Update on Long-Acting ARVs

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Update on long-acting ART

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Disclosures

- Gilead Sciences – research grants
- ViiV Healthcare - honoraria

Update on long-acting ART - outline

- Treatment
  - Cabotegravir & Rilpivirine
- Prevention
  - Cabotegravir
- Novel agents in development
  - Lenacapavir
  - Islatravir
- Conclusion

Update on long-acting ART

Mechanistic drug class	Agents	Formulation	Stage of development
Nucleoside reverse transcriptase inhibitors	EFdA (MK-8591)	Implant	Preclinical
	Tenofovir alafenamide	Implant	Preclinical
	GS-9131	Implant	Preclinical
Nonnucleoside reverse transcriptase inhibitors	Rilpivirine	Injectable	Phase III
	Elsulfavirine	Injectable	Preclinical
Protease inhibitors	Atazanavir	Injectable	Preclinical
	Ritonavir	Injectable	Preclinical
Integrase inhibitors	Cabotegravir	Injectable	Phase III
	Raltegravir	Injectable	Preclinical
Entry inhibitors	Ibalizumab	Intravenous	US FDA approved
	PRO 140	Intravenous	Phase II
	Albuvirtide	Intravenous and subcutaneous	Approved in China
	Broadly neutralizing antibodies	Intravenous	Phase II/III
	Combinectin	Intravenous	Preclinical
Capsid inhibitors	GS-CA1	Injectable	Preclinical

Abbreviation: EFdA, 4′-ethynyl-2-fluoro-2′-deoxyadenosine.

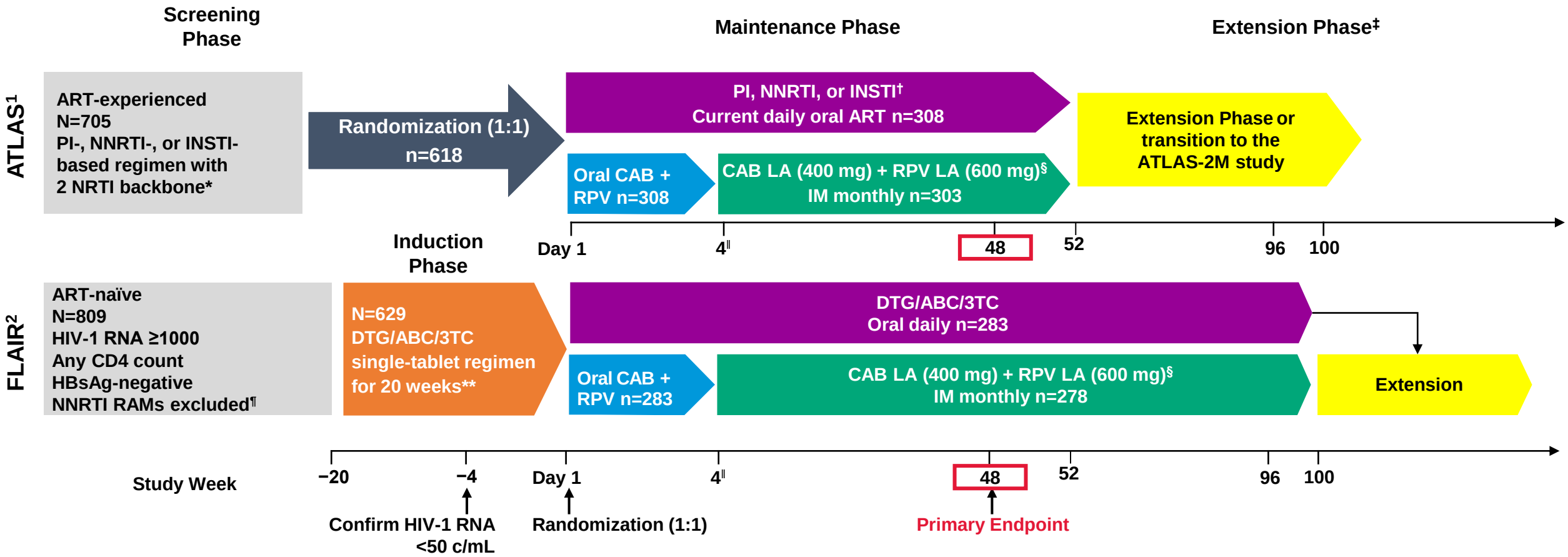
Ann. Rev. Med. 2019;70:137-50.

Update on long-acting ART - outline

- Treatment
  - Cabotegravir & Rilpivirine
- Prevention
  - Cabotegravir
- Novel agents in development
  - Lenacapavir
  - Islatravir

ATLAS and FLAIR

Randomised, multicentre, international, open-label, non-inferiority studies



*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 enrollment; Triumeq excluded from study; ‡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; ‖Participants received an initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4b. From Week 8 onwards, participants received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks; ¶NNRTI RAMs but not K103N were exclusionary; **DTG plus two alternative non-ABC NRTIs was permitted if participant was intolerant or HLA-B*5701-positive.

3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; CAR, current antiretroviral; DTG, dolutegravir; IM, intramuscular; INSTI, integrase strand transfer inhibitor; HBsAg, hepatitis B surface antigen; HLA, human leukocyte antigen;

LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance-associated mutation;

RPV, rilpivirine; VL, viral load.

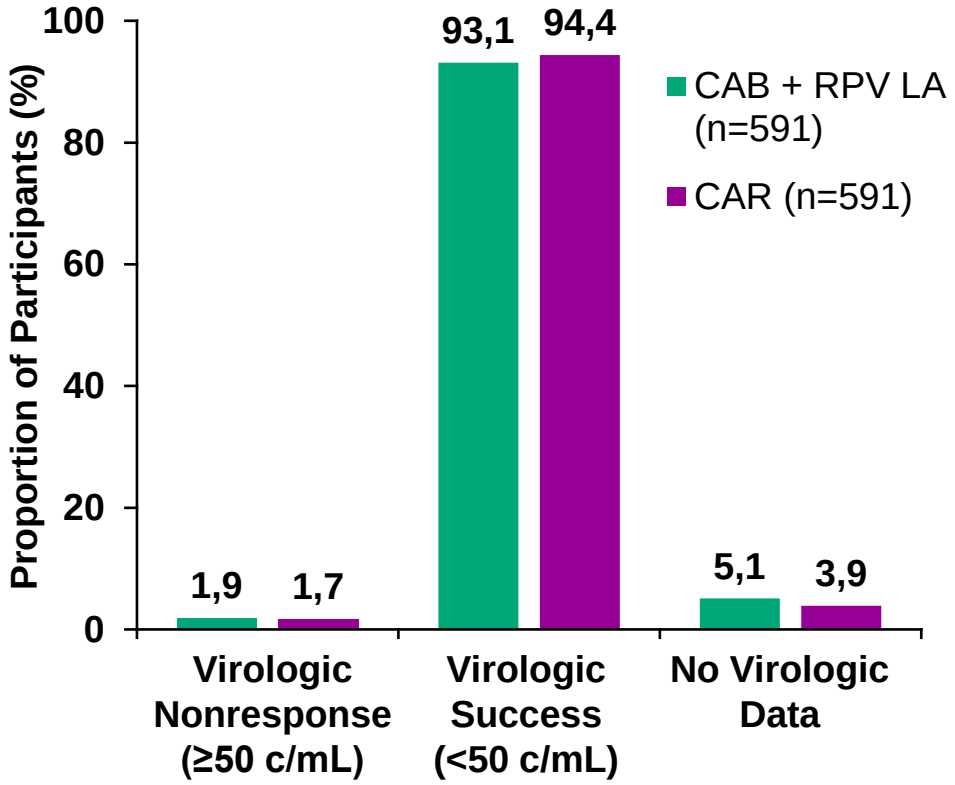
1. Swindells S, et al. CROI 2019; Seattle, WA. Abstract 1475;
2. Orkin C, et al. CROI 2019; Seattle, WA. Abstract 3947.

ATLAS and FLAIR

Virologic snapshot outcomes at Week 48 for ITT-E

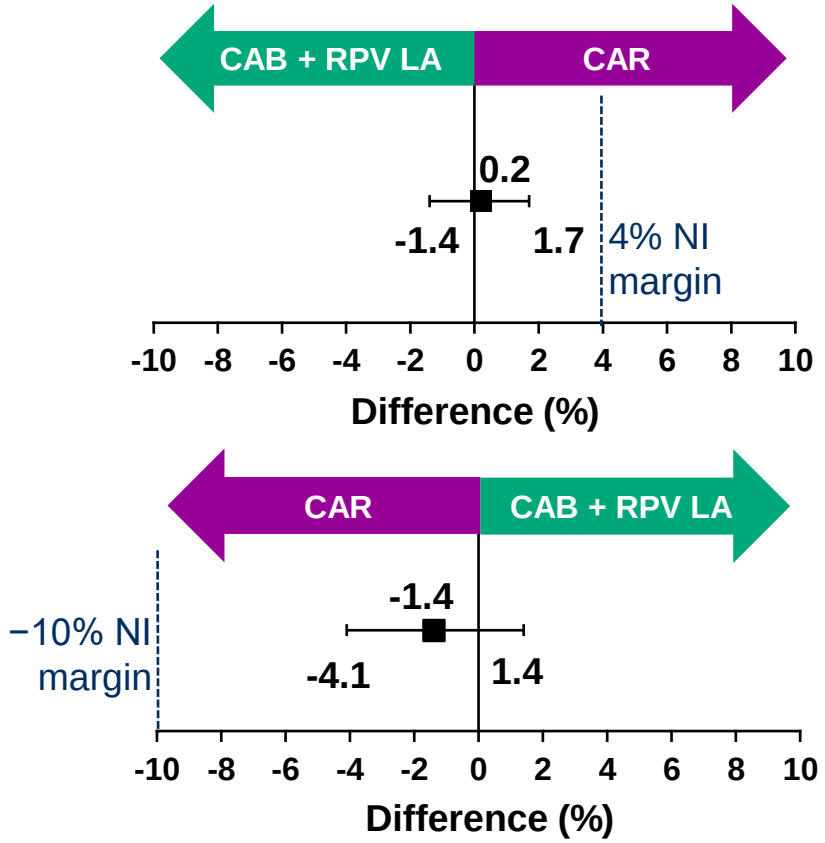
A

Virologic Outcomes



B

Adjusted Treatment Difference (95% CI)*



Primary Endpoint:

LA noninferior to CAR (HIV-1 RNA ≥50 c/mL) at Week 48

Key Secondary Endpoint:

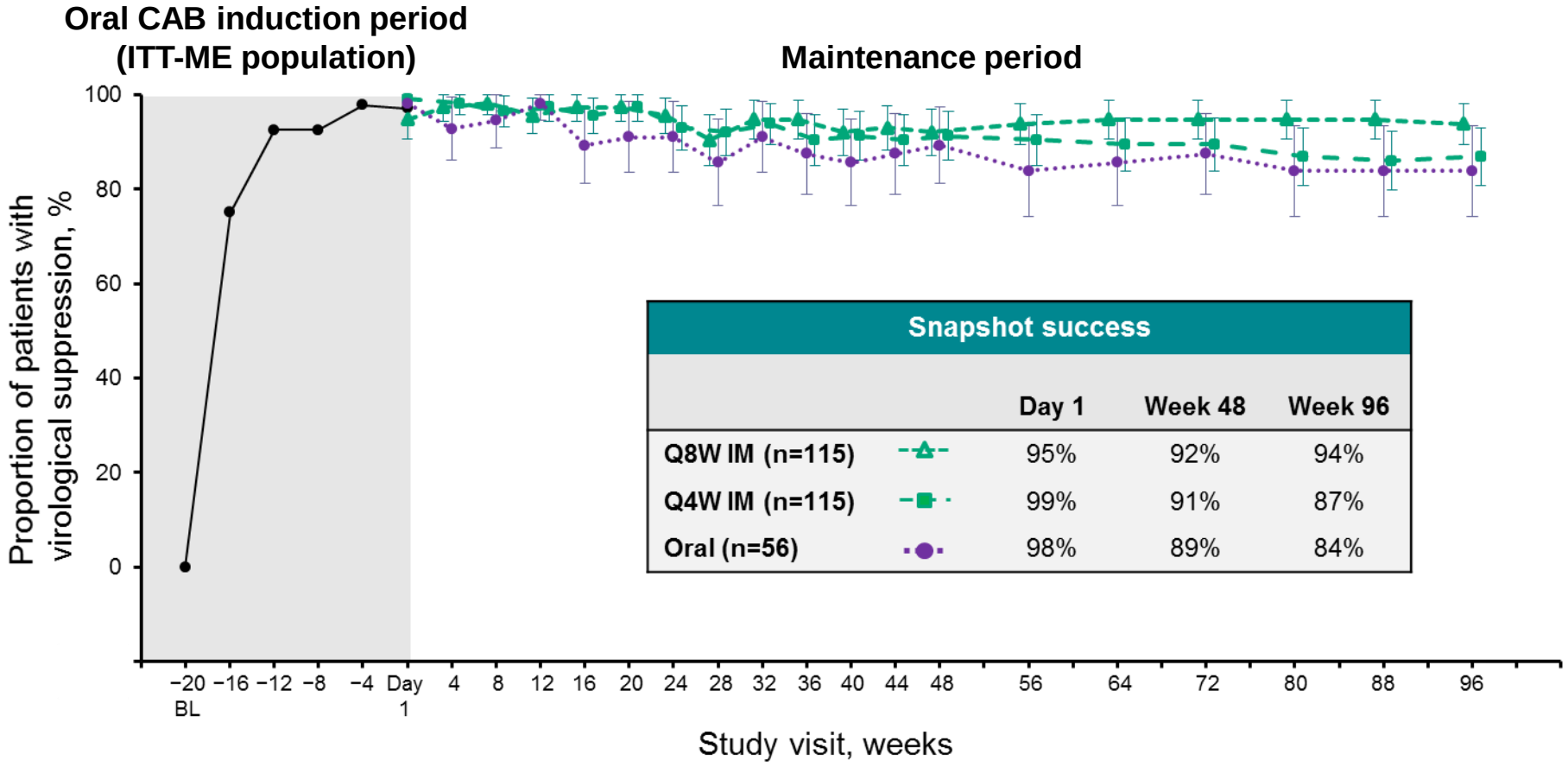
LA noninferior to CAR (HIV-1 RNA <50 c/mL) at Week 48

*Adjusted for sex and baseline third agent class.

CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.

LATTE-2 Week 96 Results

HIV-1 RNA <50 c/mL by snapshot (ITT-ME)



Snapshot success

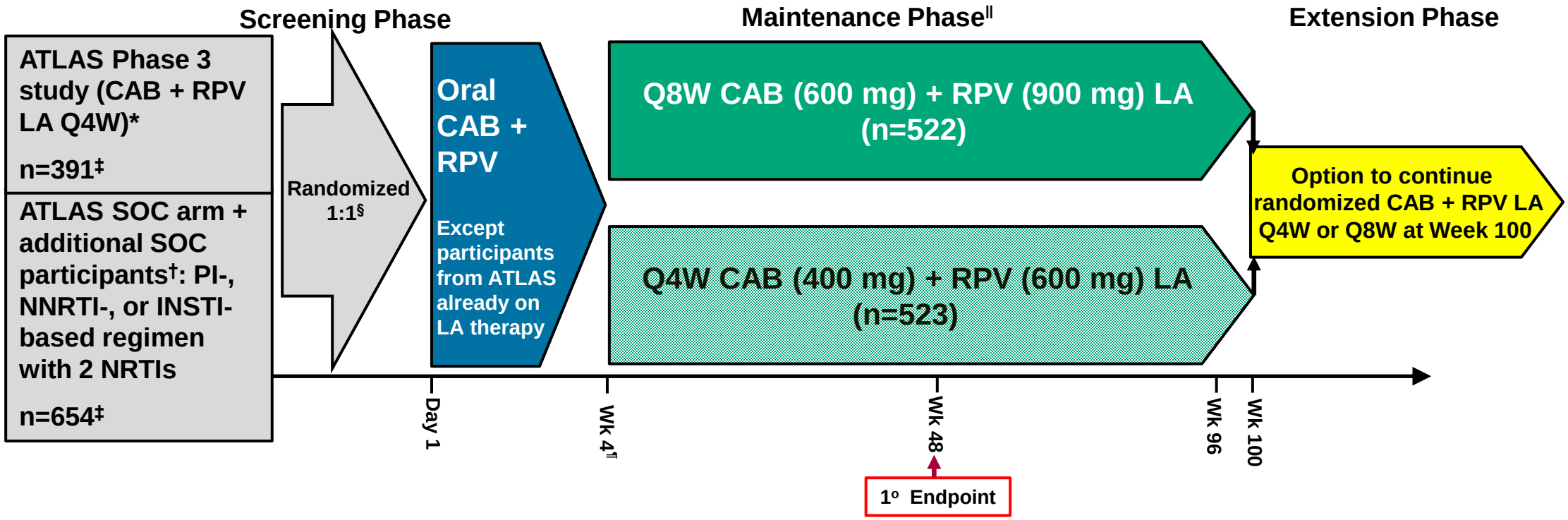
	Day 1	Week 48	Week 96
Q8W IM (n=115)	95%	92%	94%
Q4W IM (n=115)	99%	91%	87%
Oral (n=56)	98%	89%	84%

BL, baseline; CAB, cabotegravir; ITT-ME, intent-to-treat maintenance exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB.

ATLAS-2M Study Design

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



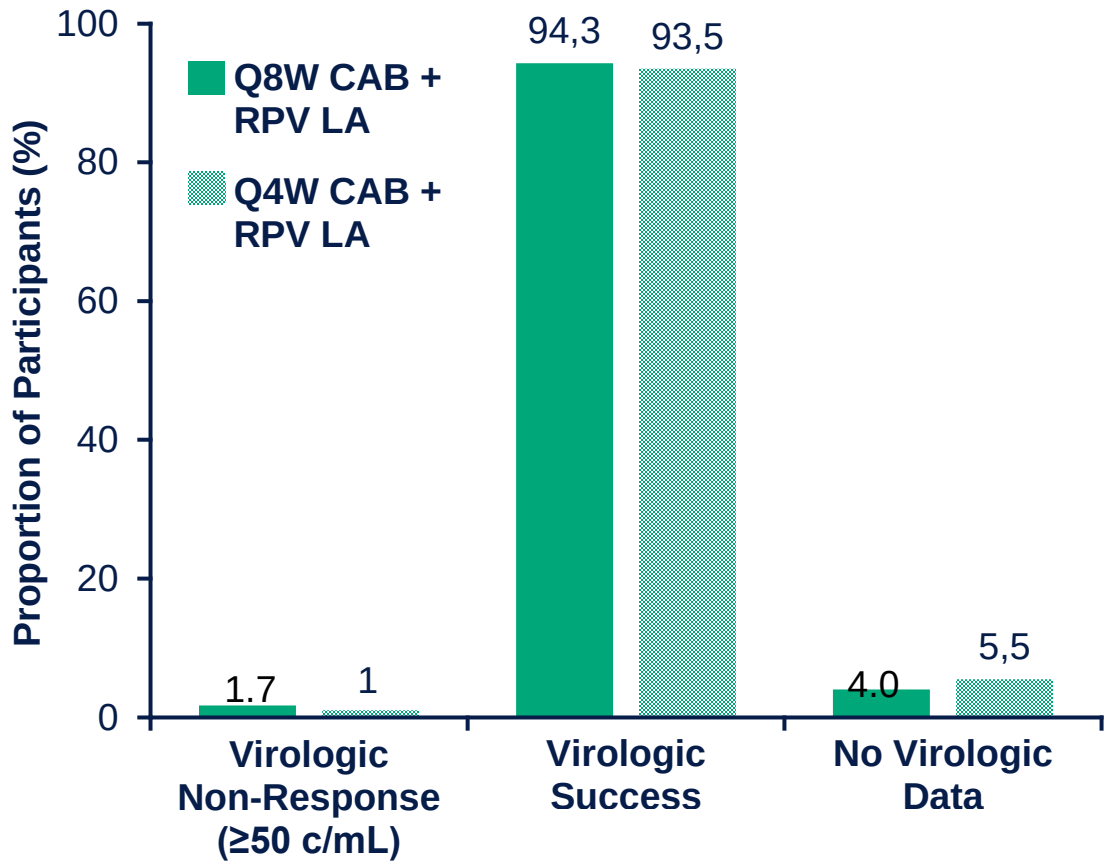
*Participants transitioning from ATLAS must have been on CAB + RPV LA Q4W or a current ART regimen through at least Week 52 of the ATLAS study and had plasma HIV-1 RNA <50 c/mL at screening. †SOC participants not transitioning from the ATLAS study were to be on uninterrupted current regimen (either the 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.

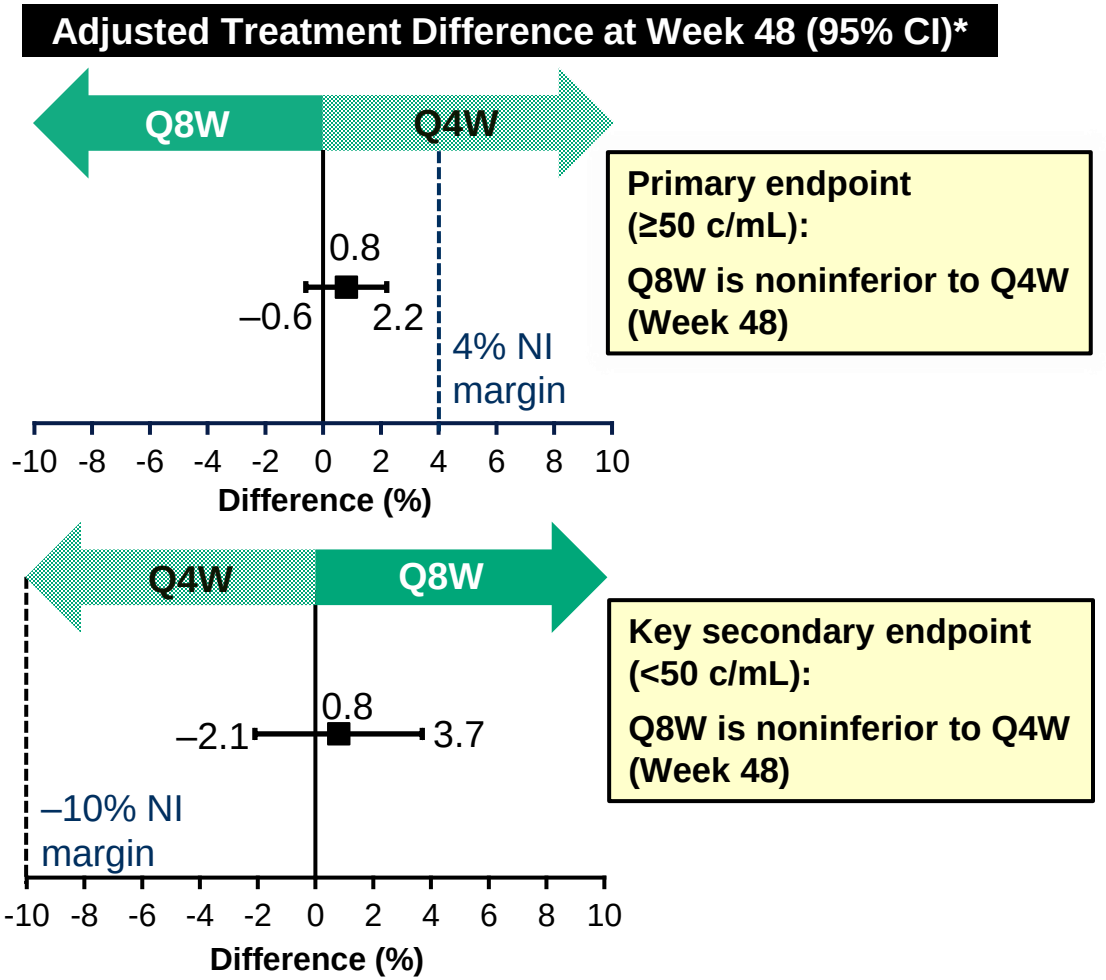
ART, antiretroviral therapy; CAB, cabotegravir; IM, intramuscular; INSTI, integrase stand transfer inhibitor; ITT-E, intent-to-treat exposed; LA, long-acting; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SOC, standard of care; Wk, week.

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
Safety and tolerability (excluding ISRs)

	Q8W (n=522) n (%)	Q4W (n=523) n (%)
Any AE	403 (77)	441 (84)
Drug-related AEs	109 (21)	125 (24)
Any Grade ≥3	29 (6)	30 (6)
Drug-related Grade ≥3	4 (<1)	5 (<1)
AEs leading to withdrawal	8 (2)	10 (2)
Drug-related AEs leading to withdrawal	5 (<1)	8 (2)
Any SAE	26 (5)	19 (4)
Drug-related SAEs*	2 (<1)	1 (<1)
Fatal SAEs†	1 (<1)	0
Drug-related fatal SAEs	0	0

*Drug-related SAEs were presyncope and acute pancreatitis in the Q8W group and allergic reaction in the Q4W group. †The fatal SAE was sepsis. The death was not considered related to study drug. A further participant died during screening (did not receive study drug).

- AEs were similar between the Q8W and Q4W dosing arms
- Overall, 96% of drug-related AEs were Grade 1–2
- Drug-related AEs led to withdrawal in 5 participants in the Q8W arm and 8 in the Q4W arm

AE, adverse event; ISR, injection site reaction; Q4W, every 4 weeks; Q8W, every 8 weeks; SAE, serious adverse event.

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 are being further evaluated (e.g. baseline ART resistance, HIV subtype polymorphisms, BMI and drug concentrations)
- PBMC HIV-1 DNA analysis underway across Phase 3 program
  - See Margolis D et al. *A combination of viral and participant factors influence virologic outcome to long-acting cabotegravir and rilpivirine: multivariable and baseline factor analyses across ATLAS, FLAIR, and ATLAS-2M phase III studies*. Conference on HIV Drug Therapy Glasgow. Thursday 08 October 2020.

*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

Overall ISRs

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)

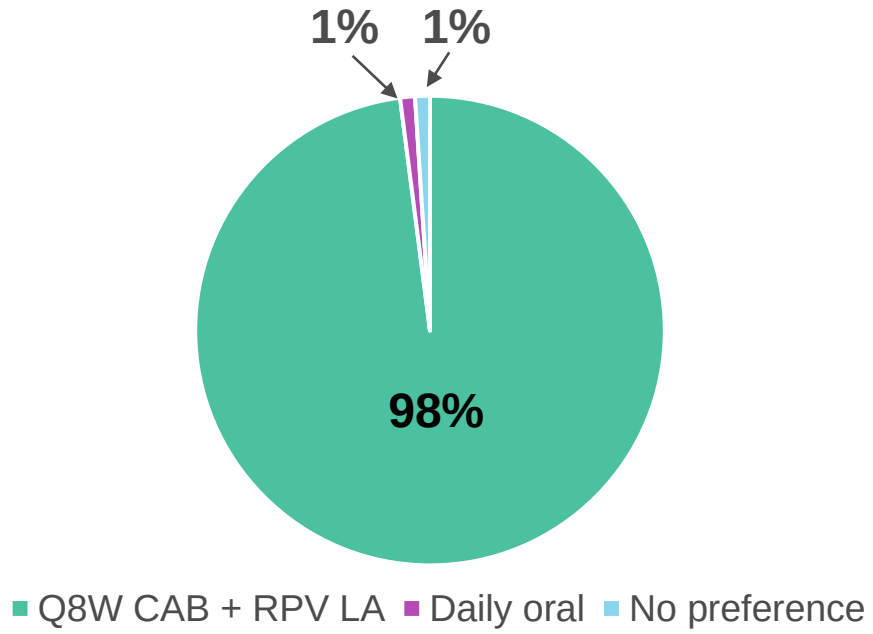
*All event-level ISR percentages are calculated from the total number of injections. Note: A single injection could result in more than one ISR. †There were no Grade 4 or Grade 5 ISRs. ‡ISRs occurring in >1% of injections in either the Q4W or Q8W arms are shown. §Q8W: 5 participants had an ISR leading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

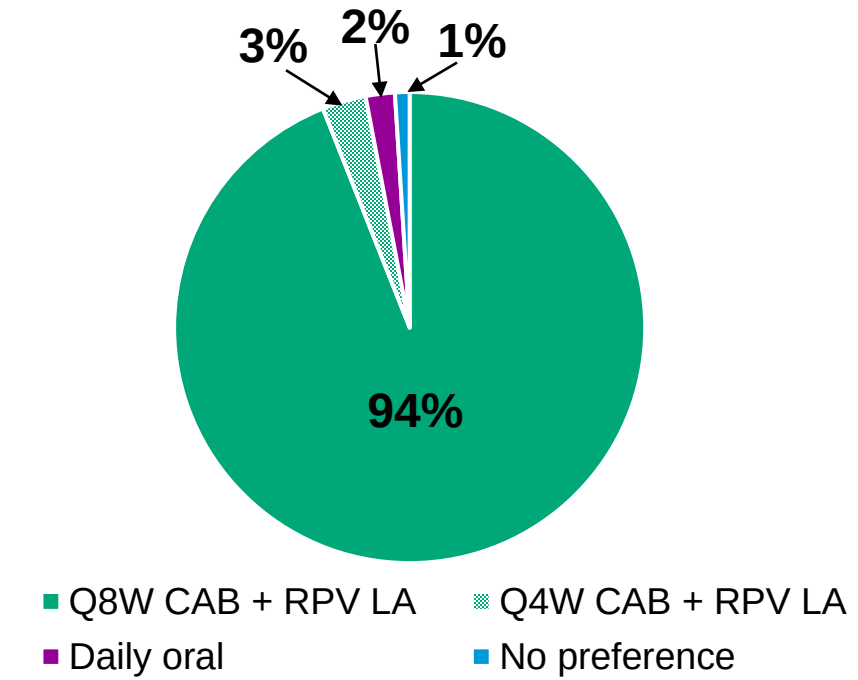
ATLAS-2M
Dosing frequency preference

Participants in Q8W arm from SOC (no prior Q4W experience)*



*306 participants responded to the preference question.

Participants in Q8W arm with prior Q4W experience in ATLAS†



†191 participants responded to the preference question.

Daily oral therapy refers to CAB + RPV oral therapy that was received during the oral lead-in period for either this study or the ATLAS study.
Percentages are calculated out of those participants with recorded response to the preference.
CAB, cabotegravir; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SOC, standard of care.

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- Novel agents in development
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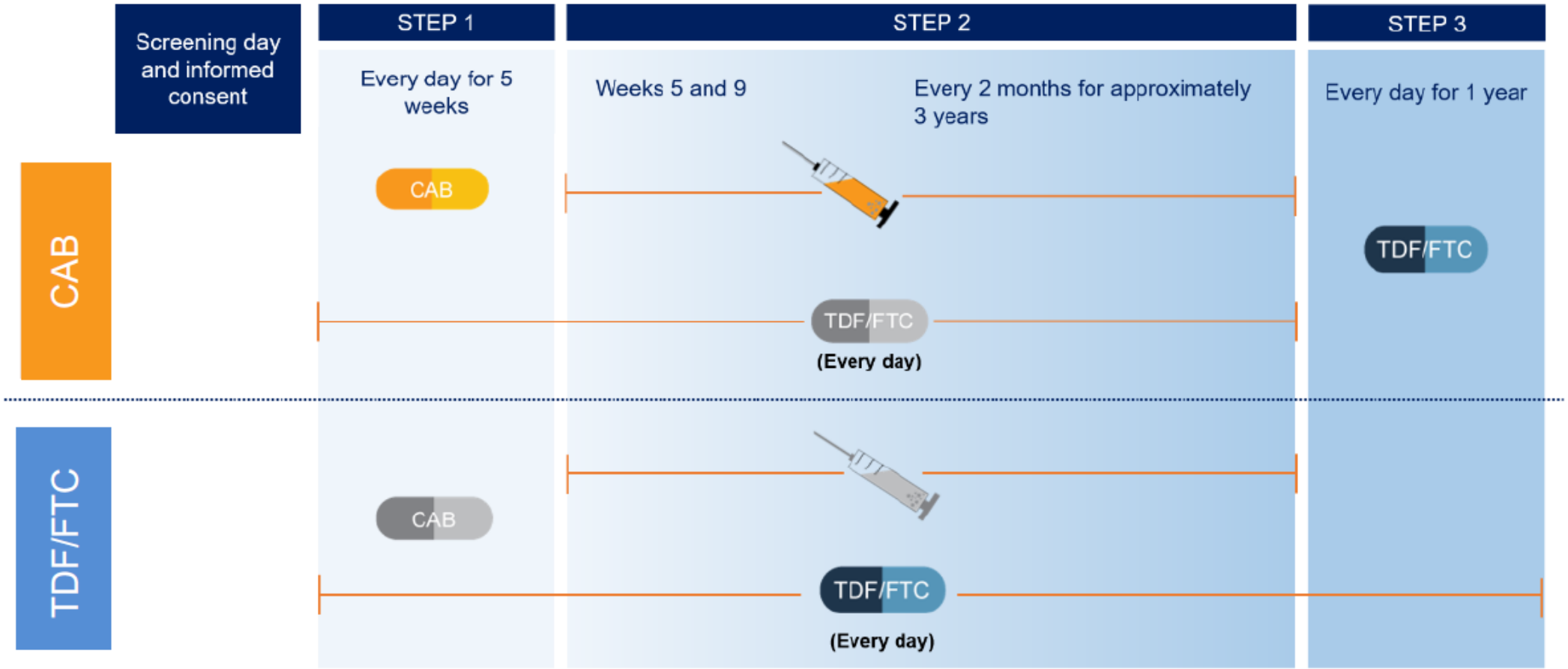
  - Islatravir

HPTN 083 Study Design



Landovitz RJ et al. AIDS 2020, #OAXLB01

Study Population

	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)
Gender Identity, n (%)			
MSM	3995 (87.5)	1981 (86.7)	2014 (88.3)
TGW	567 (12.4)	302 (13.2)	265 (11.6)
Age, median (IQR)	26 (22, 32)	26 (22, 32)	26 (22, 32)
Age, n (%)			
18-29	3079 (67.4)	1508 (66.0)	1571 (68.8)
30-39	1049 (23)	550 (24.1)	499 (21.9)
40-49	315 (6.9)	170 (7.4)	145 (6.4)
50-59	110 (2.4)	50 (2.2)	60 (2.6)
≥60	13 (0.3)	6 (0.3)	7 (0.3)
Region, n (%)			
United States	1698 (37.2%)	849 (37.2%)	849 (37.2%)
Latin America	1964 (43.0%)	984 (43.2%)	980 (42.9%)
Asia	752 (16.5%)	377 (16.5%)	375 (16.5%)
Africa	152 (3.3%)	74 (3.2%)	78 (3.4%)
Education, n (%)			
Post-Secondary (YES)	3477 (76.1)	1715 (75.1)	1762 (77.2)
Relationship Status, n (%)			
Single (YES)	3750 (82.1)	1863 (81.6)	1887 (82.7)

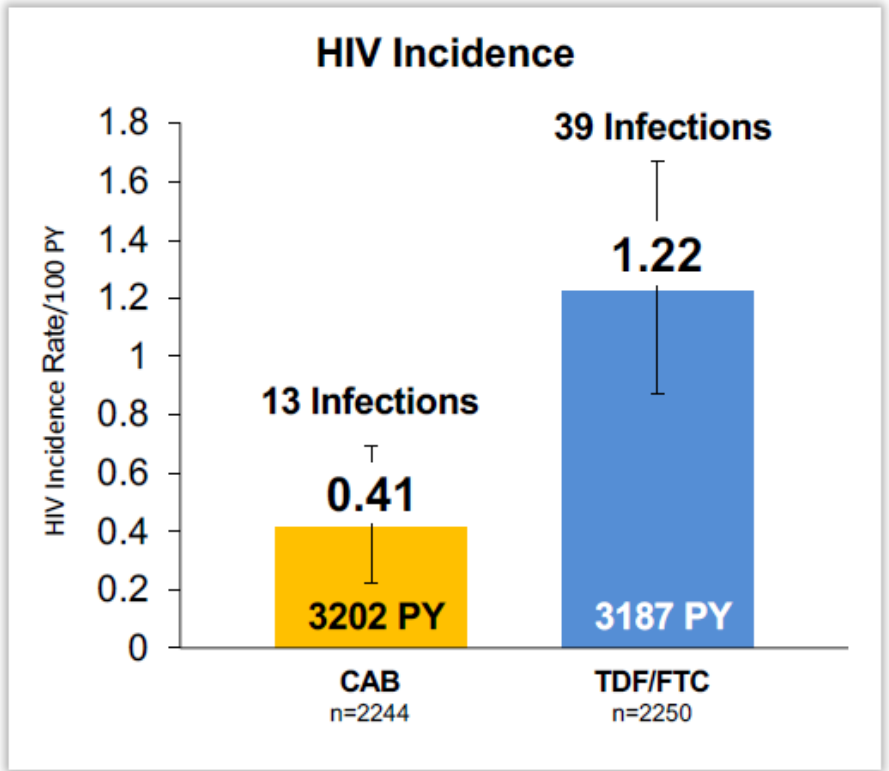
Study Population

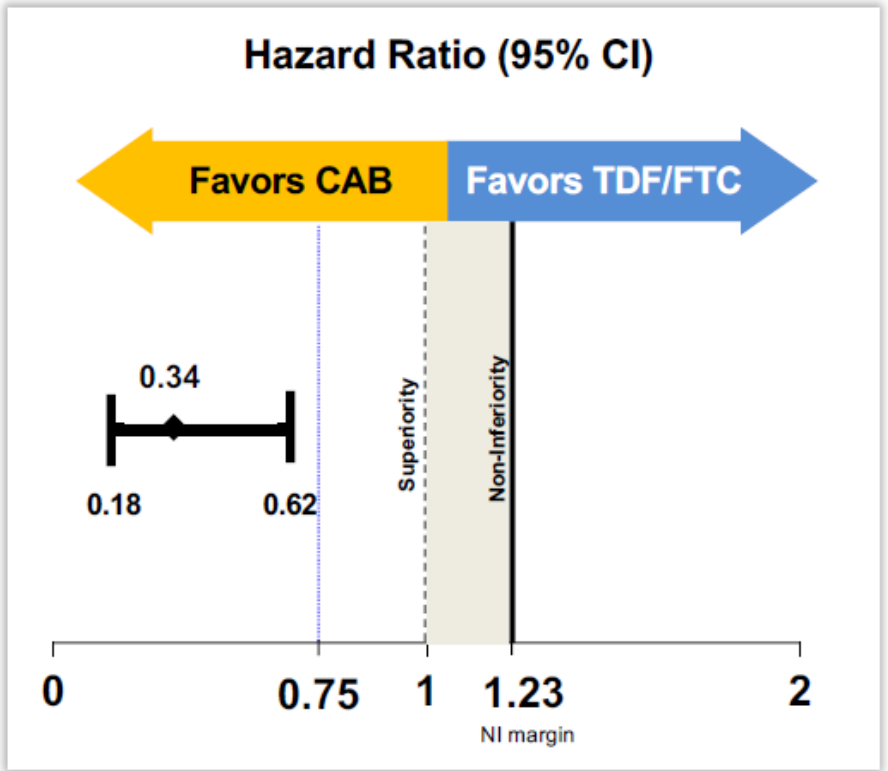
	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)
Race, n (%)			
United States			
Black/African American	844 (49.7)	433 (51.0)	411 (48.9)
White/Asian/Native/Other	854 (50.4)	416 (49.0)	438 (51.1)
Latin America			
Black/Afro-Carribean	395 (20.1)	196 (19.9)	199 (20.3)
Native	858 (43.7)	425 (43.2)	433 (44.2)
White/Asian/Other	711 (59.6)	363 (36.8)	348 (35.5)
Asia			
Asian	749 (99.6)	375 (99.5)	374 (99.7)
Other	3 (0.4)	2 (0.5)	1 (0.3)
Africa			
Black	119 (78.3)	57 (77.0)	62 (79.5)
Other	5 (3.3)	3 (4.1)	2 (2.6)
Ethnicity, n (%)			
United States: Latinx	303(17.8)	154 (18.1)	149 (17.6)
Latin America: Latinx	1805 (91.9)	912 (92.7)	893 (91.1)

Landovitz RJ et al. AIDS 2020, #OAXLB01

HIV Incidence
CAB vs. TDF/FTC

52 HIV infections in 6389 PY of follow-up
1.4 (IQR 0.8-1.9) years median per-participant follow-up
Pooled incidence 0.81 (95%CI 0.61-1.07) per 100 PY





CI, confidence interval

Landovitz RJ et al. AIDS 2020, #OAXLB01

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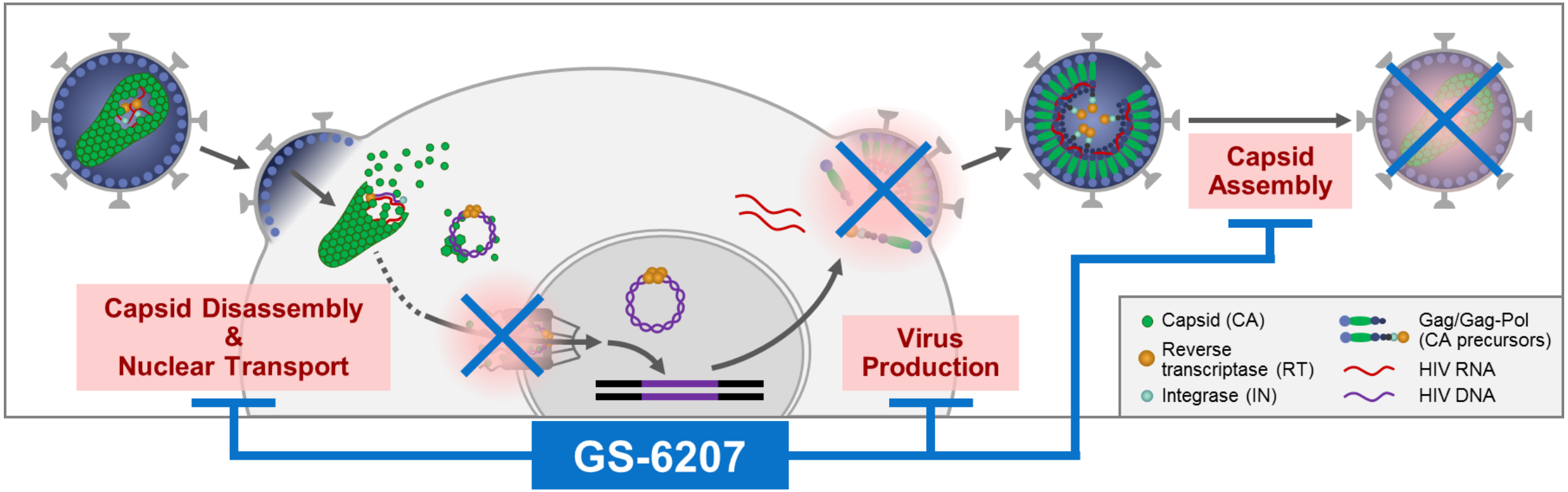
Lenacapavir SC (first-in-class HIV capsid inhibitor)

Mechanism of Action

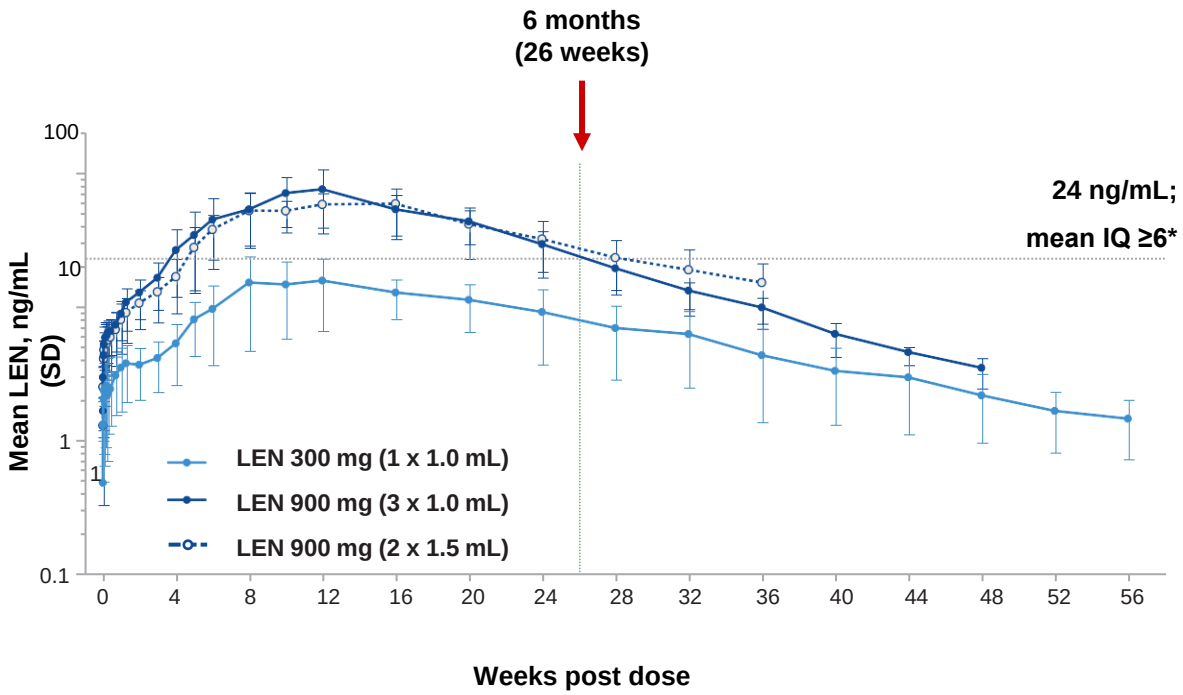


- GS-6207 inhibits multiple processes essential for viral replication
- GS-6207 modulates the stability and/or transport of capsid complexes

Yant SR, et al. CROI 2019. Seattle, WA. Poster 480
Sager JE, et al. CROI 2019. Seattle, WA. Oral 141

Lenacapavir SC
Pharmacokinetics and Safety in HVs

Mean (SD) LEN Single Dose Plasma Concentration-Time Profiles



- Single SC doses of up to 900 mg LEN were generally safe and well tolerated
  - No serious or Grade 2, 3, or 4 AEs related to study drug†
  - No AEs leading to discontinuation
  - ISRs were common (80%) and all mild
- Target concentrations sustained for ≥6 months after single 900 mg dose
  - Slow release necessitates oral PK loading dose prior to first injection

Preliminary PK and safety data support continued clinical development of long-acting SC LEN in conjunction with an oral LEN loading dose

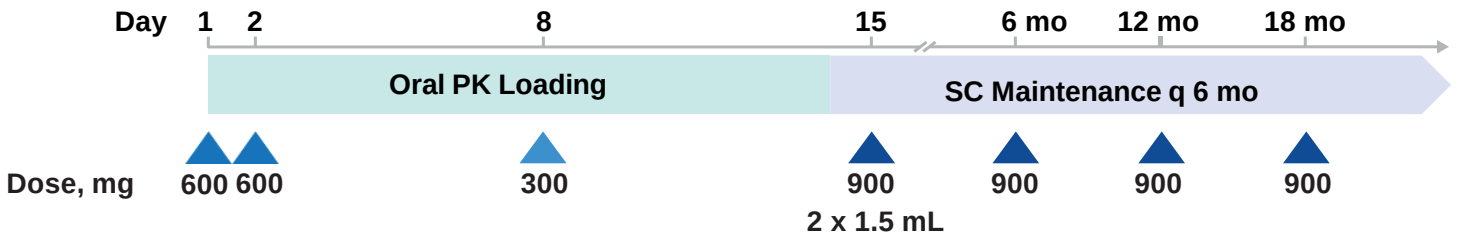
ISRs, injection site reactions
IQ: Ratio of LEN plasma concentration/EC_{95} *$paEC_{95}$ =1.16 ng/mL (macrophages), 2.32 ng/mL (CD4+ T cells), and 3.87 ng/mL (MT-4 cells)
†One participant had Grade 3 AEs of abscess (also serious AE), cellulitis, and MRSA infection, none of which were related to LEN

Begley R, et al. AIDS 2020. PEB0265

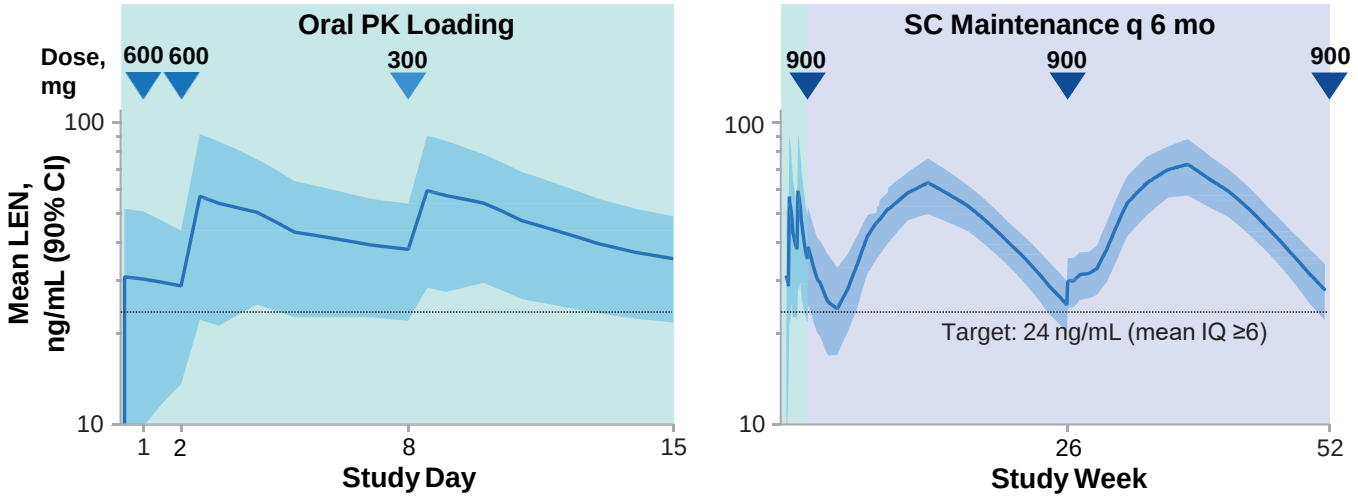
Lenacapavir

Simulations Supporting Phase 2/3 LEN Dosing Regimen in HVs

LEN Oral + SC Dosing Regimen in Ongoing Phase 2 and 3 Studies



Predicted LEN PK for Phase 2/3 Oral + SC Combination Regimen



- The new formulation exhibits a slow initial release necessitating an oral loading regimen
  - 14-d oral loading: 600 mg on Days 1 and 2, and 300 mg on Day 8
  - SC maintenance: 900 mg on Day 15, followed by 900 mg q 6 months
- Mean LEN target concentration is 24 ng/mL, corresponding to a mean IQ ≥6 (range 6.2–20.3)
- The regimen was predicted to achieve target concentrations within a few days of initiation and maintain them with a 6-month dosing interval

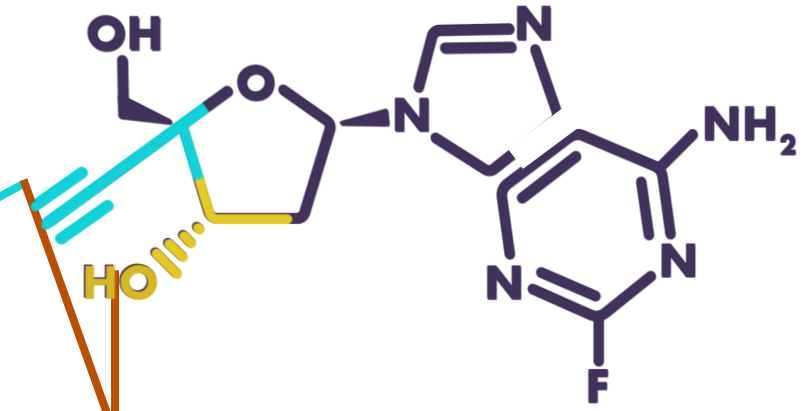
PK simulations support development of LEN regimen with oral loading dose, followed by SC maintenance every 6 months

Begley R, et al. AIDS 2020. PEB0265

Islatravir (MK-8591)

First-in-class nucleoside reverse transcriptase translocation inhibitor

‡



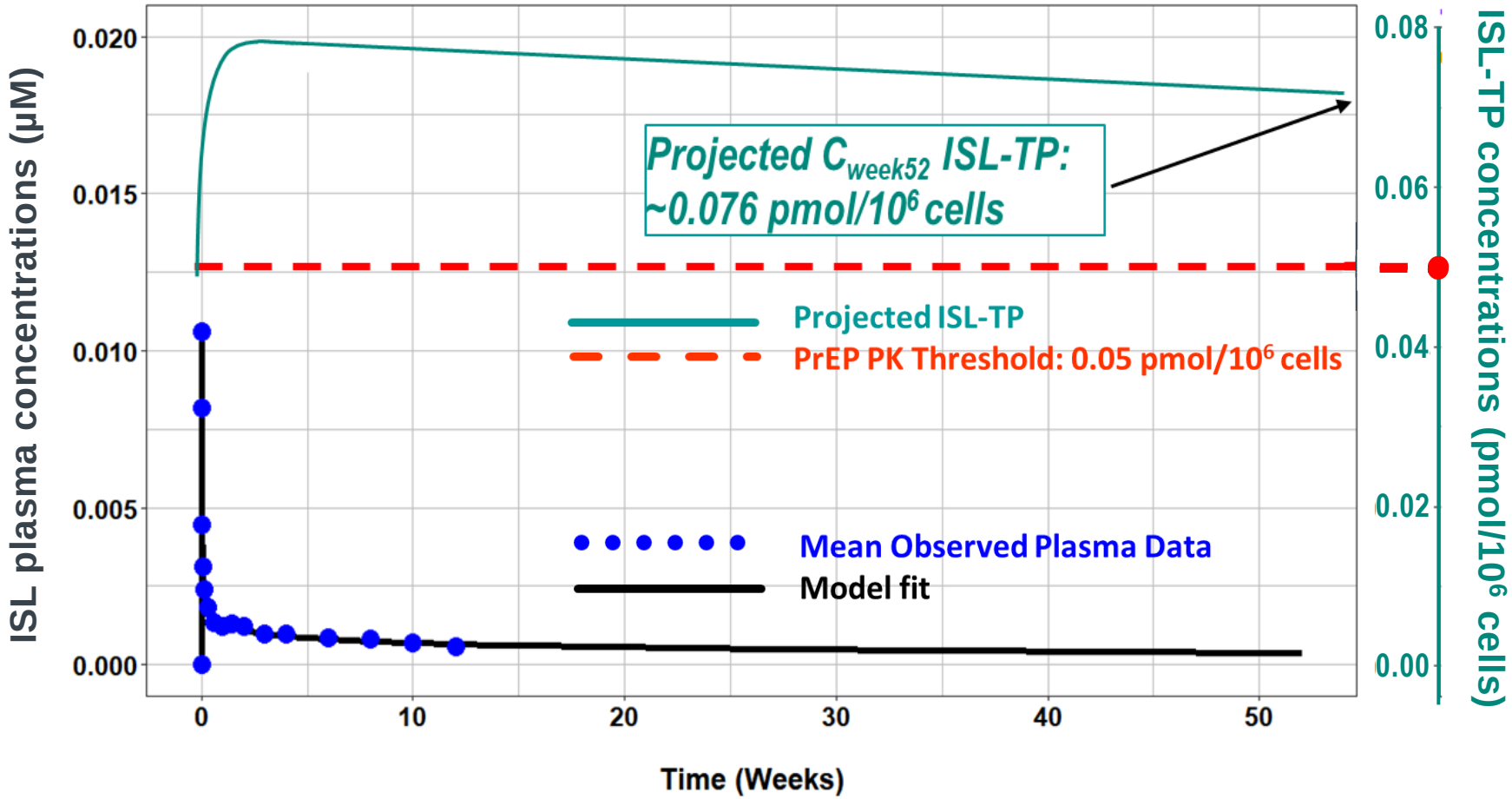
Translocation Inhibition
Due to the 4’-ethynyl Group

Delayed Chain Termination
Due to the 4’-ethynyl and 3’-hydroxyl Groups

Multiple mechanisms contribute to islatravir high potency against HIV-1, drug-resistant variants and high barrier to resistance.

Islatravir (62mg implant)

Projected to lead to concentrations above threshold for at Least 12 months



- 62 mg implant will continue to release through 52 weeks
- ISL-TP should be above threshold (0.05 pmol/10^6 cells) for >12 months
  - Projected concentration at 12 months: **0.076 pmol/10^6 cells**
  - Projected time at which concentration falls below 0.05 pmol/10^6 cells: 68-70 weeks (~**16 months**)

Conclusions

- Monthly, long acting, dual, intramuscular therapy with CAB + RPV is ready for prime time
- CAB + RPV 2 monthly non-inferior to monthly in ATLAS-2M
  - 'SOLAR' will compare 2M intramuscular CAB + RPV versus daily oral Biktarvy over 48 weeks in PLHIV with suppressed VL on Biktarvy
    - Scheduled to commence recruitment in Q4 2020
    - ClinicalTrials.gov Identifier: NCT04542070
- Implementation studies for translation into clinics will be important
  - e.g. CUSTOMIZE and CARISEL studies
- CAB intramuscular monotherapy is superior to TDF/FTC for HIV prevention in high risk MSM
- New long-acting agents are in development with potential for use in treatment and prevention
- The potential for very long acting ART in treatment and prevention is under investigation
  - e.g. drug-eluting implants, s/c rate-limiting semi-permeable membranes, vaginal rings

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