoea	2 (2)	10 (8)
Dizziness	8 (7)	4 (3)
Gastroenteritis	7 (6)	3 (2)
Headache	7 (6)	3 (2)
Common (≥3% in either arm) drug-related AEs, n (%)		
Pyrexia	6 (5)	2 (2)
Dizziness	3 (3)	2 (2)

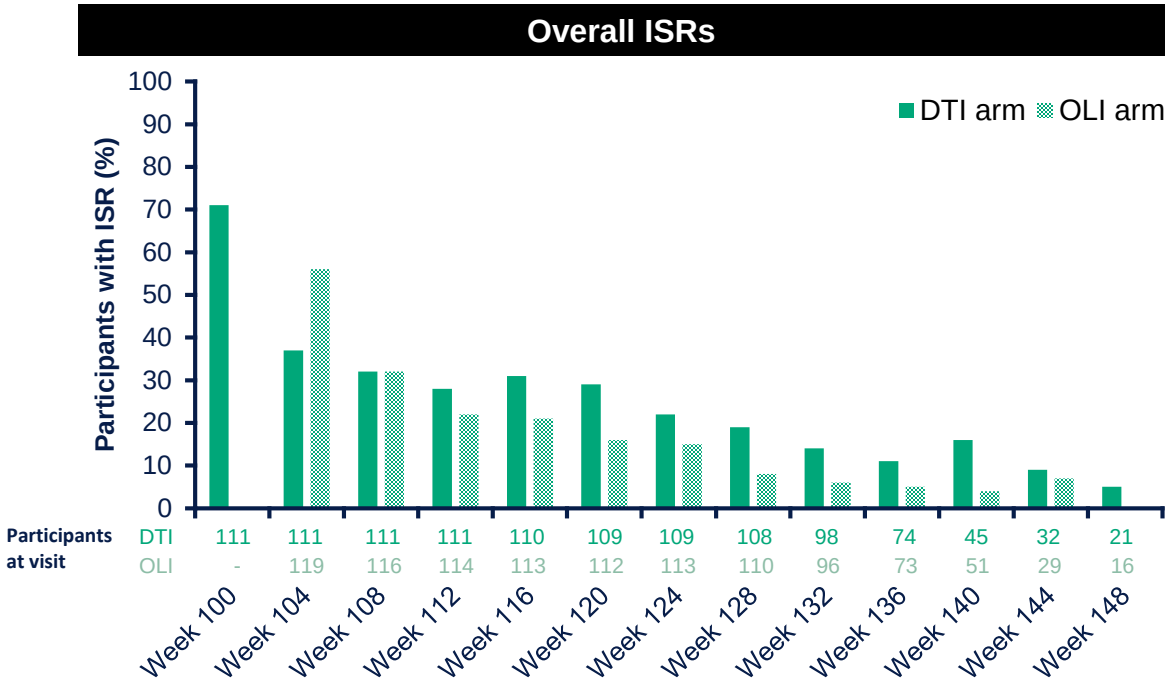
- **There were no liver monitoring/stopping events, confirmed hypersensitivity reactions or other significant dermatological manifestations observed in either treatment arm**
- The incidence of Grade 3 or 4 emergent chemistry toxicities (13 vs. 5)* and rash (4 vs. 2; all Grade 1 or 2)† was higher in the DTI arm than the OLI arm

*DTI arm: Grade 3 AST, CPK, GFR, lipase and phosphate toxicities and Grade 4 CPK and lipase toxicities; OLI arm: Grade 3 CPK and lipase toxicities and Grade 4 CPK toxicities.
†One AE of rash pruritic (Grade 1), reported during the OLI period in the OLI arm, was considered related to study drugs.

AE, adverse event; AST, aspartate aminotransferase; CPK, creatine phosphokinase; DTI, direct to inject; GFR, glomerular filtration rate; ISR, injection site reaction; OLI, oral lead-in.

D'Amico et al. HIV Glasgow 2020; Virtual. Slides O414.

FLAIR OLI: Extension Phase ISRs (Extension Switch)



Parameter	DTI arm n=111	OLI arm n=121
Number of injections	2314	2128
Number of ISR events	576	338
Grade 1 – mild, n (% of total injections)	478 (20.7)	271 (12.7)
Grade 2 – moderate, n (% of total injections)	97 (4.2)	62 (2.9)
Grade 3 – severe, n (% of total injections)	1 (<1)	5 (<1)
Median duration of ISR events, days	3	3
ISR events leading to withdrawal, n (% of ISRs)	0	2 (<1)

- 4442 injections were administered in total
  - Only 1 participant discontinued due to two Grade 3 ISRs (one for each injection at the same visit)
- The majority (>99%, 908/914) of ISRs were Grade 1 (82%, 749/914) or Grade 2 (17%, 159/914), and their incidence decreased over the study period
  - 89% of these events were injection site pain

DTI, direct to inject; ISR, injection site reaction; OLI, oral lead-in.

D'Amico et al. HIV Glasgow 2020; Virtual. Slides O414.

Oral Lead-in CONS

- Il paziente anche se per poco tempo deve adattarsi ad un nuovo regime
- Rischio errore nella assunzione della terapia
- Ulteriore aumento degli accessi in ospedale

Oral Lead-in PROS

- Attenta valutazione alla tollerabilità delle due molecole
- Attuazione di un percorso verso il LA che responsabilizza il paziente

Established and other potentially significant drug interactions for CAB + RPV LA

Concomitant drug class	Anti-convulsants	Anti-mycobacterials		Glucocorticoid (systemic)	Herbal product	Macrolide or ketolide antibiotics*	Narcotic analgesic
Drug name	Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Rifampicin Rifapentine	Rifabutin	Dexamethasone†	St. John's wort‡	Clarithromycin Erythromycin	Methadone
Metabolic enzyme impacted	CYP3A UGT	CYP3A UGT	CYP3A UGT	CYP3A	CYP3A	CYP3A	CYP3A
Effect on concentration	↓ CAB ↓ RPV	↓ CAB ↓ RPV	↓ CAB ↓ RPV ↔ RIF	↓ RPV	↓ RPV	↔ CAB ↑ RPV	↔ CAB ↔ RPV ↓ Methadone
Advice	**Do not co-administer**					**Potential significant interaction** ***Caution is recommended***	**Potential significant interaction** ***Clinical monitoring is recommended***

↑, increase; ↓, decrease; ↔, no change

*Consider alternatives to clarithromycin and erythromycin because of risk of TdP with these drugs
†More than a single-dose treatment
‡Hypericum perforatum
TdP, Torsade de Pointes

Patel P, et al. IWCP of HIV 2020. Oral 11193

EACS European AIDS Clinical Society

GUIDELINES
Version 11.0
October 2021

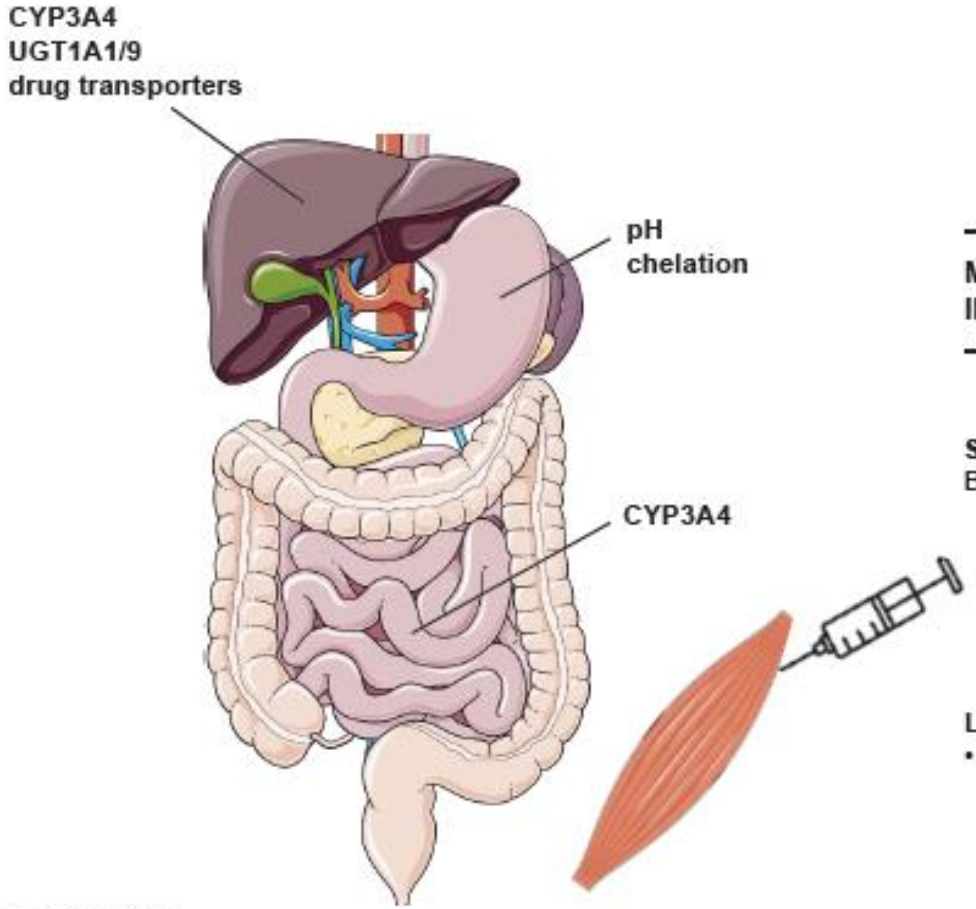
Drug-Drug Interactions after Oral and Intramuscular Administration of CAB and RPV

Intramuscular administration: → DDIs at the gastrointestinal level are avoided
→ DDIs at the hepatic level can still occur (magnitude of DDIs with inducers is not mitigated)

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

MANAGEMENT OF MISSED INJECTIONS

Dose initiation and the ±7-day dosing window for Q2M dosing regimen

Choose a ‘target date’ for injections[1,2,3]

- Injections should be given on the same date of the month
- Consider 1st–28th of the month (not all months have equal number of days)

±7-day dosing window[1,2,3]

- If necessary, injections can be given up to 7 days before OR 7 days after the target date*
- Patients should return to their target date (or as close as possible) for the following injection

Example target treatment date of 15th

Sun	Mon	Tue	Wed	Thu	Fri	Sat
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	**15**	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

Patients who miss a scheduled injection visit should be clinically reassessed to ensure resumption of therapy remains appropriate[1,3,4]

NP-IT-CBR-PPT-220016

*Remain as close to the target date as possible

1. Teichner P, et al. IDWeek 2019. Oral 884; 2. Vocabria EU SmPC. Jan 2022; 3. Rekambys EU SmPC. Feb 2022

Managing interruptions in injection dosing with oral bridging therapy: Every 2-month dosing regimen

- CAB and RPV oral tablets QD can be used to replace LA injections for up to 2 months[1,2]
  - For oral therapy durations greater than 2 months, an alternative oral regimen is recommended[1,2]
- The first dose of oral therapy should be taken on the target date for injection (±7 days)[1,2]
- Resume injection dosing on the day* oral dosing completes[1,2]

Resumption of injections after planned missed injections (with oral bridging)[1,2]

Time since MISSED Target Treatment Date	Injection dosing recommendation
≤1 month	Continue with the every 2-month (600 mg CAB and 900 mg RPV) IM injections dosing schedule as soon as possible
>1 month	Re-initiate injections (600 mg and 900 mg RPV): two initiation injections 1 month apart, then every 2 months thereafter

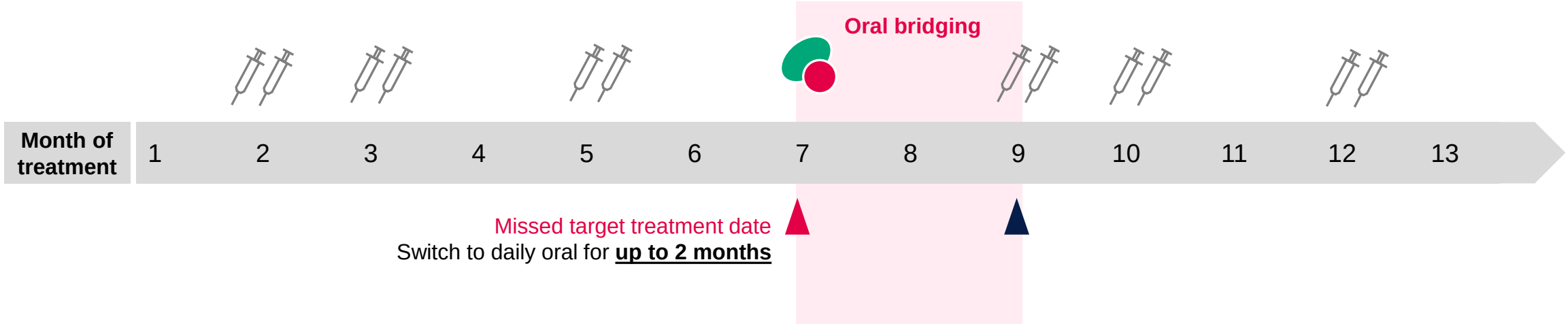
*This day becomes the new target treatment date

1. Vocabria EU SmPC. Jan 2022
2. Rekambys EU SmPC. Feb 2022

NP-IT-CBR-PPT-220016

Managing planned missed injections (<u>with</u> oral bridging): Every 2-month dosing regimen

- CAB and RPV oral tablets QD can be used to replace CAB + RPV LA injections for up to 2 months[1,2]
  - For oral therapy durations greater than 2 months, an alternative oral regimen is recommended[1,2]
- The first dose of oral therapy should be taken on the missed target treatment date for injection (±7 days)[1,2]
- It is recommended to resume injection dosing on a target treatment date. Oral dosing completes on the same day as injections restart[1,2]



1. Vocabria EU SmPC. Jan 2022; **2.** Rekambys EU SmPC. Feb 2022

Dosi dimenticate

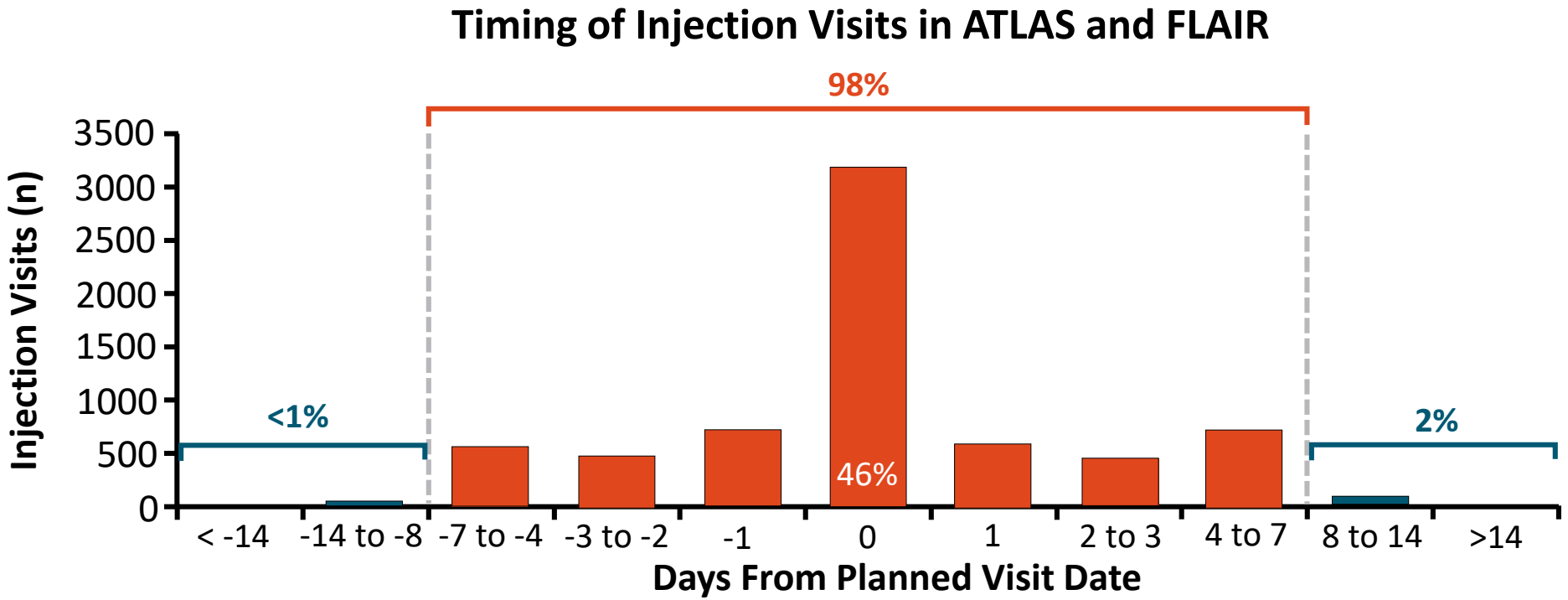
I pazienti che non si presentano ad una visita programmata per la somministrazione dell'iniezione dovranno essere sottoposti nuovamente a valutazione clinica per garantire che la ripresa della terapia sia appropriata

Mancata somministrazione di un'iniezione con frequenza bimestrale

Se un paziente prevede di non potersi sottoporre alla visita programmata per l'iniezione di CAB/RPV entro il termine massimo di 7 giorni rispetto alla data inizialmente stabilita, è possibile sostituire una visita programmata per la somministrazione iniettiva bimestrale con la terapia orale (una compressa di cabotegravir da 30 mg e una compressa di rilpivirina da 25 mg, una volta al giorno). Nel caso in cui sia necessario sopperire alla mancanza di terapia per più di due mesi, ossia qualora venga saltata più di una iniezione bimestrale, si dovrà avviare un regime orale alternativo.

La prima dose della terapia orale dovrà essere assunta due mesi (+/- 7 giorni) dopo le ultime iniezioni di cabotegravir e rilpivirina. La somministrazione delle iniezioni dovrà essere ripresa l'ultimo giorno della somministrazione orale giornaliera

ATLAS and FLAIR: High Adherence to Injection Visits and Outcomes for Missed Injections



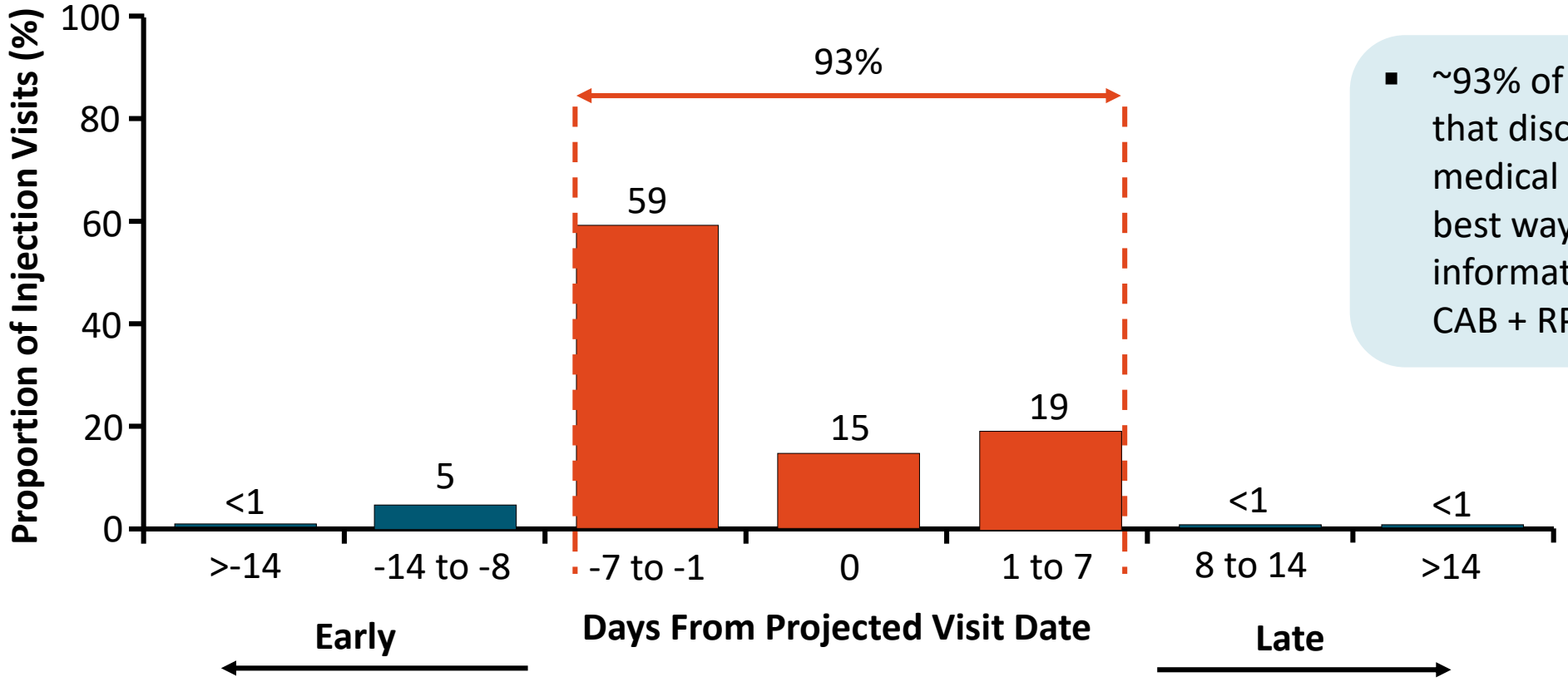
- **No participants** receiving injections outside of +7 days dosing window met criteria for confirmed virologic failure or had HIV-1 RNA ≥50 copies/mL at 48 wk
- All patients in both trials continued injection dosing schedule after oral bridging, maintained virologic suppression, and reported no safety events of concern

Teichner. IDWeek 2019. Abstr 884.

Slide credit: clinicaloptions.com

CARISEL: European Phase IIIb Implementation-Effectiveness Study of LA IM CAB + RPV Every 2 Mo

- 91.2% of participants felt "very" or "extremely positive" about LA CAB + RPV treatment at Mo 4
- 96.6% felt it was acceptable to return for an injection every 2 mo



- ~93% of participants felt that discussion with a medical provider was the best way to receive information about LA IM CAB + RPV

Hocqueloux. EACS 2021. Abstr PE2/37.

Slide credit: clinicaloptions.com

LONG ACTING – ASPETTI ORGANIZZATIVI

- Revisione strutture ambulatoriali

(ambulatori, frigoriferi, percorsi)

- Revisione orari di apertura

(aperture dedicate)

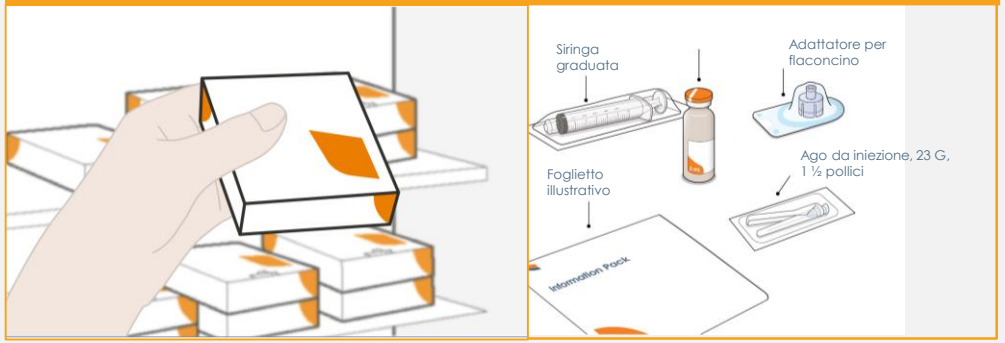
- Revisione modalità di prenotazione visite
- Ridistribuzione personale

COME INIZIARE

ASSICURARSI DI AVER PREDISPOSTO TUTTO IL NECESSARIO PER PREPARARE LE INIEZIONI[1,2]

- Assicurarsi di avere entrambe le confezioni sia di cabotegravir che di rilpivirina e che il contenuto delle confezioni sia completo prima di cominciare a preparare i medicinali per l'iniezione intramuscolare in sede ventrogluteale[1,2]

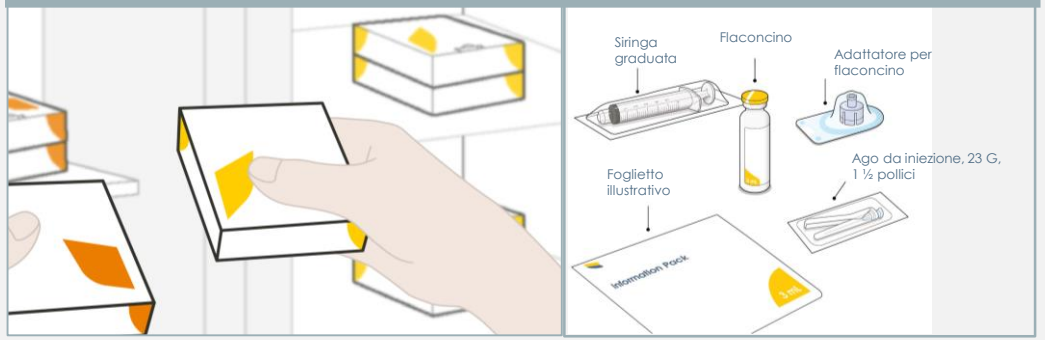
Confezione di cabotegravir:



- Prendere la confezione di cabotegravir dallo **scaffale**

Nota: La fiala di **cabotegravir** ha il vetro di colore marrone.[1]

Confezione di rilpivirina:

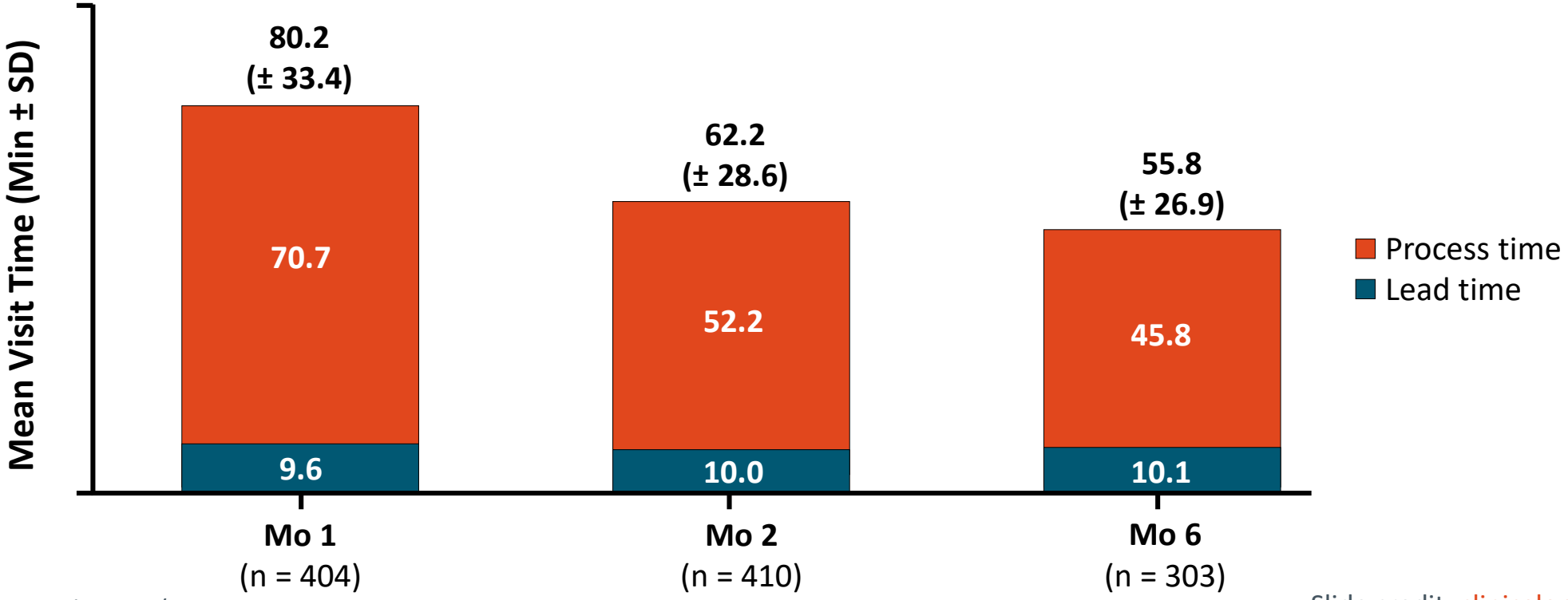


Estrarre la confezione di rilpivirina dal **frigorifero** e attendere che il contenuto del flaconcino raggiunga la temperatura ambiente prima di effettuare l'iniezione[2]

Bibliografia: 1. Cabotegravir Foglietto illustrativo. **2.** Rilpivirina Foglietto illustrativo.

CARISEL: Visit Time for LA CAB + RPV Injections at Interim Analysis

- At Mo 4, most participants (51%) spent ≤40 min in clinic, and 84% spent ≤20 min in exam room
- From Mo 1-6, mean appointment duration decreased by 30.4% (24.4 min), mostly driven by reduced processing time



Hocqueloux. EACS 2021. Abstr PE2/37.

Slide credit: clinicaloptions.com

LONG ACTING – ADERENZA

- Regolarità nella somministrazione del LA
- Aderenza alle terapie concomitanti

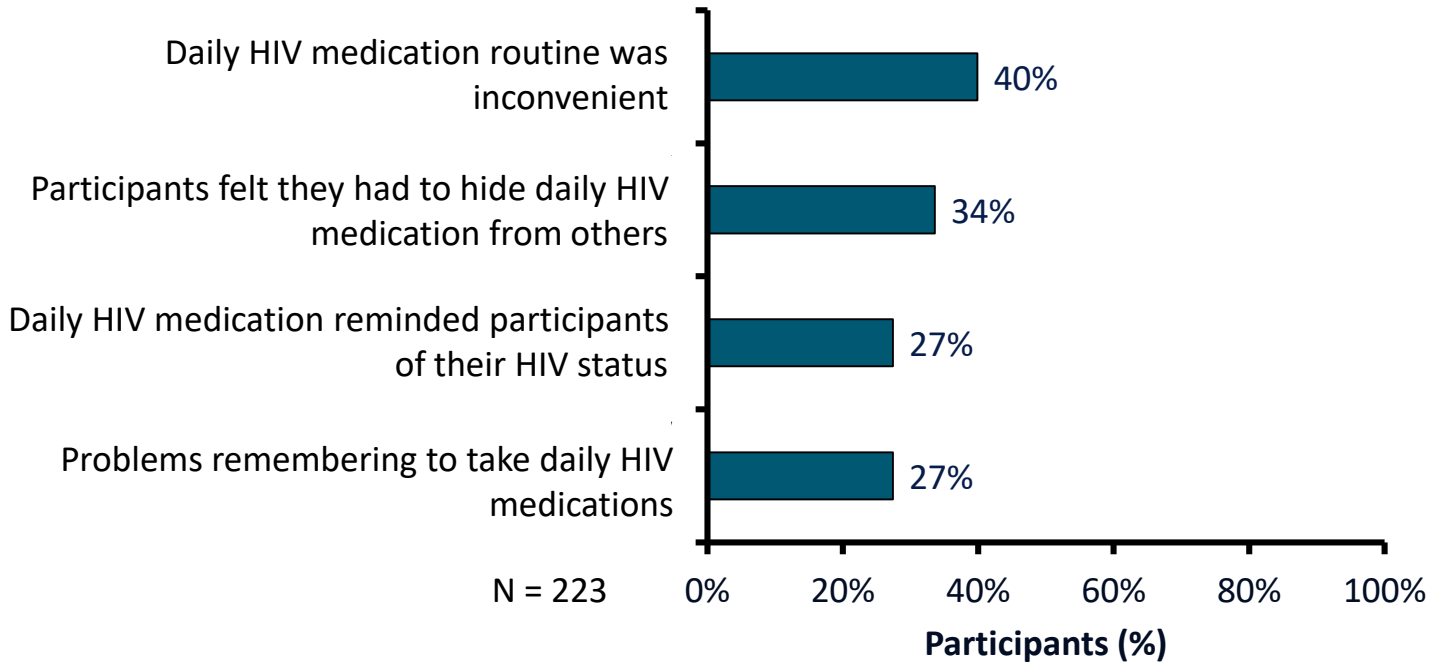
LONG ACTING – GESTIONE DEL PAZIENTE

- Maggiori contatti con personale infermieristico
- Riorganizzazione visite con infettivologo e altri specialisti
- Maggiore utilizzo di strumenti informatici

(mail, videochiamate, whtsapp,…)

CARLOS Study: Challenges With Daily HIV Medication Before Deciding to Switch to LA CAB + RPV

- 32% of participants had no problems with their daily ART
- Most common challenges (>20% of participants) with daily oral ART before deciding to switch to LA CAB + RPV (multiple answers possible) were:



Wyen. AIDS 2022. Abstr EPB179.

Slide credit: clinicaloptions.com

LONG ACTING – NEXT STEP

Study Design

N = 72

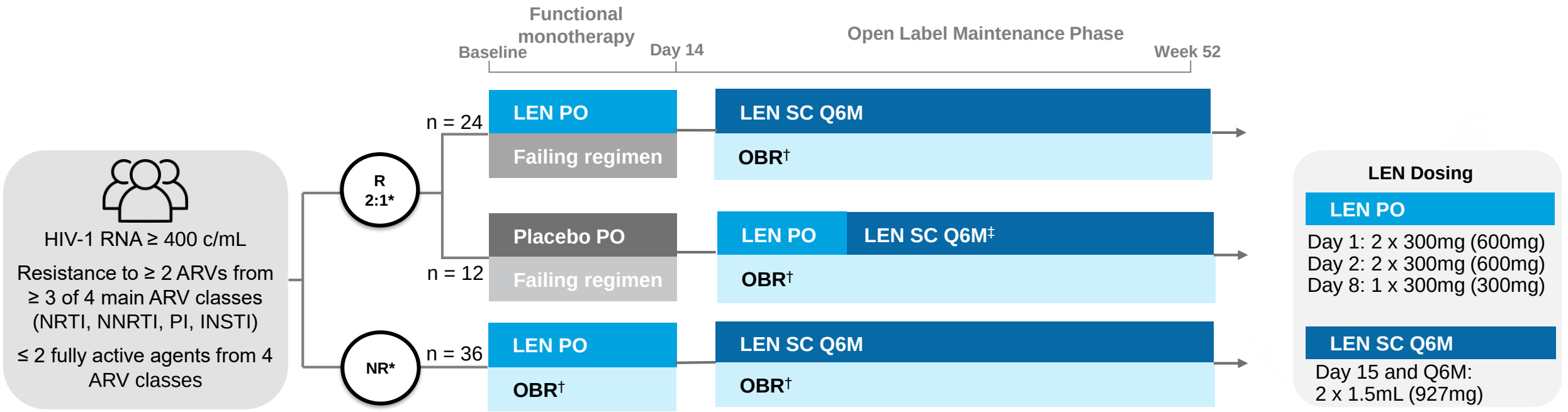
HTE PLWH with MDR, aged ≥ 12 years and weighing ≥ 35 kg

Outcomes (randomized cohort)

Primary: ≥ 0.5 $\log_{10}$ c/mL reduction in HIV-1 RNA from BL at Day 15

Secondary: HIV-1 RNA < 50 c/mL and < 200 c/mL at W26 and W52 (FDA Snapshot)

2019 – present (ongoing)



LEN Dosing

LEN PO

Day 1: 2 x 300mg (600mg)
Day 2: 2 x 300mg (600mg)
Day 8: 1 x 300mg (300mg)

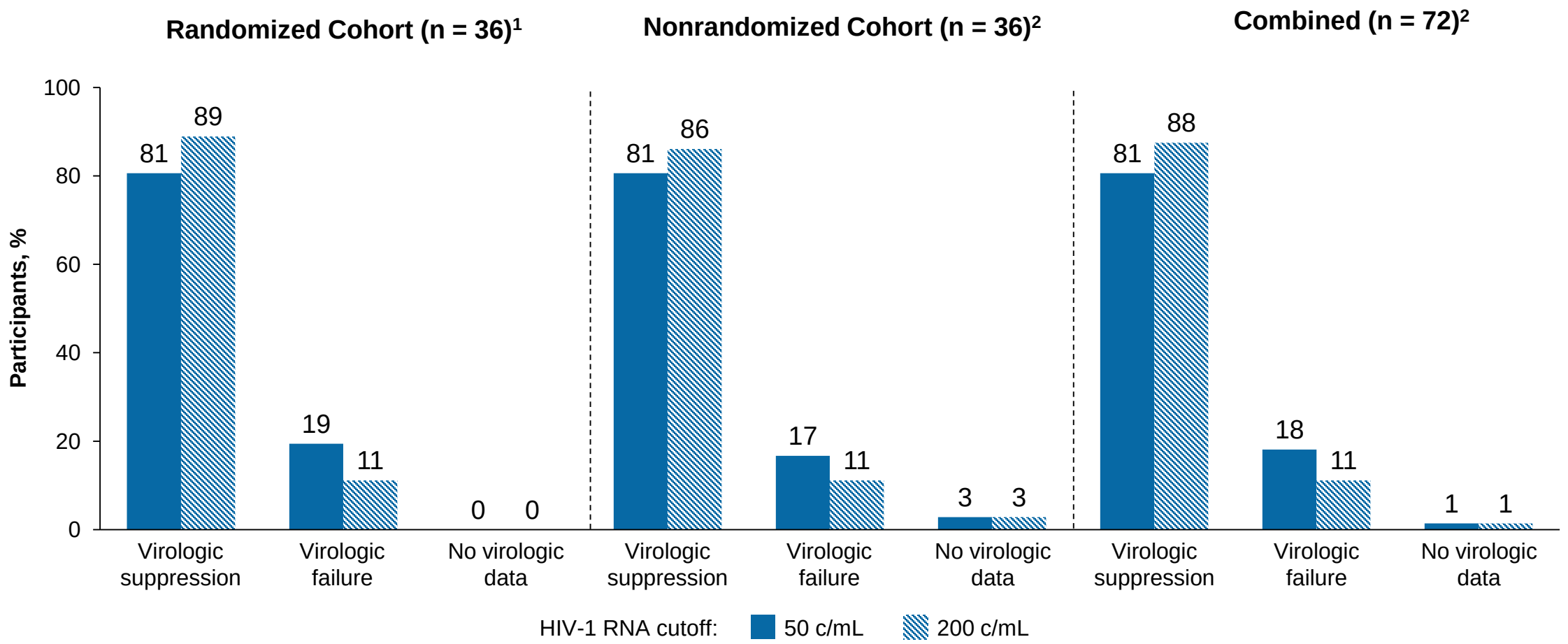
LEN SC Q6M

Day 15 and Q6M:
2 x 1.5mL (927mg)

*Participants with < 0.5 $\log_{10}$ c/mL decline in HIV-1 RNA during screening entered the randomized cohort; participants with ≥ 0.5 $\log_{10}$ c/mL decline in HIV-1 RNA during screening entered the nonrandomized cohort; †Investigational agents (e.g., fostemsavir) permitted, atazanavir, atazanavir/cobicistat, atazanavir/ritonavir, efavirenz, etravirine, nevirapine, tipranavir not permitted
BL, baseline; D, day; HTE, heavily treatment-experienced; MDR, multidrug resistance; NR, nonrandomized; OBR, optimized background regimen; OLM, open-label maintenance; PO, by mouth; Q6M, every 6 months; R, randomized; SC, subcutaneous(ly); W, week

1. Clinicaltrials.gov. NCT04150068 Accessed July 11, 2022 2. Ogbuagu O, et al. CROI 2022, Poster 491

Efficacy at Week 26: Randomized and Nonrandomized Cohorts



LEN in combination with OBR achieved high rates of virologic suppression at Week 26 in HTE PLWH

HTE, heavily treatment-experienced

1. Molina JM, et al. vIAS 2021, OALX01LB02; 2. Ogbuagu O, et al. CROI 2022, Poster 491

Study Design

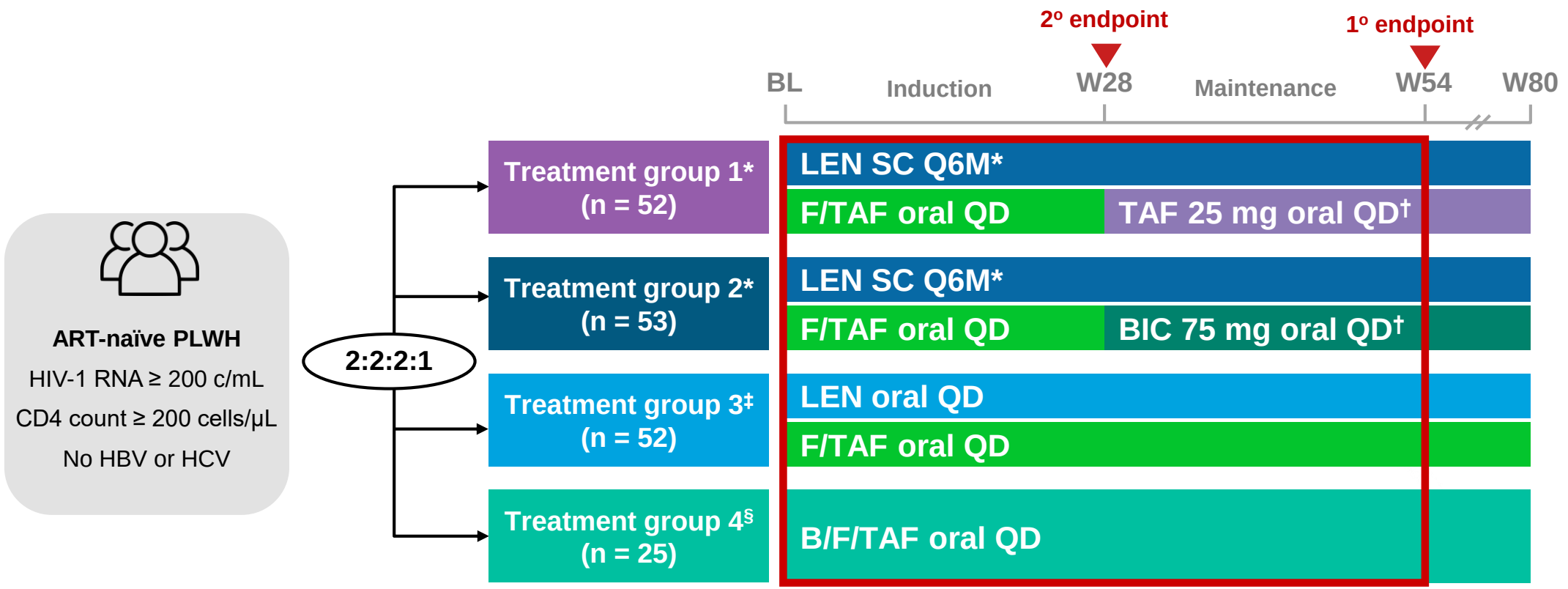
N = 182

Treatment-naïve PLWH with HIV-1 RNA ≥ 200 c/mL and no HBV or HCV[2]

Outcomes[2]

Primary (Week 54): HIV-1 RNA < 50 c/mL at Week 54. Secondary (Weeks 28, 38 & 80): HIV-1 RNA < 50 c/mL, and change from BL in log_{10} HIV-1 RNA and CD4 count

2019 – present (ongoing)



*LEN oral initiation (600 mg on Day 1 and 2, 300 mg on Day 8) followed by LEN SC 927 mg on Day 15; F/TAF, 200/25 mg; †Participants in treatment group 1 and 2 required HIV-1 RNA < 50 c/mL at W16 and W22 to initiate either TAF or BIC at W28; those with HIV-1 RNA ≥ 50 c/mL discontinued study at W28 ; ‡LEN 600 mg on Day 1 and 2, followed by LEN 50 mg from Day 3; F/TAF, 200/25 mg; §B/F/TAF, 50/200/25 mg. BL, baseline; Q6M, every 6 months (Q26 weeks); QD, once daily; W, week

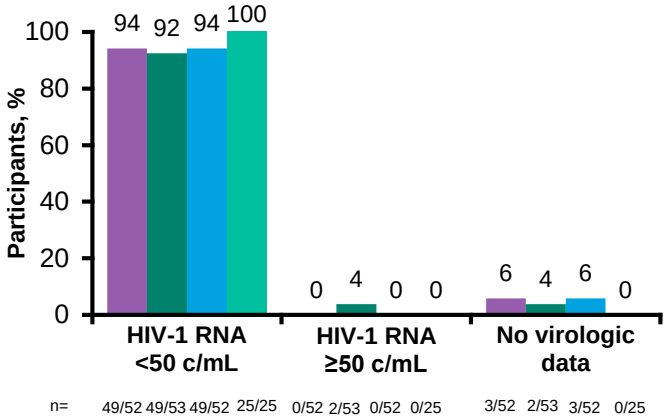
1. Gupta SK, et al. CROI 2022, Oral 138 **2.** https://www.clinicaltrials.gov/ct2/show/NCT04143594?term=lenacapavir%2C+calibrate&cond=hiv&draw=2&rank=1, accessed March 4, 2022

Calibrate ‡

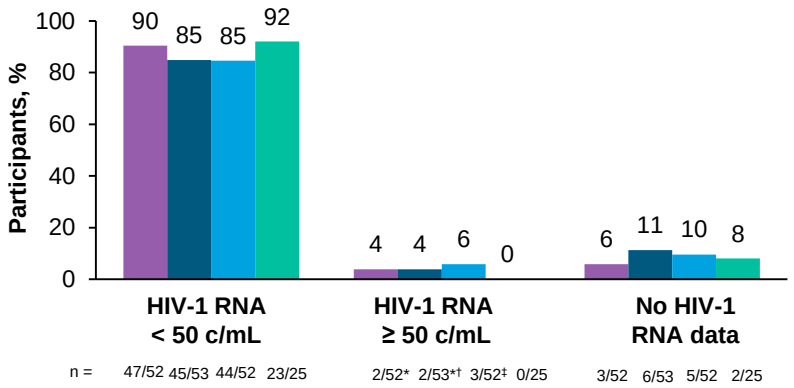
TG 1: LEN SC + F/TAF to LEN SC + TAF
TG 2: LEN SC + F/TAF to LEN SC + BIC
TG 3: LEN QD + F/TAF
TG 4: B/F/TAF

Efficacy at Week 28 and 54

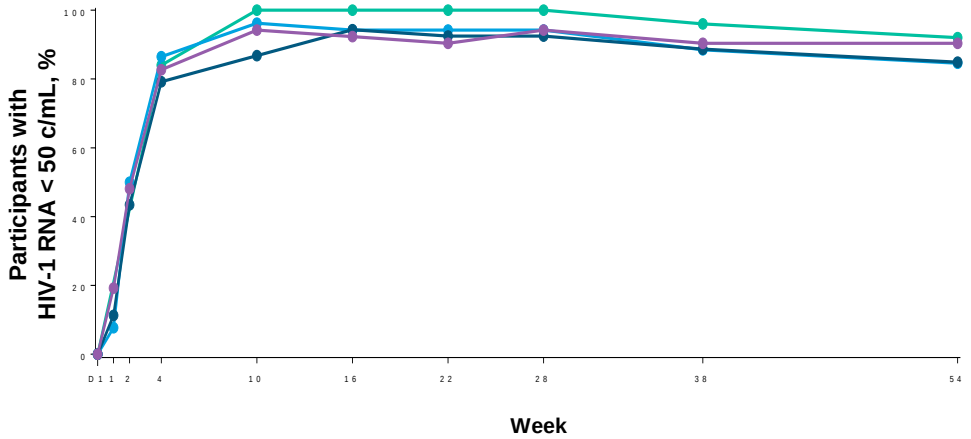
Virologic Outcome at W28 (FDA Snapshot; ITT)



Efficacy at Week 54 (FDA Snapshot)



Participants With HIV-1 RNA < 50 c/mL by Visit (M = F; On Treatment)



- In the pooled SC LEN group (TG 1 + 2), 88% (92/105) achieved and maintained virologic suppression at Week 54; and of participants who were virologically suppressed at Week 28, 93% (91/98) maintained virologic suppression at Week 54

In TN PLWH, SC LEN in combination with oral F/TAF, TAF or BIC and oral LEN in combination with F/TAF rapidly achieved and maintained high rates of virologic suppression at 1 year.

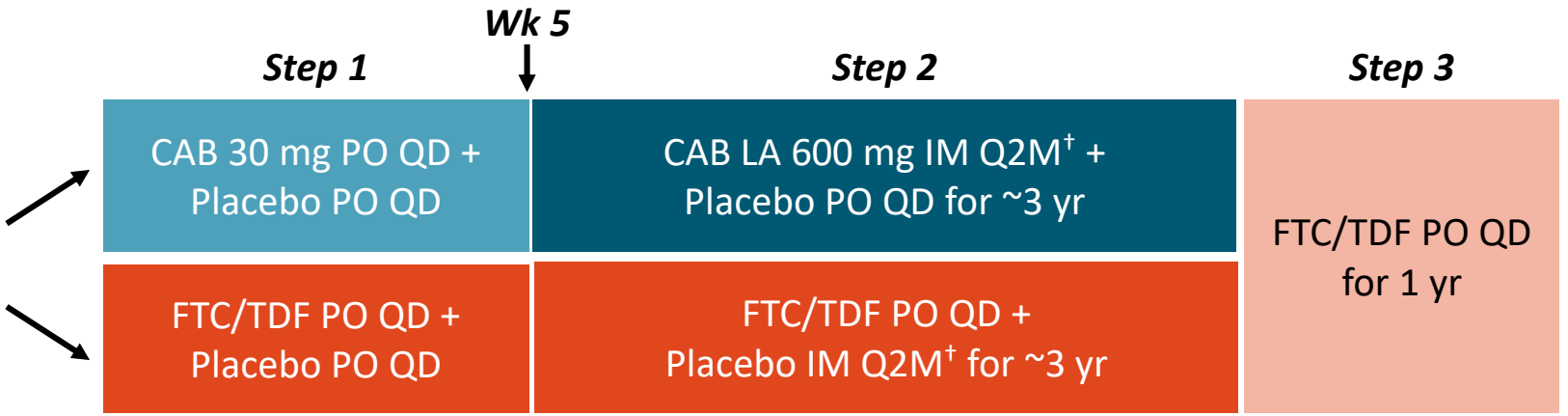
*Three participants (two in TG 1 and one in TG 2) discontinued on account of not meeting the protocol criteria of having HIV-1 RNA < 50 c/mL prior to Week 28; †One participant discontinued on Day 2 (TG 2); ‡Two of the three participants (TG3) with HIV-1 RNA ≥ 50 c/mL at Week 54 were suppressed in the subsequent visit M = F, missing equals failure; QD, once daily; TG, treatment group; TN, treatment naive

Gupta SK, et al. CROI 2022, Oral 138

HPTN 083 and 084: Efficacy and Safety of LA Injectable CAB vs Daily Oral FTC/TDF for PrEP

- International, randomized, double-blind phase IIb/III (083) and phase III (084) trials

083: MSM and TGW ≥18 yr of age at high risk of HIV infection (N = 4566)[1,2]
084: Sexually active cisgender women, 18-45 yr of age, at high risk of HIV infection (N = 3224)[3]



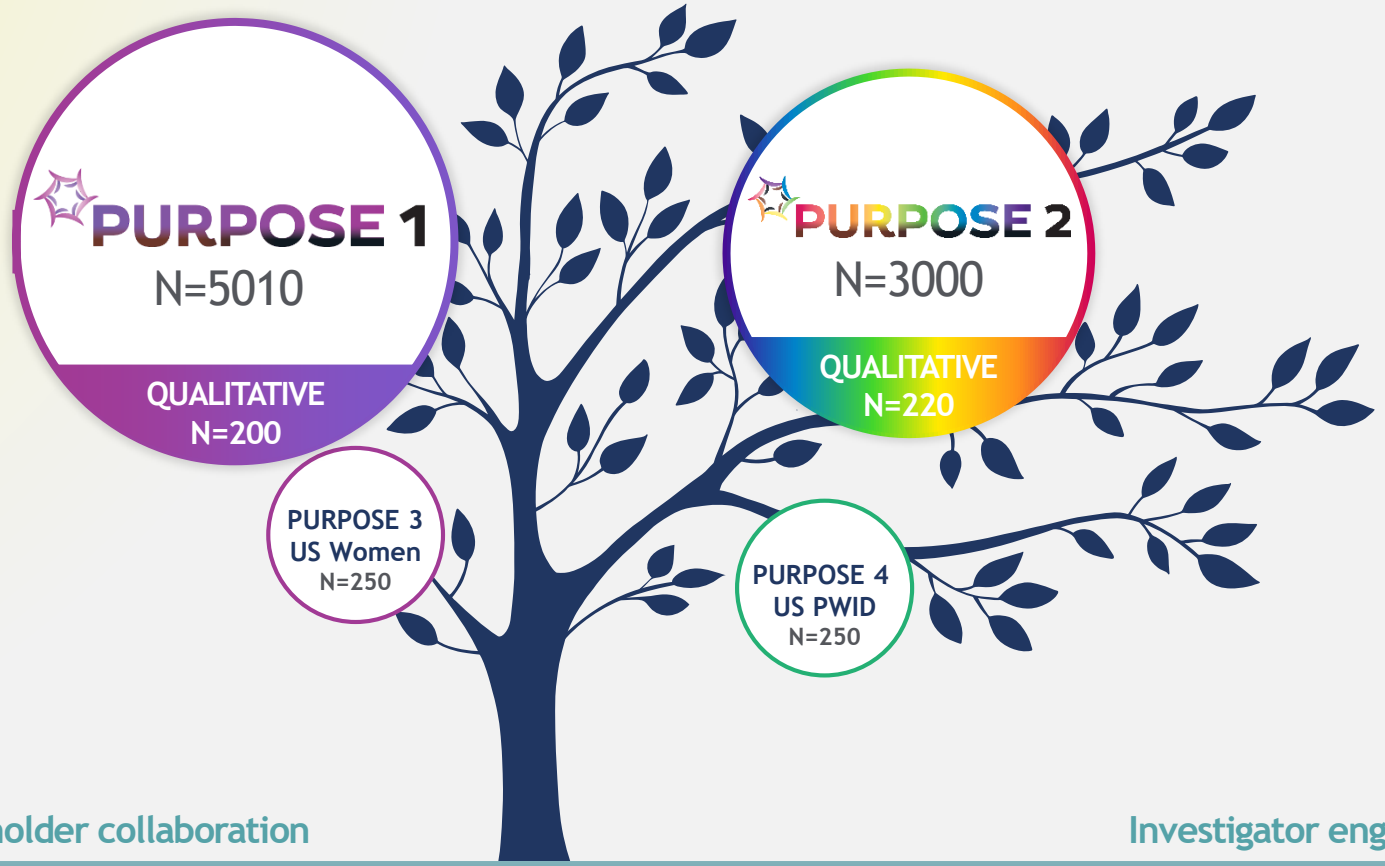
Primary Efficacy Endpoint	HPTN 083[1,2]		HPTN 084[3,4]	
	CAB (n = 2244)	FTC/TDF (n = 2247)	CAB (n = 1614)	FTC/TDF (n = 1610)
HIV infections, n	13*	39	4*	36
HR for CAB vs FTC/TDF (95% CI)	**0.34 (0.18-0.62)**		**0.11 (0.04-0.32)**	

*Includes 1 case readjudicated post hoc as a baseline infection

1. Landovitz. NEJM.. 2021 Aug 12;385:595. 2. Landovitz. AIDS 2020. Abstr OAXLB0101.
3. Delany-Moretlwe. HIVR4P 2021. Abstr HY01.02. 4. Marzinke. IAS 2021. Abstr PECLB25.

Collaboration
Transparency

Prevention with PURPOSE



Community & stakeholder collaboration

Investigator engagement

Proof of Concept that Capsid Inhibitors Prevent SHIV in Non-Human Primates
Robust Pharmacokinetic and Safety Database in persons with and without HIV

Phase 1 Studies **LEN Mucosal Pk** Capella Highly treatment experienced Calibrate Antiretroviral naïve

Può la terapia long-acting migliorare lo stigma verso le persone HIV+ ??

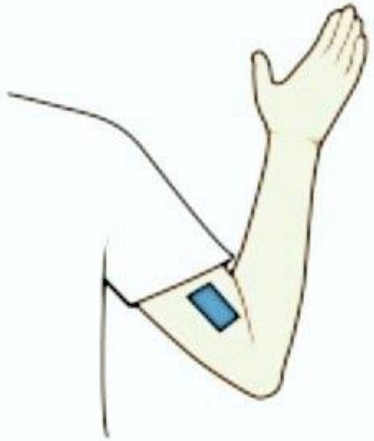
LONG ACTING– UNA NUOVA SFIDA

- Personale medico ed infermieristico insufficiente
- Scarsa attenzione da parte degli Amministratori
- Mancanza di una rete efficiente con il territorio

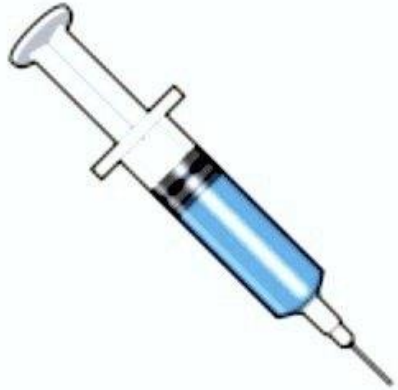
THE NEW ERA

INTRAVAGINAL RING (IVR)

IMPLANT



INJECTABLE



ANTIBODY

15° CONGRESSO NAZIONALE

BARI 14-16 GIUGNO 2023
UNIVERSITA' DEGLI STUDI ALDO MORO

ICAR

Italian Conference on **AIDS** and **Antiviral Research**

From prevention to cure: ready for new challenges

Presidenza
del Congresso:
F. Ceccherini Silberstein
M. Formisano
S. Lo Caputo
A. Saracino

DEADLINE ABSTRACT 5 APRILE 2023

www.icar2023.it

Promosso da
SIMIT
Società Italiana di Malattie Infettive e Tropicali