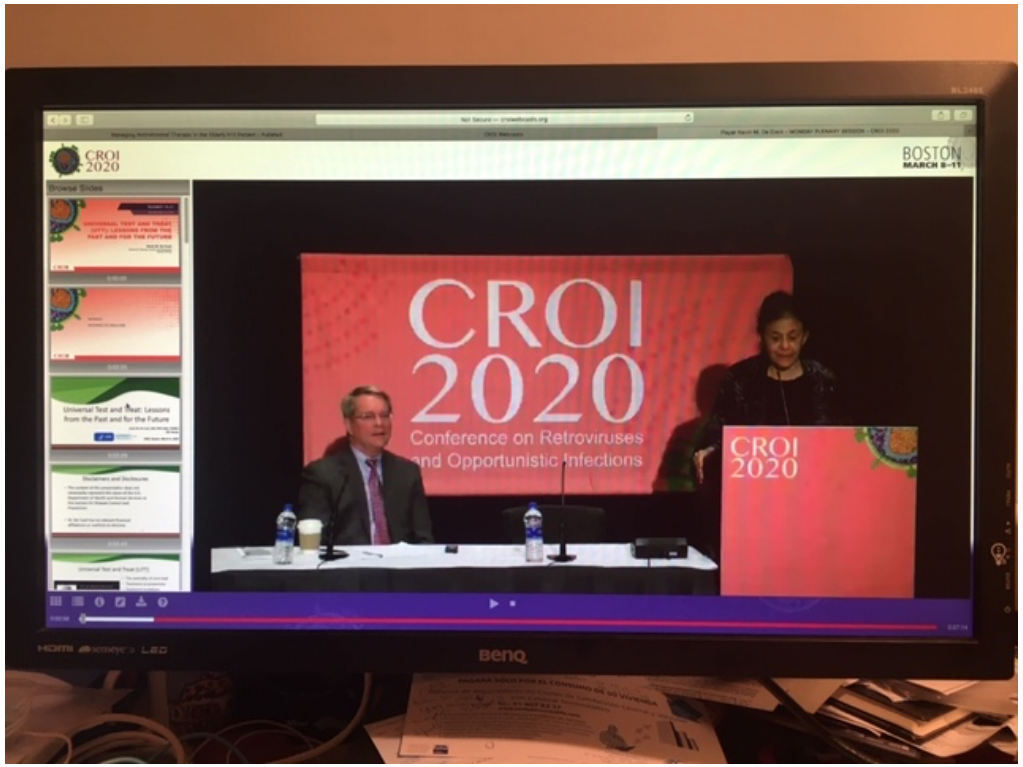
Post-CROI *(virtual)* 2020

Tratamiento antirretroviral II



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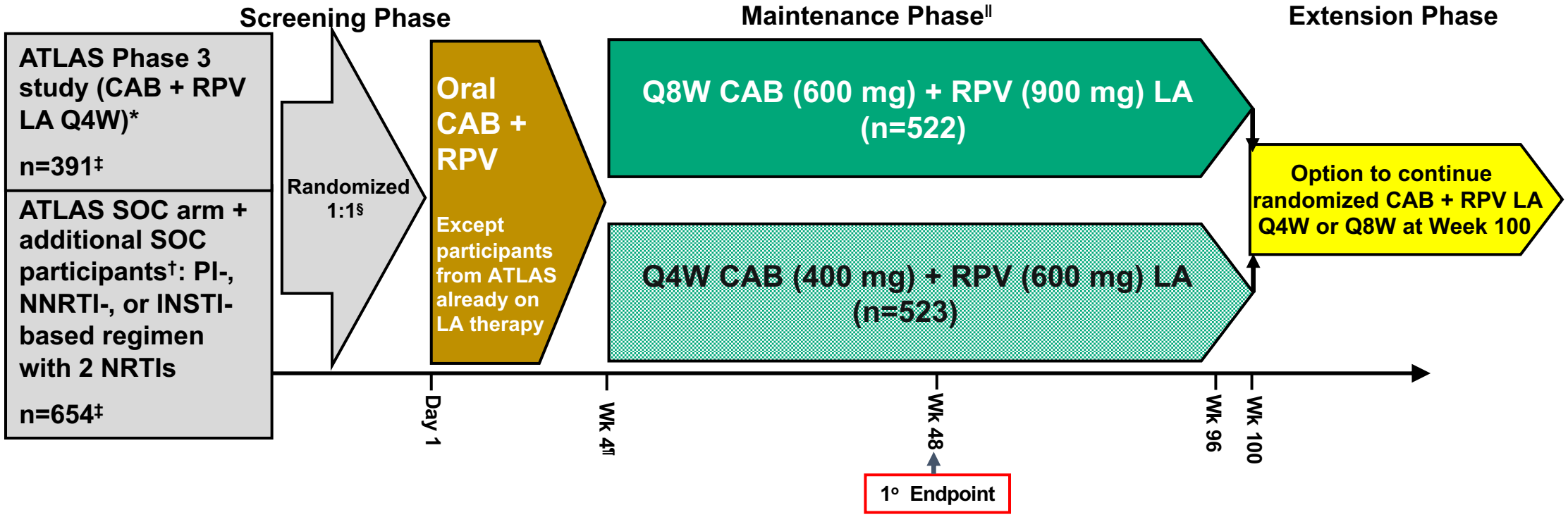
Hospital General Universitario Gregorio Marañón

Madrid, 9 de junio de 2020

ATLAS-2M Study Design

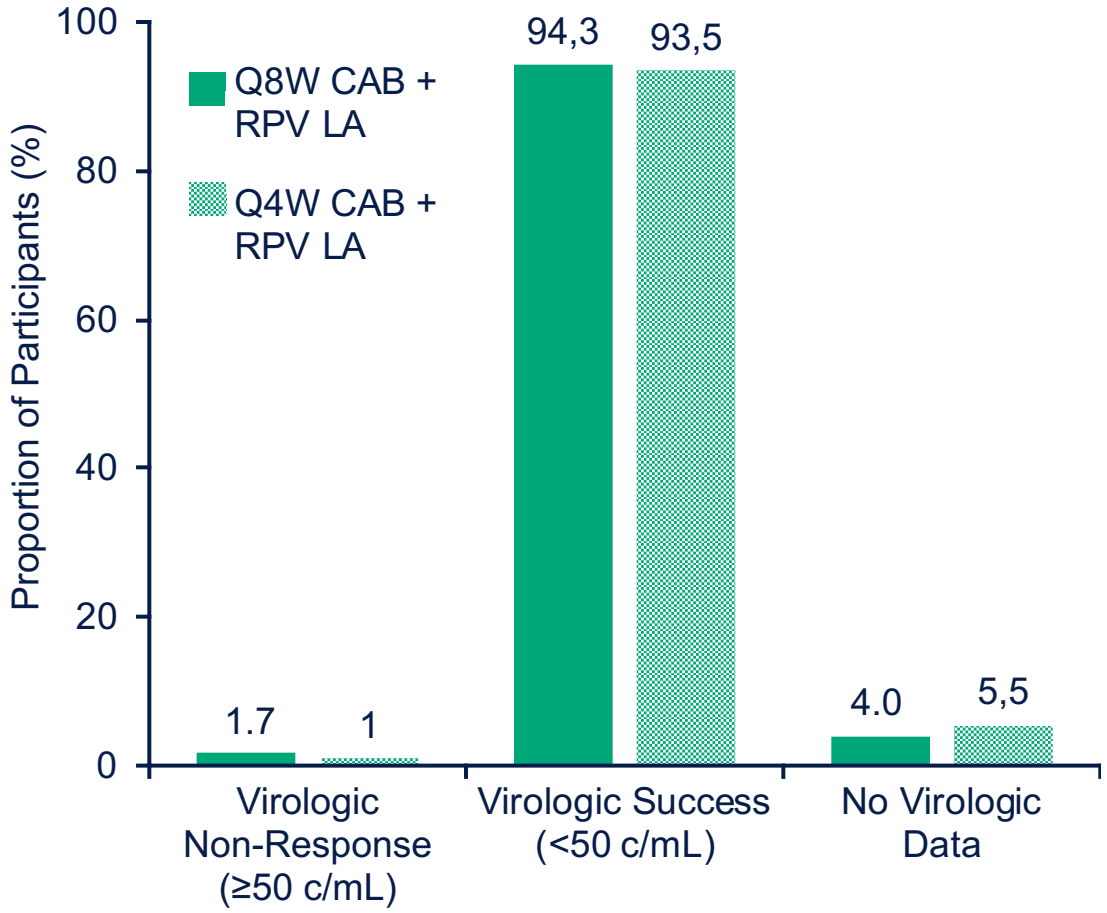
Phase 3, randomized, multicenter, parallel-group, noninferiority, open-label study

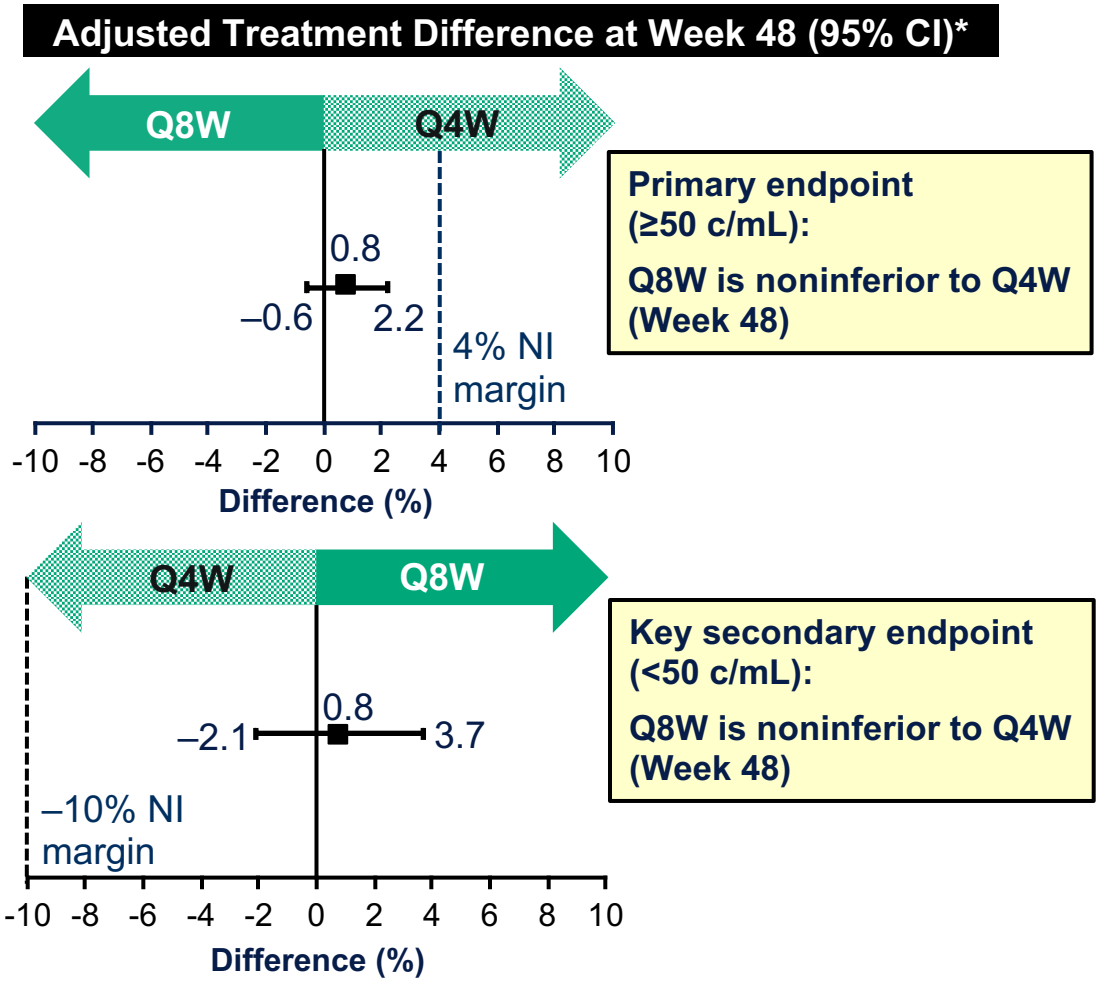


*Participants transitioning from ATLAS must have been on CAB + RPV LA Q4W or a current ART regimen through at least Week 52 of the ATLAS study and had plasma HIV-1 RNA <50 c/mL at screening. †SOC participants not transitioning from the ATLAS study were to be on uninterrupted current regimen (either the initial or second combined ART regimen) for at least 6 months prior to screening. Documented evidence of at least two plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to screening, one within the 6- to 12-month window and one within 6 months prior to screening, was required. Participants were excluded if they had a history of virologic failure; evidence of viral resistance based on the presence of any resistance-associated major INSTI or NNRTI mutation (except K103N) from prior genotype assay results. ‡Intent-to-treat exposed population. §1149 participants were screened, and 1049 participants were randomized. 4 participants did not receive study drug and therefore were not part of the ITT-E population. ‖Participants who withdraw from the IM regimen must go into 52-week long-term follow-up if randomized regimen is not yet locally approved and commercially available. ¶Participants on oral lead-in treatment attended a Week 4 visit to assess tolerability. In participants in the Q4W arm who had an oral lead-in, the first LA dose was CAB 600 mg + RPV 900 mg.

Overton et al. CROI 2020; Boston, MA. Presentation 3334.

ATLAS-2M virologic Snapshot Outcomes at Week 48 for ITT-E





Participant numbers: n=522 Q8; n=523 Q4; CAB, cabotegravir; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; LA, long-acting; NI, noninferiority; RPV, rilpivirine; Q4W, every 4 weeks; Q8W, every 8 weeks.

*Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks).

Overton et al. CROI 2020; Boston, MA. Presentation 3334.

ATLAS-2M virologic Snapshot Outcomes at Week 48 for ITT-E

Snapshot outcome, ITT-E, n (%)	Q8W (n=522)	Q4W (n=523)
HIV-1 RNA <50 c/mL at Week 48	492 (94.3)	489 (93.5)
HIV-1 RNA ≥50 c/mL at Week 48	9 (1.7)	5 (1.0)
Data in window not <50 c/mL	3 (0.6)	2 (0.4)
Discontinued for lack of efficacy	6 (1.1)	2 (0.4)
Discontinued for other reasons while not <50 c/mL	0	1 (0.2)
No virologic data	21 (4.0)	29 (5.5)
Discontinued for AE or death	9 (1.7)*	13 (2.5)†
Discontinued for other reasons	12 (2.3)‡	16 (3.1)§

*Discontinuations for AEs (event level) include Q8W: Injection site pain (n=2), injection site abscess, injection site discomfort, skin lesion, fatigue, acute hepatitis B, asthenia, presyncope, pancreatitis acute, headache, rash maculo-papular (all n=1). †Q4W: injection site pain (n=11), abnormal dreams (n=2), injection site swelling (n=2), hyperhidrosis (n=2), fatigue (n=2), injection site nodule, influenza, headache, acute hepatitis B, dizziness, glioblastoma, allergic reaction, transaminase increase, depression, chills, insomnia, myalgia, nausea, presyncope, pyrexia, sleep disorder, disturbance in attention (all n=1). ‡Q8W: Withdrawal by participant (n=4), investigator decision (n=4), lost to follow-up (n=2), protocol deviation (n=1), lack of efficacy (n=1). §Q4W: Withdrawal by participant (n=12), protocol-specified withdrawal criteria met (pregnancy) (n=3), protocol deviation (n=1).

AE, adverse event; ITT-E, intent-to-treat exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

ATLAS-2M: Summary of Confirmed Virologic Failures

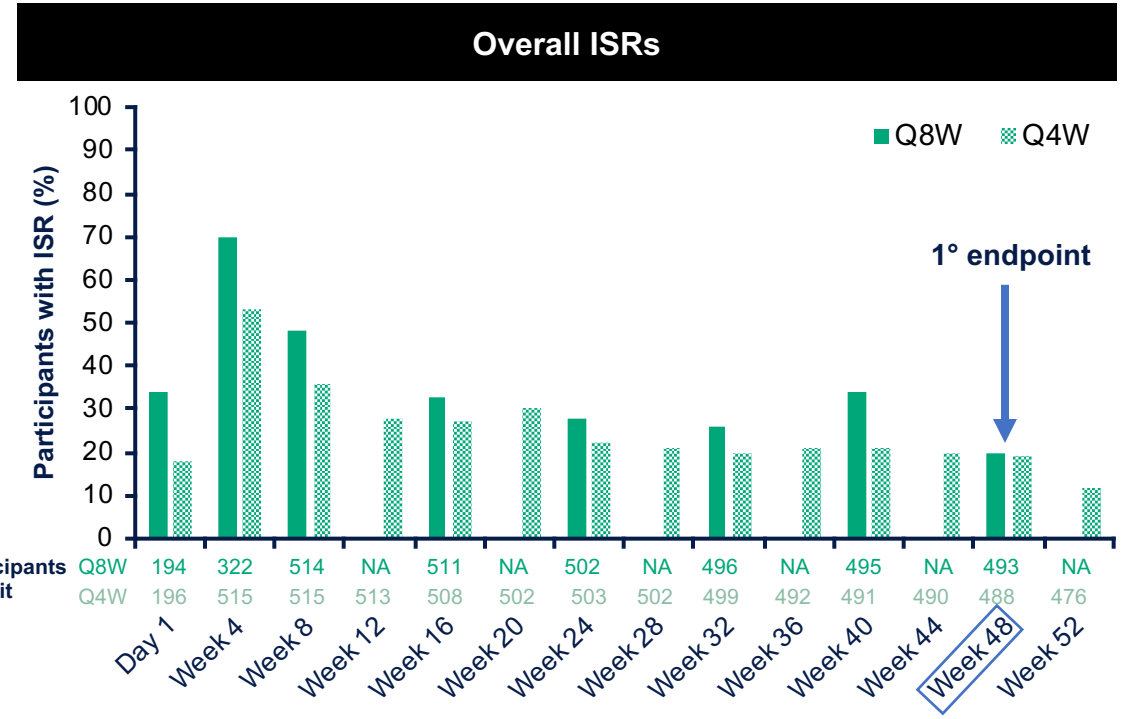
	n	CVFs n (%)	CVFs with RPV RAMs*	RPV RAMs Observed at Failure	CVFs with IN RAMs*	IN RAMs Observed at Failure
Q8W	522	8 (1.5)	6/8	K101E, E138E/K, E138A, Y188L	5/8	Q148R,† N155H†
Q4W	523	2 (0.4)	1/2	K101E, M230L	2/2	E138E/K, Q148R, N155N/H

- *Post hoc* baseline PBMC HIV-1 DNA results **for Q8W arm**:
  - 5/8 CVFs had pre-existing major RPV RAMs (E138A, Y188L, Y181Y/C, H221H/Y, E138E/A, Y188Y/F/H/L)
  - 1/8 CVFs had a pre-existing major IN RAM (G140G/R)
  - 5/8 CVFs had L74I polymorphism (3 subtype A or A1, 1 subtype C, 1 complex subtype)
- 9/10 CVFs re-suppressed on fully active oral HAART (1/10 non-compliance on PI-based ART)
  - All CVFs retained phenotypic sensitivity to dolutegravir
- Factors contributing to CVF (e.g. baseline resistance and drug concentrations) are being further evaluated
  - PBMC HIV-1 DNA analysis underway across Phase 3 program

*For those with observed RAMs at failure: 6/6 Q8W and 1/1 Q4W CVFs had RPV resistance (fold-change >2), and 3/5 Q8W and 1/2 Q4W CVFs had CAB resistance (fold-change >2.5); CVF definition: 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL. †Or mixture

ART, antiretroviral therapy; CVF, confirmed virologic failure; HAART, highly active antiretroviral therapy; IN, integrase; PBMC, peripheral blood mononuclear cell; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

ATLAS-2M Injection Site Reactions



Note: Day 1 only included participants with prior CAB + RPV exposure due to the oral lead-in phase.

Outcome, n (%), ITT-E	Q8W (n=522)	Q4W (n=523)
Number of injections	8470	15,711
Number of ISR events (events/injections)*	2507 (30)	3152 (20)
Grade ≥3 – severe†	43 (<1)	48 (<1)
Injection site reactions‡		
Pain	2014 (24)	2567 (16)
Nodule	113 (1)	204 (1)
Discomfort	92 (1)	110 (1)
Withdrawals due to injection-related reasons, participant n (%)§	6 (1)	11 (2)

*All event-level ISR percentages are calculated from the total number of injections. Note: A single injection could result in more than one ISR. †There were no Grade 4 or Grade 5 ISRs. ‡ISRs occurring in >1% of injections in either the Q4W or Q8W arms are shown. §Q8W: 5 participants had an ISR leading to withdrawal and 1 participant withdrew consent from the study due to injection intolerability; Q4W: 5 participants had an ISR leading to withdrawal and 6 participants withdrew consent from the study due to injection intolerability.

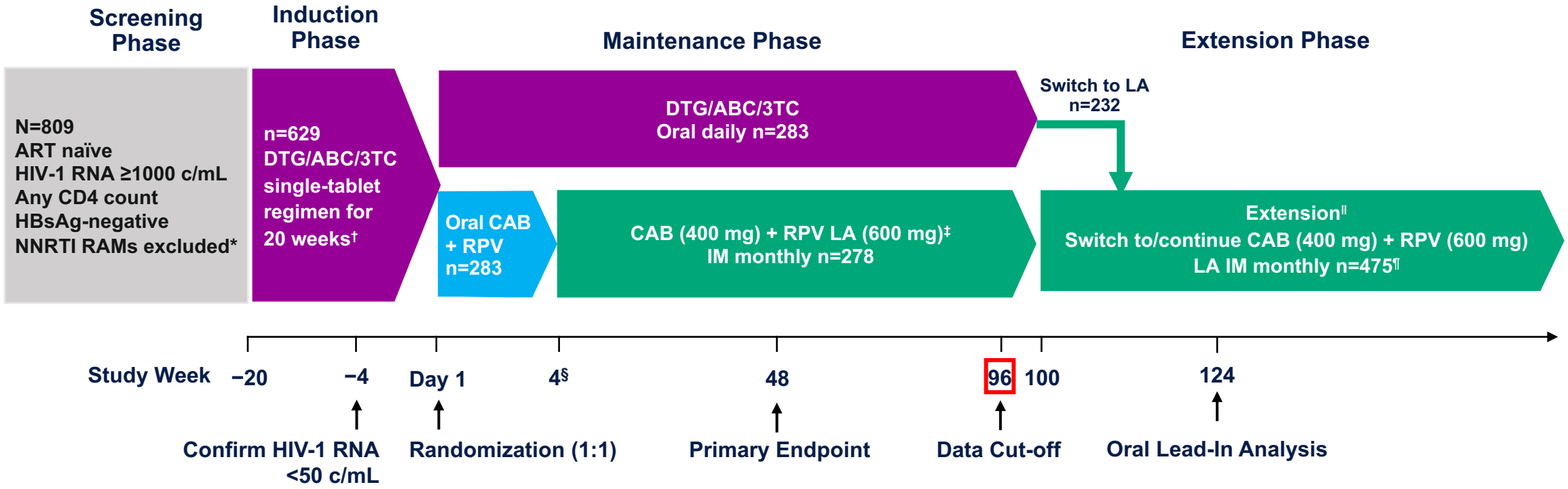
- 24,181 injections were administered in total
  - <2% of participants discontinued due to injection-related reasons
- The majority (98%, 5568/5659) of ISRs were Grade 1–2, with a median duration of 3 days in both arms

AE, adverse event; ISR, injection site reaction; ITT-E, intent-to-treat exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

Overton et al. CROI 2020; Boston, MA. Presentation 3334.

FLAIR Study Design

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

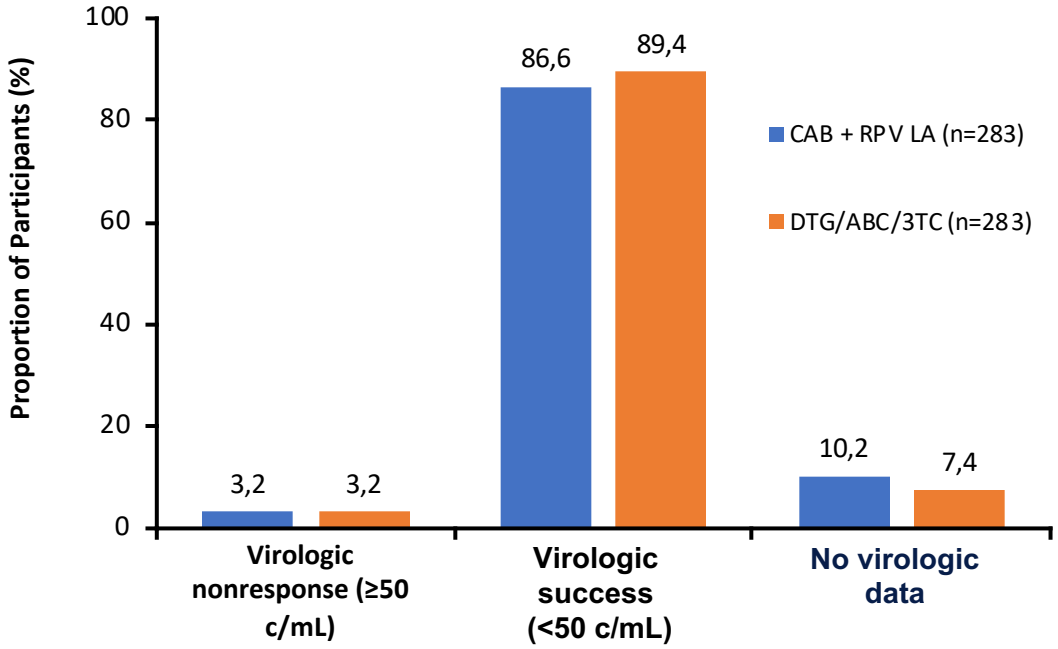


*NNRTI RAMs but not K103N were exclusionary or any known resistance to INIs. †If the participant had toxicity or intolerability in association with DTG/ABC/3TC, one switch to an approved alternative background NRTI was permitted. Participants who were positive for HLA-B*5701 received DTG plus two alternative 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.

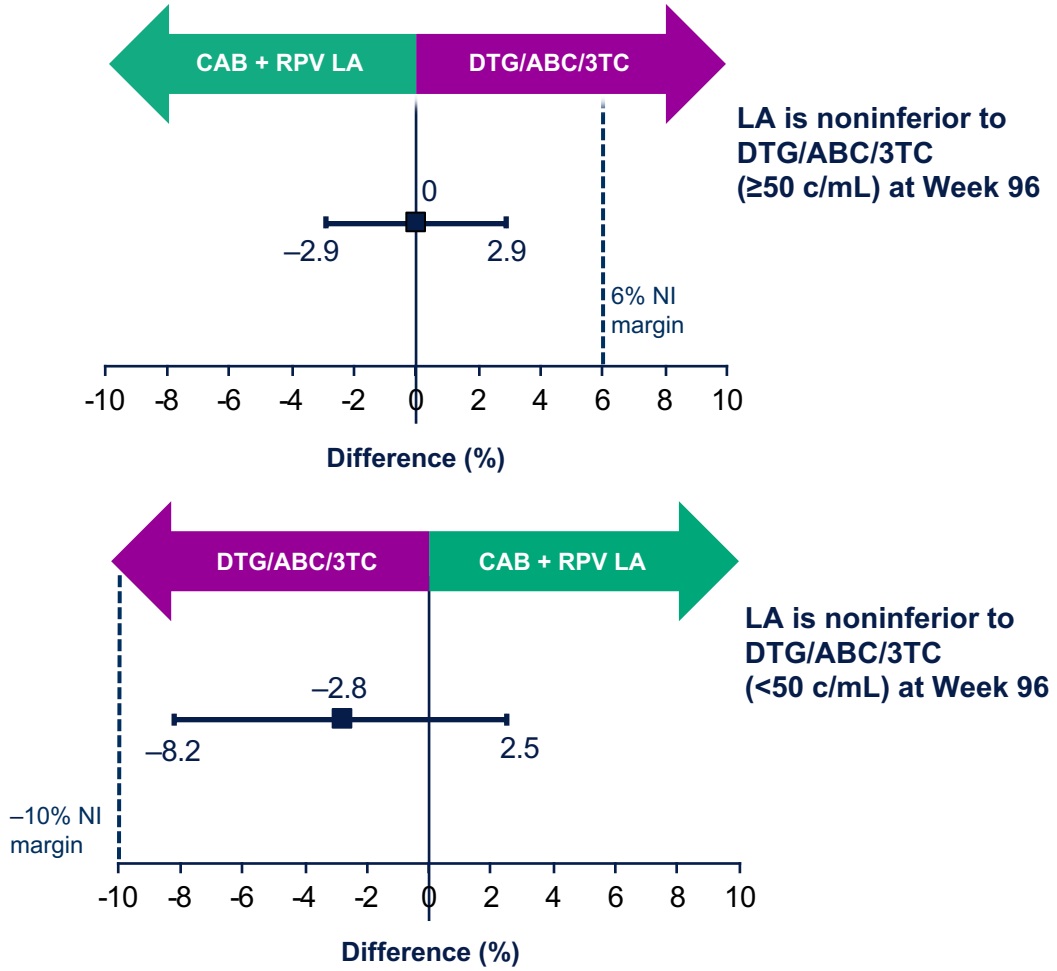
FLAIR Week 96 Virologic Response

Virologic Outcomes



*Adjusted for sex and baseline HIV-1 RNA (< vs. ≥100,000 c/mL).

Adjusted Treatment Difference (95% CI)*



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Snapshot Outcomes at FLAIR Week 96 (ITT-E)

	CAB + RPV LA n=283, n (%)	DTG/ABC/3TC n=283, n (%)
HIV-1 RNA <50 c/mL*	**245 (86.6)**	**253 (89.4)**
HIV-1 RNA ≥50 c/mL*	**9 (3.2)**	**9 (3.2)**
Data in window not below threshold	3 (1.1)	2 (0.7)
Discontinued for lack of efficacy	6 (2.1)	5 (1.8)
Discontinued for other reason while not below threshold	0	2 (0.7)†
No virologic data in Week 96 window	**29 (10.2)**	**21 (7.4)**
Discontinued due to AE‡	12 (4.2)	4 (1.4)
Discontinued for other reasons	16 (5.7)§	17 (6.0)‖
On study but missing data in window	1 (0.4)	0

*Per FDA Snapshot algorithm. †1 relocation, 1 lost to follow-up. ‡No deaths occurred during the maintenance phase. §In the LA arm, 16 participants discontinued due to reasons other than AEs: 3 relocations, 2 intent to become pregnant, 2 tolerability of injections, 2 lost to follow-up, 1 need to initiate prohibited medication, 1 incarceration, 1 pregnancy, 1 frequency of visits, 1 burden of travel, 1 change of job, 1 unreliable with visits. ‖In the DTG/ABC/3TC arm, 17 participants discontinued due to reasons other than AEs: 4 frequency of visits, 3 non-compliance with study treatment and protocol procedures, 1 relocation, 1 participant decision to stop treatment, 1 late to attend visits, 1 lost to follow-up, 1 pregnancy, 1 burden of travel, 1 unspecified reason, 1 prohibited medication use, 1 substance abuse, 1 met protocol stopping criteria.

- ‡LA arm: injection site pain (2), acute hepatitis B (2), discomfort/injection site pain/diarrhea/vomiting, hepatitis A/secondary syphilis, hepatitis A, hepatitis C, acute hepatitis C, transaminases increased, depression, and adenocarcinoma of the colon
- ‡DTG/ABC/3TC arm: suicide attempt, disturbance in attention/dysarthria/amnesia, dizziness/fatigue/nausea, renal failure

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No New CVFs at FLAIR Week 96 in the LA Arm

Variable	CAB + RPV LA n=283, n (%)	DTG/ABC/3TC n=283, n (%)
CVF* between Week 48 and Week 96	**0**	**1 (<1)[†]**
Total CVF* through Week 96	4 (1.4)[‡]	4 (1.4)
Total treatment-emergent resistance	3 (1.1)[§]	0

*CVF is defined as rebound as indicated by 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL. [†]DTG/ABC/3TC CVF occurred at Week 64 with no resistance mutations. [‡]One participant in FLAIR had oral CAB/RPV dosing interrupted due to a false-positive pregnancy test and upon re-initiation of oral therapy, had suspected virologic failure that was confirmed. [§]Subtype A1 assignment based on Monogram Algorithm which does not include reference sequences for A6, a predominant subtype in Russia. Further in-house analysis suggests that the subtype for all 3 is A6.

There were no virologic failures in the LA arm from Week 48 to Week 96

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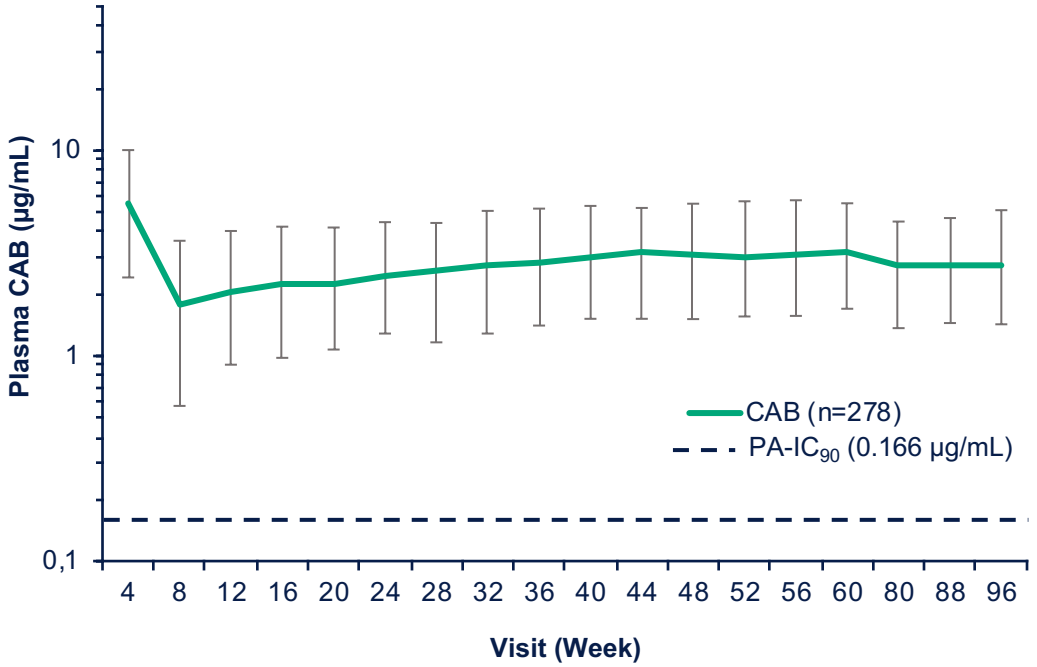
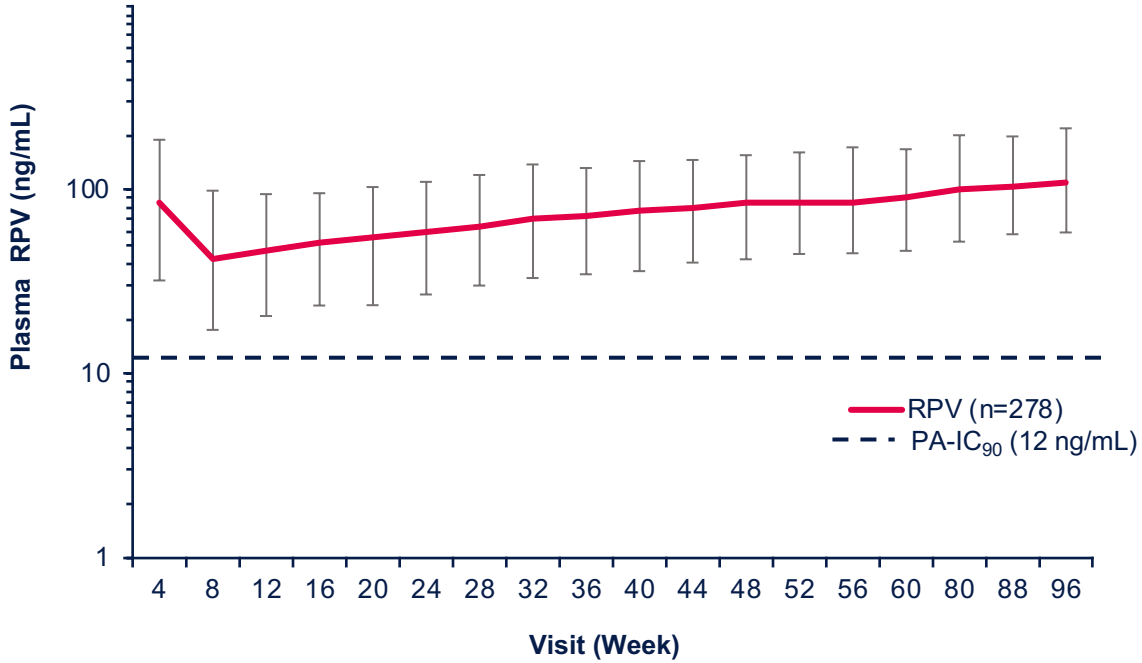
FLAIR Plasma CAB and RPV Trough Concentrations





- Throughout the maintenance phase, plasma concentrations after IM CAB + RPV LA were comparable with those during efficacious oral regimens
- Achievement of steady state for CAB was confirmed at Week 44 and was not reassessed using data through Week 96
- RPV had not achieved steady state by Week 44 and was not reassessed using data through Week 96. However, RPV pre-dose concentrations appeared to plateau between Week 60 and Week 96

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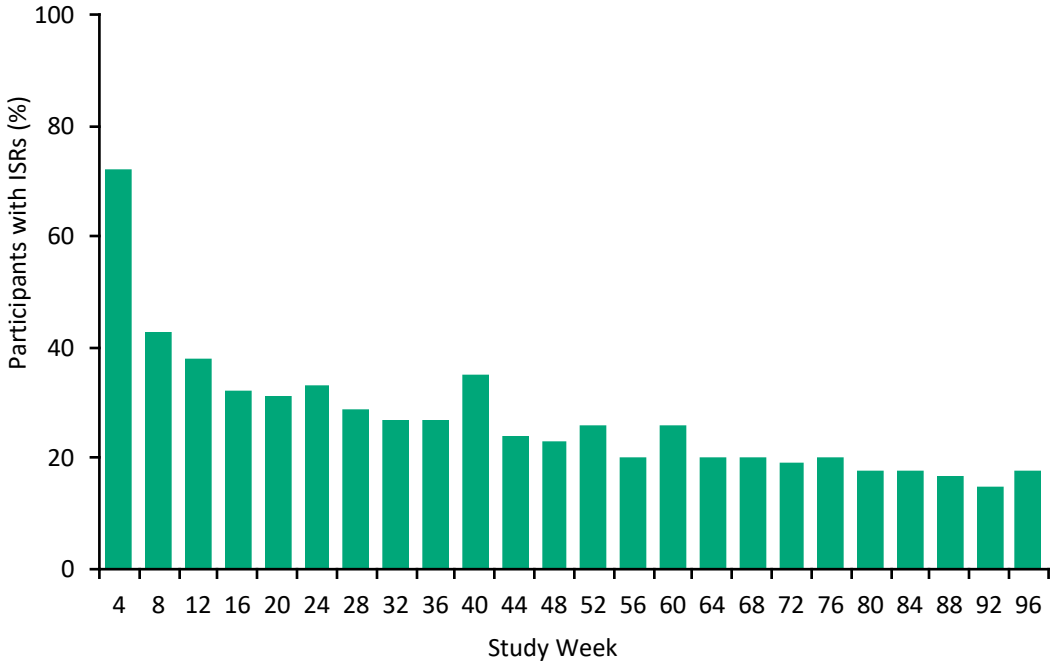
FLAIR Injection Site Reactions

Overall ISRs*



Outcome, n (%)	CAB + RPV LA n=283
Number of injections	12,552
ISR events, n (% of total injections)	3100 (24.7)
Grade 1 – mild	2730 (21.7)
Grade 2 – moderate	352 (2.8)
Grade 3 – severe	18 (<1)
ISR events (most frequent), n (% of total injections)	
Pain	2613 (20.8)
Nodule	132 (1.1)
Induration	119 (<1)
Warmth	59 (<1)
Pruritus	56 (<1)
Swelling	45 (<1)
Median duration of ISRs, days	3

Participant withdrawals due to ISR-related reasons, n (%)	6 (2.1)
• ISRs leading to withdrawal	3 (1.1)
• Withdrew consent due to intolerability of injections	3 (1.1)

- The majority (3082/3100, 99%) of ISRs were Grade 1–2 and most (89%) resolved within ≤7 days (median duration, 3 days)
- Between Week 48 and 96, 2 participants withdrew due to ISR-related reasons, 1 for an ISR and 1 for intolerability of injections

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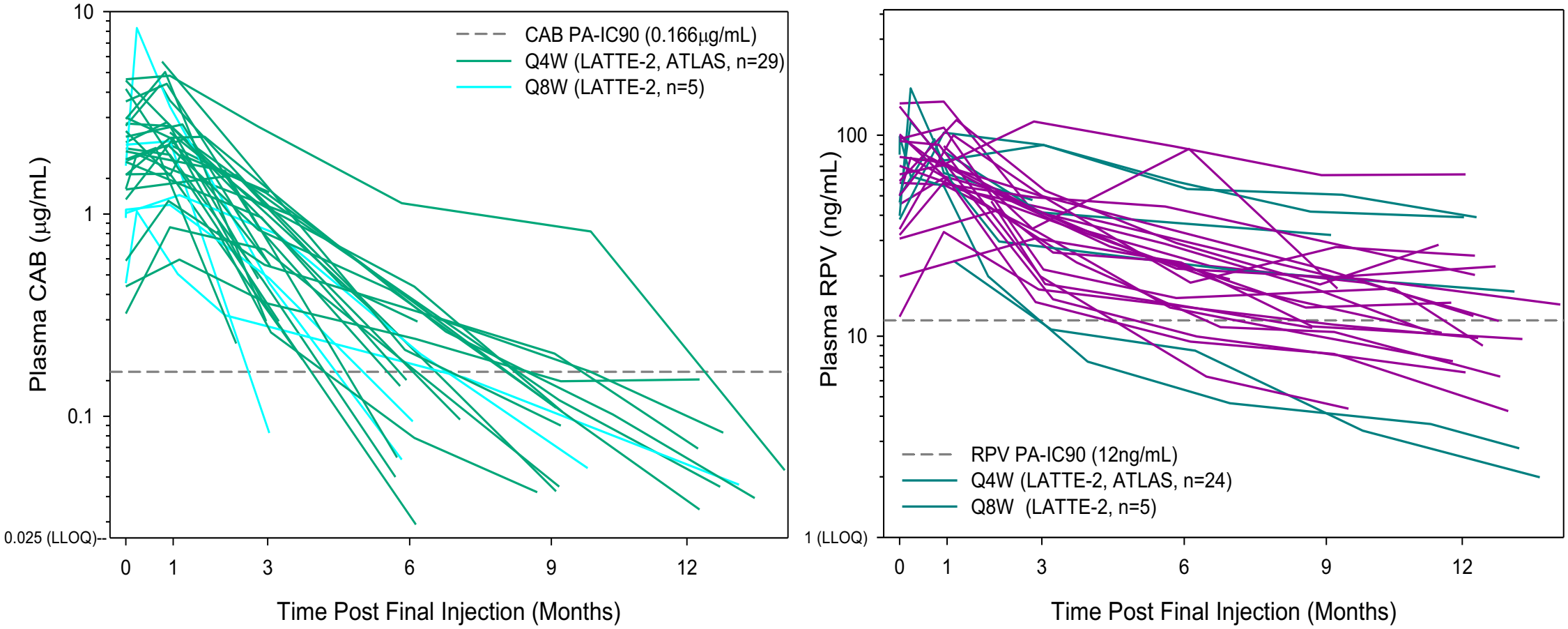
Treatment discontinuation CAB + RPV LA

Parameter		LATTE-2 (P2b) (n=14)	ATLAS (P3) (n=24)	Overall (n=38)
Study Regimen	Q4W	9	24	33
	Q8W	5	NA	5
Sex	Female	1	8	9
	Male	13	16	29
Age (years) (median, range)		34.5 (21 - 48)	38 (21 - 51)	37.5 (21 - 51)
Baseline Weight (kg) (median, range)		72.3 (52.7 - 95.0)	71.6 (41.2 - 120)	72.3 (41.2 - 120)
Baseline BMI (kg/m^2) (median, range)		24.2 (19.4 - 29.3)	23.3 (15.3 - 37.9)	23.7 (15.3 - 37.9)

Ford et al. CROI 2020; Boston, MA. Poster 466.

Individual Concentration-Time Profiles Following Discontinuation of Long-Acting Treatment in LATTE-2 and ATLAS (CAB left, RPV right)



- LLOQ, lower limit of quantification; PA-IC90, protein adjusted IC90.

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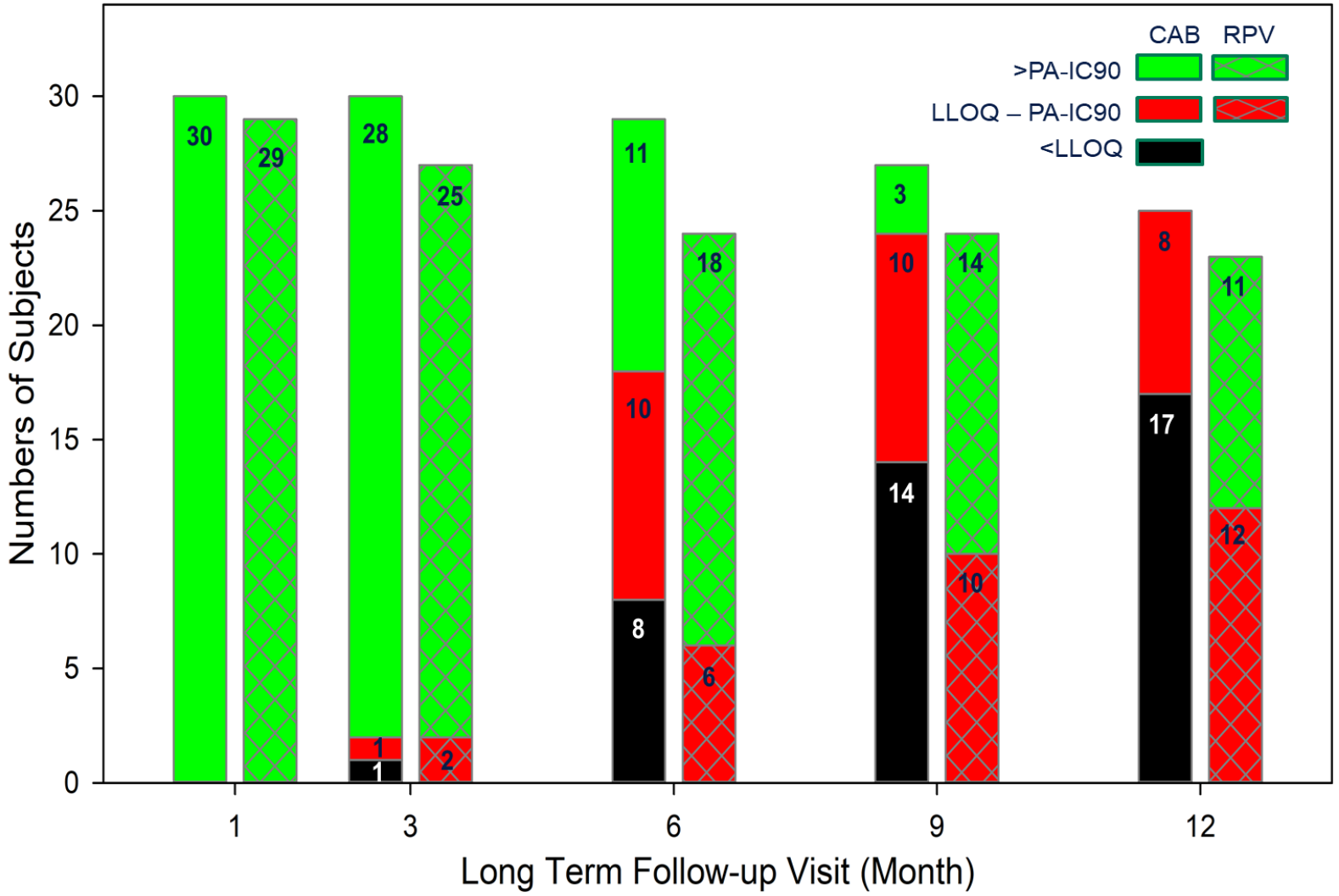
Median (5th, 95th Percentile) Parameter Estimates of Individual LTFU Concentration-Time Data

Parameter	CAB (n=34)	RPV (n=27)
Slope (hr^{-1})	0.00064 (0.00028, 0.00183)	0.00014 (0.00008, 0.0003)
Half-life (weeks)[a]	6.4 (2.3, 14.7)[a]	29.6 (15.2, 56.7)[a]

- [a]Apparent terminal phase half-life should be interpreted with caution as data were insufficient (<2 half-life lengths) for accurate estimation in some profiles.

Range of CAB (left) and RPV (right) Concentrations by LTFU Visit Following Discontinuation of Q4W and Q8W Regimens



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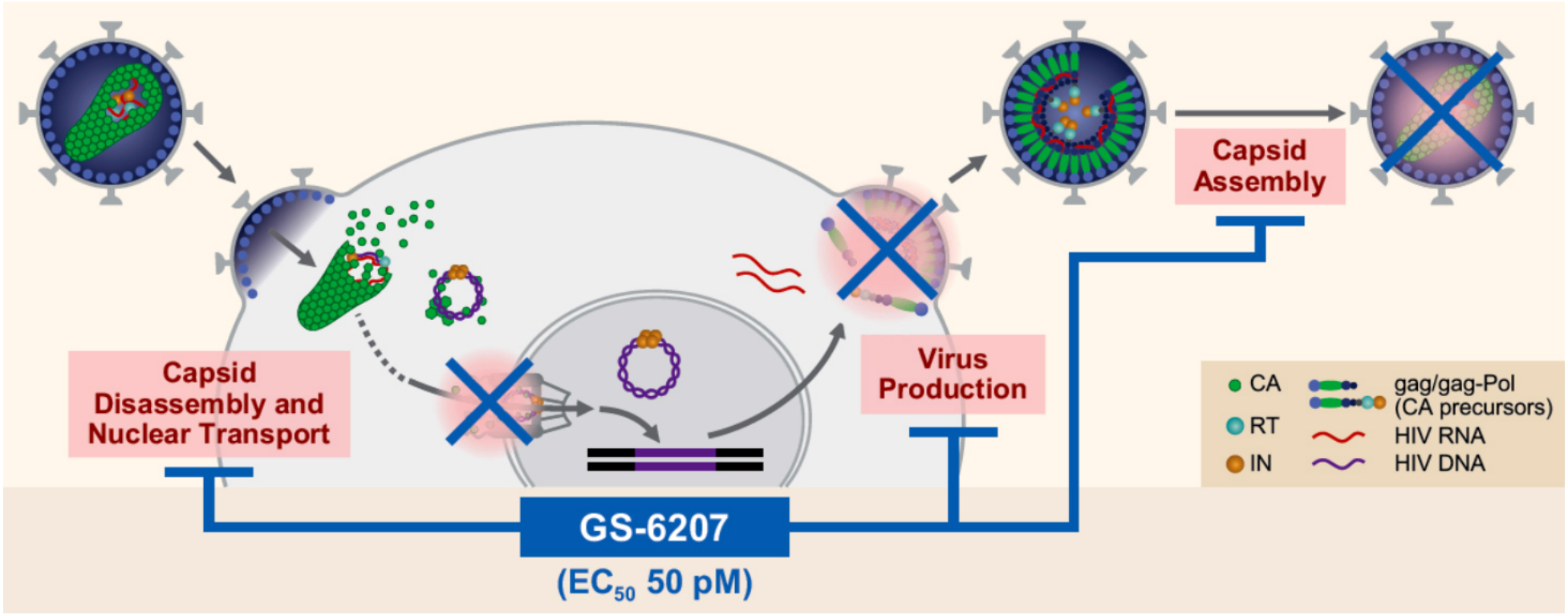
Novel Capsid Inhibitor (GS-6207): Experience to Date

Multistage Mechanism of Action of GS-6207

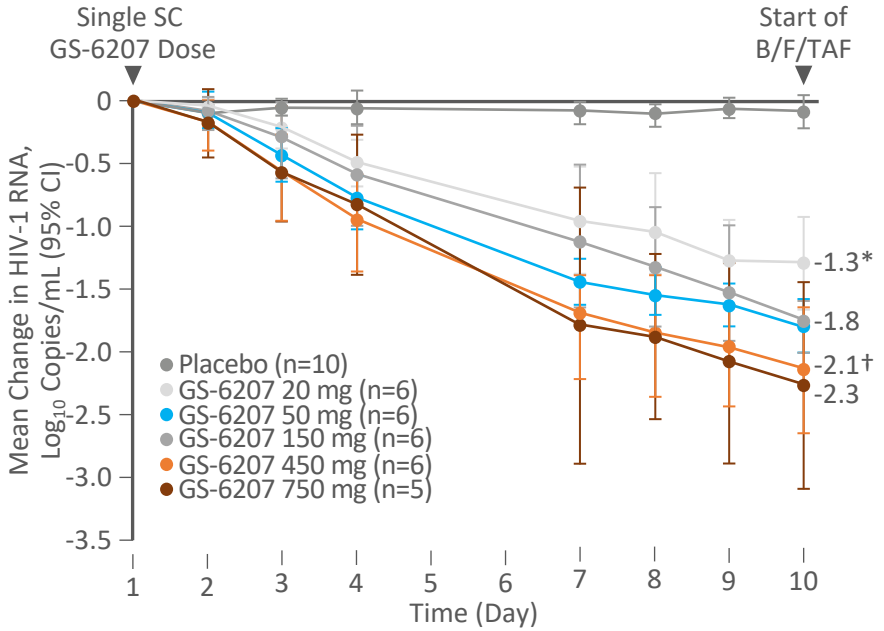


EC_{50} half-maximal effective concentration determined in peripheral blood mononuclear cells using wild-type (WT) HIV-1 patient isolates with various HIV-1 subtypes. IN, integrase; Pol, polymerase; RT, reverse transcriptase.

Daar E et al. Abstract 469. Begley R et al. Abstract 470. Margot NA. Abstract 529.

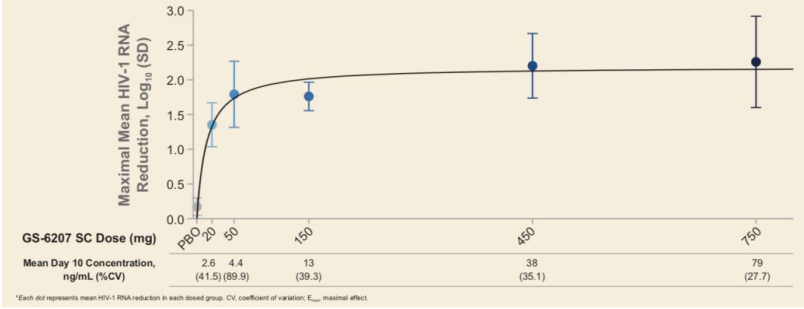
Novel Capsid Inhibitor (GS-6207): Experience to Date

Dose-dependent Antiviral Activity of Subcutaneous, Long-acting GS-6207 (Phase 1b)



* Change (mean) on Day 10 in 20-mg cohort was -1.3 log_{10} copies/mL, while maximal change (mean) through Day 10 was -1.4 log_{10} copies/mL;
† Change (mean) on Day 10 in 450-mg cohort was -2.1 log_{10} copies/mL, while maximal change (mean) through Day 10 was -2.2 log_{10} copies/mL

Dose-response Relationship Between GS-6207 and Antiviral Activity: E_{max} Model*



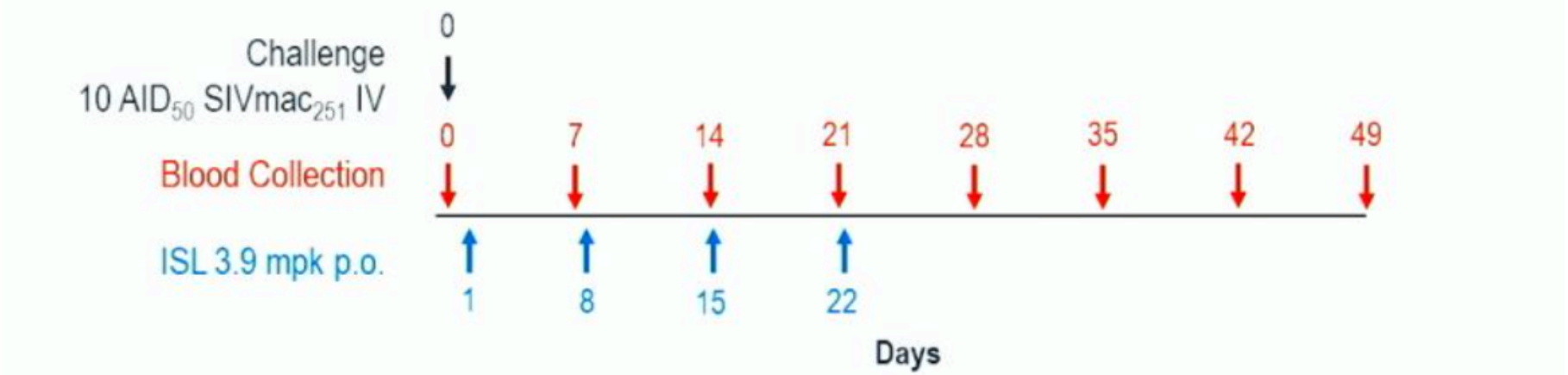
Site-directed mutagenesis → GAG mutations had no effect on potency of GS-6207

GS-6207 oral tablets can be administered without regard to food[3]

2 ongoing clinical trials in PLWH evaluating GS-6207 900 mg, with a 6-month dosing interval:
– In treatment-naïve PLWH (NCT04143594)
– In heavily treatment-experienced PLWH (NCT04150068)

Daar E et al. Abstract 469. Begley R et al. Abstract 470. Margot NA. Abstract 529.

WEEKLY ORAL ISLATRAVIR EFFECTIVE AS PEP



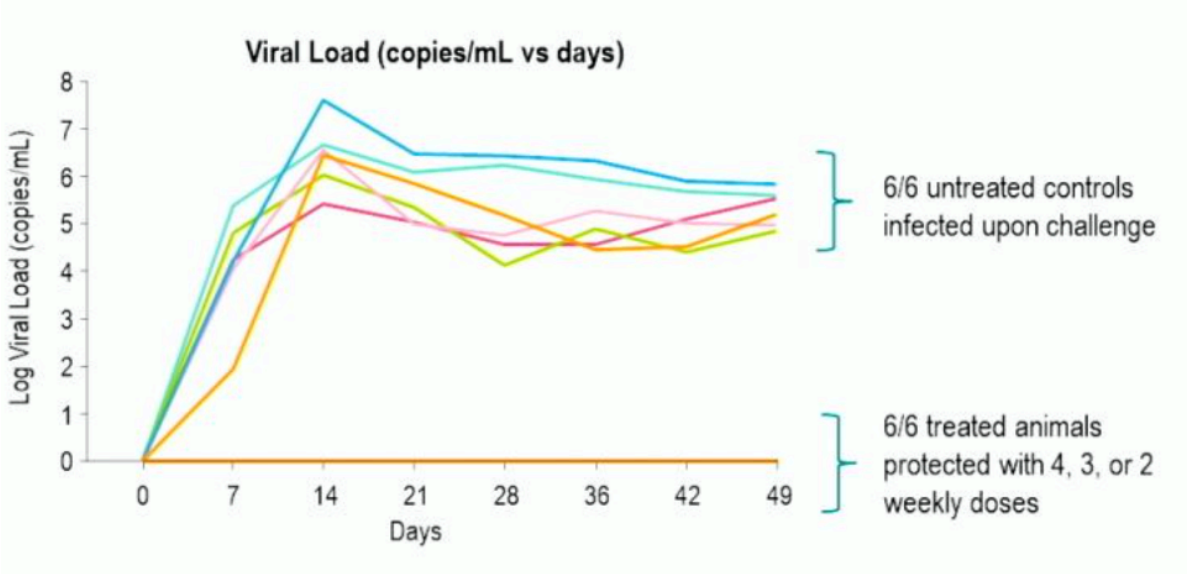
Stage 1: 4 weekly doses starting 24 hours after inoculation
Stage 2: 3 weekly doses starting 24 hours after inoculation
Stage 3: 2 weekly doses starting 24 hours after inoculation
Stage 4: Single dose administered 24 hours after inoculation

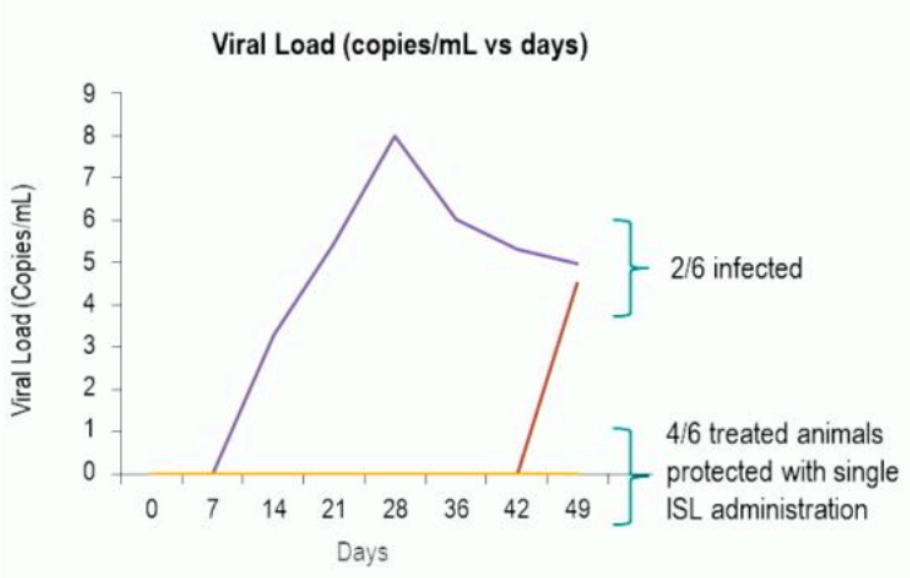
- The same animals were used in each stage
- Stages were separated by **7 weeks** after the last ISL dose*

*ISL-TP is not detectable in rhesus PBMCs **3 weeks** following the last dose of 3.9-mpk ISL

Markovitz M et al. Abstract 89

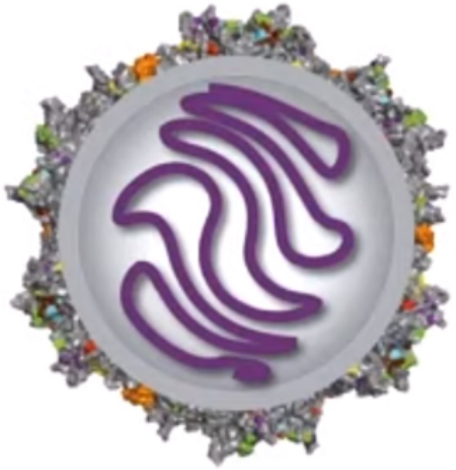
WEEKLY ORAL ISLATRAVIR EFFECTIVE AS PEP





Markovitz M et al. Abstract 89

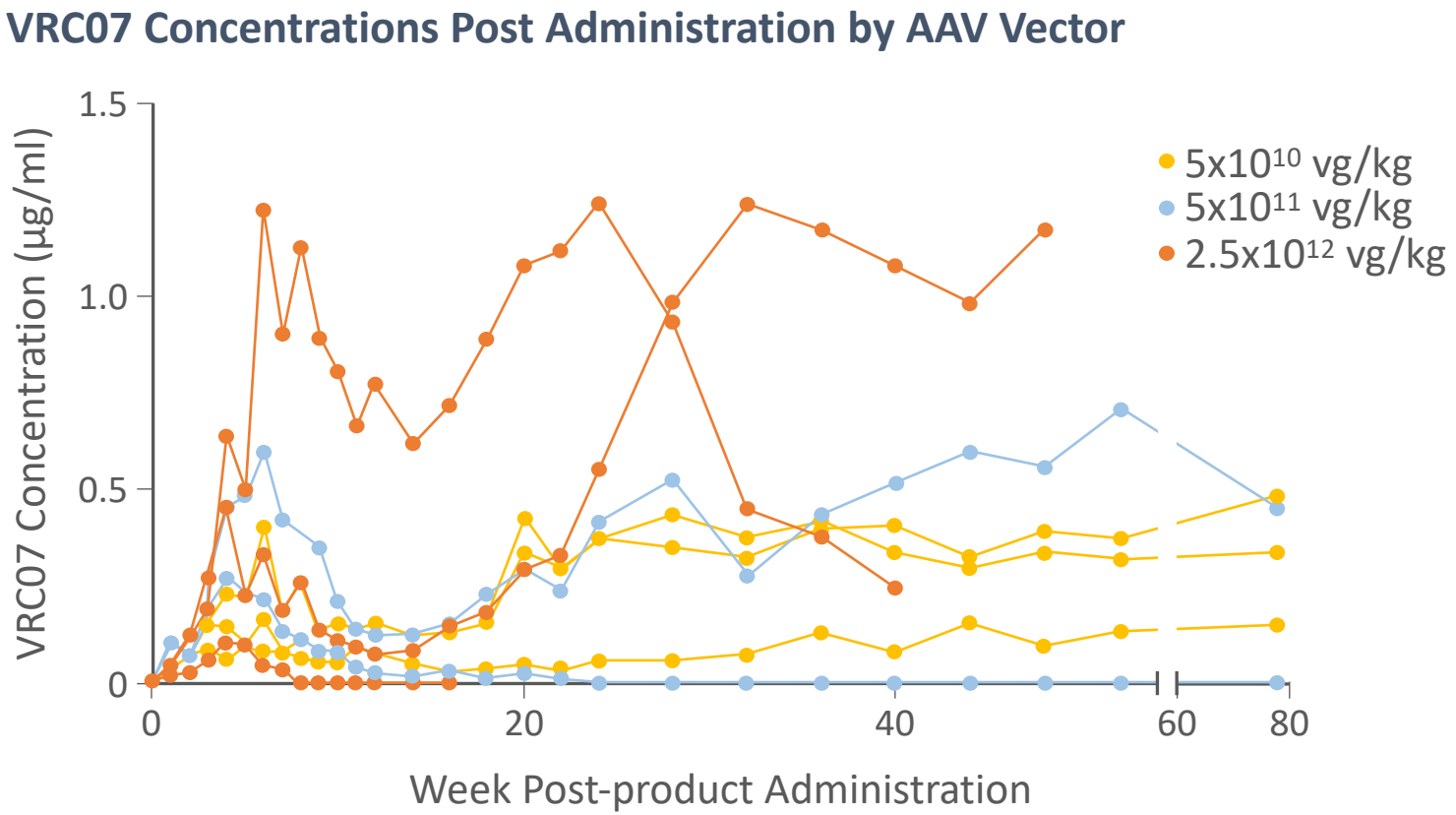
AAV8 Vector to Deliver VRC07



- Adenovirus-associated viral (AAV) vectors have an established safety record in humans
- AAV8 vector encoding HIV bNAb VRC07 has been developed
- 7 HIV-infected participants on effective ARV therapy
  - 5x 10^{10} vg/kg (n = 3)
  - 5x 10^{11} vg/kg (n = 2)
  - 2,5 x 10^{12} vg/kg (n = 2)
- IM injection
- Follow-up 7-12 months
- Adverse effects: local reactogenicity

Casazza JP, et al. CROI 2020. Abstract 41LB.

AAV8 Vector to Deliver VRC07



AAV8-mediated gene transfer may offer a safe means to generate effective vectored immunoprophylaxis in humans.

Casazza JP, et al. CROI 2020. Abstract 41LB.

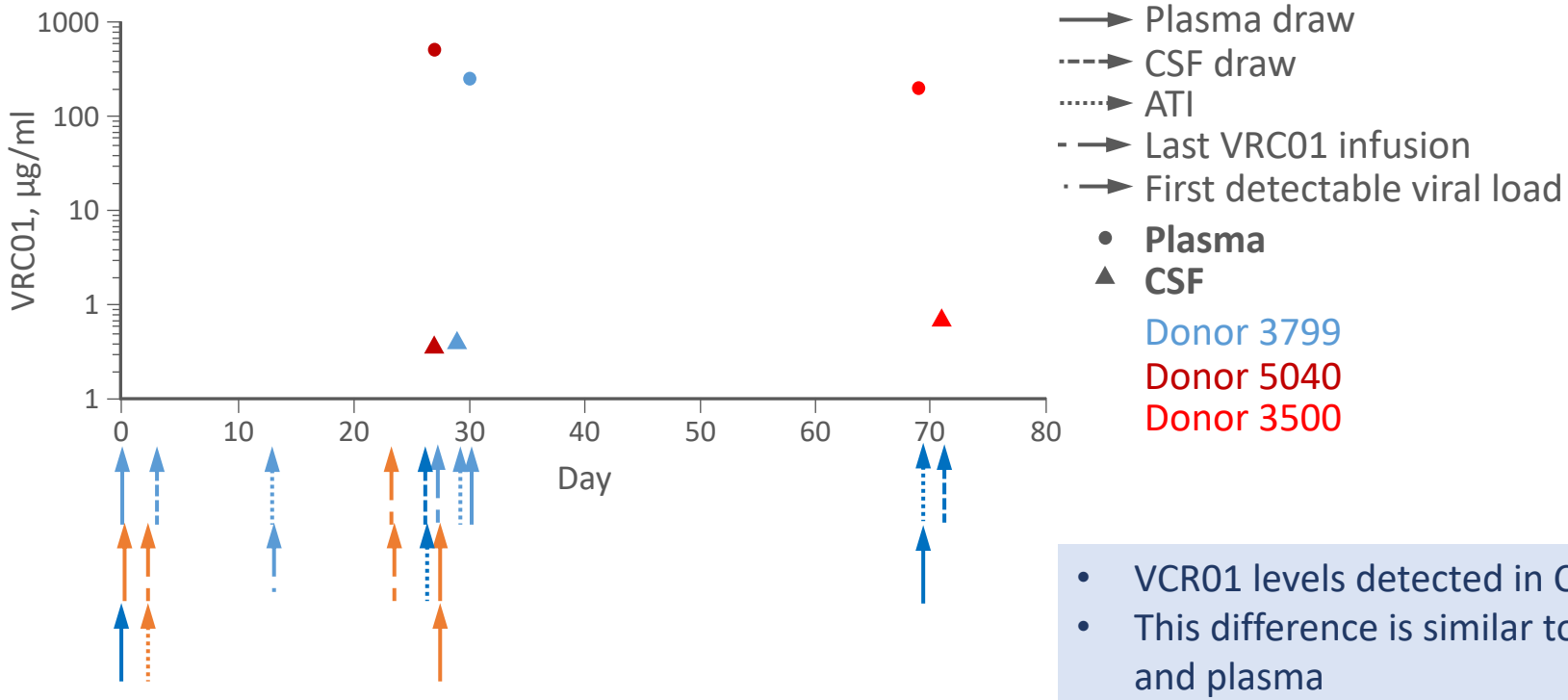
Infiltration of VRC01 Into the Cerebrospinal Fluid in Humans: The RV397 Study

- RV397 was a randomized, double-blind, placebo-controlled trial of participants who initiated who initiated suppressive ART during acute HIV infection
- At month 24 ATI + bNAb VRC01 IV every 3 weeks
- VRC01 levels in CSF and blood before and after infusion
- Three males, aged 18-47 years, Fiebig stages 1 or 2
- All CSF HIV RNA was <80 copies/ml, CSF WBC <2 cells/l, CSF protein <38 mg/dL,

Prabhakaran M, et al. CROI 2020. Abstract #453.

Infiltration of VRC01 Into the Cerebrospinal Fluid in Humans: The RV397 Study

VRC01 levels measured in the CSF and plasma of 3 participants



- VCR01 levels detected in CSF were 1000-fold lower to plasma levels
- This difference is similar to 1000-fold difference in IgG between CSF and plasma
- On average, 6% of all IgG in CSF was VCR01, while it was 2% in plasma

Prabhakaran M, et al. CROI 2020. Abstract #453.

Conclusiones

- CAB + RPV LA puede administrarse cada 8 semanas
  - Seguro y pocos efectos adversos
  - Cola farmacocinética larga (mas con RPV)
  - Asegurar TAR supresivo durante mas de 1 año

- Vienen fármacos potentes y con largas farmacocinéticas

- Los bNAbs continúan su andadura y prometen tener un sitio en el TAR