18ª edición

POSTCROI 2021

Una actualización de la 28ª Conference on Retroviruses and Opportunistic Infections

Nuevos fármacos, enfoques terapéuticos y PrEP

Arkaitz Imaz

Hospital Universitari de Bellvitge

Bellvitge Hospital Universitari

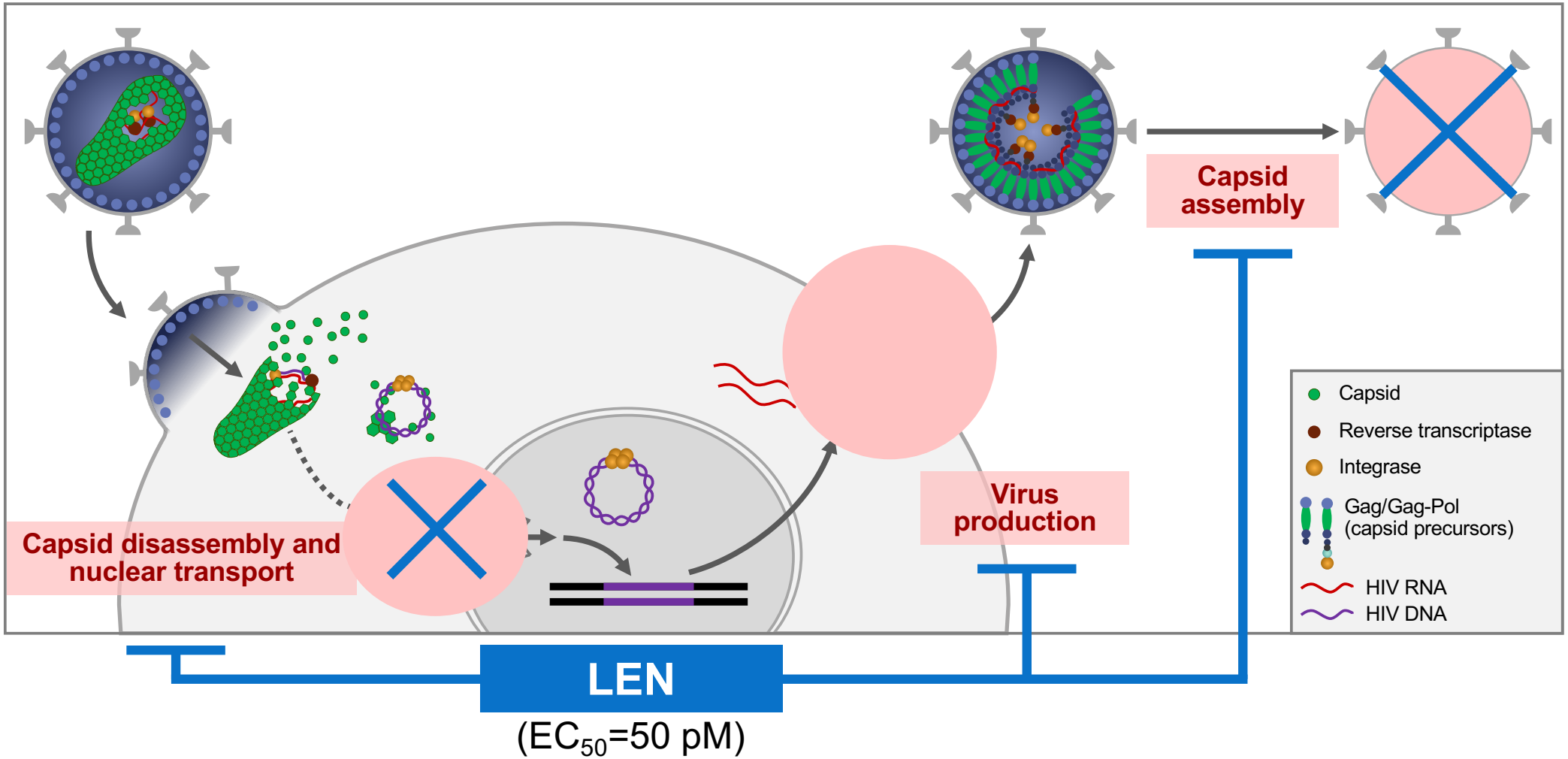
IDI BELL Institut d'Investigació Biomèdica de Bellvitge

FUNDACIÓN LUCHA CONTRA EL SIDA Y LAS ENFERMEDADES INFECCIOSAS

FLS SCIENCE

- Nuevos fármacos antirretrovirales en desarrollo
- Nuevos Ensayos Clínicos con fármacos antirretrovirales ya comercializados
- Nuevos fármacos y estrategia de PrEP

Lenacapavir (LEN): Novel, First-in-class HIV Capsid Inhibitor Highly Potent and Long-acting



EC_{50}, half maximal effective concentration.

Segal-Maurer, S. et al. CROI 2021. Virtual. Abstract 127.

Study Design

Key eligibility criteria:
- HIV-1 RNA ≥400 copies/mL
- Resistance to ≥2 agents from 3 of 4 main ARV classes
- ≤2 fully active agents

Screening Period
Pre-randomization repeat HIV-1 RNA
- Decline of ≥0.5 $\log_{10}$ copies/mL (vs screening) or
- <400 copies/mL

YES → **Nonrandomized cohort (Open label)** → n=36 → Oral LEN* + OBR → SC LEN* Q6M for 52 weeks + OBR

NO → **Randomized cohort (Double blind)**

Functional monotherapy (14-d)

Maintenance

n=24 → Oral LEN* + Failing regimen → SC LEN* Q6M for 52 weeks + OBR

n=12 → Placebo + Failing regimen → Oral LEN* + SC LEN* Q6M for 52 weeks + OBR

*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15.
OBR, optimized background regimen (investigational agents, such as fostemsavir, were allowed; ATV, ATV/co, ATV/r, EFV, ETV, NVP, TPV were not allowed).

Segal-Maurer, S. et al. CROI 2021. Virtual. Abstract 127.

Baseline Characteristics

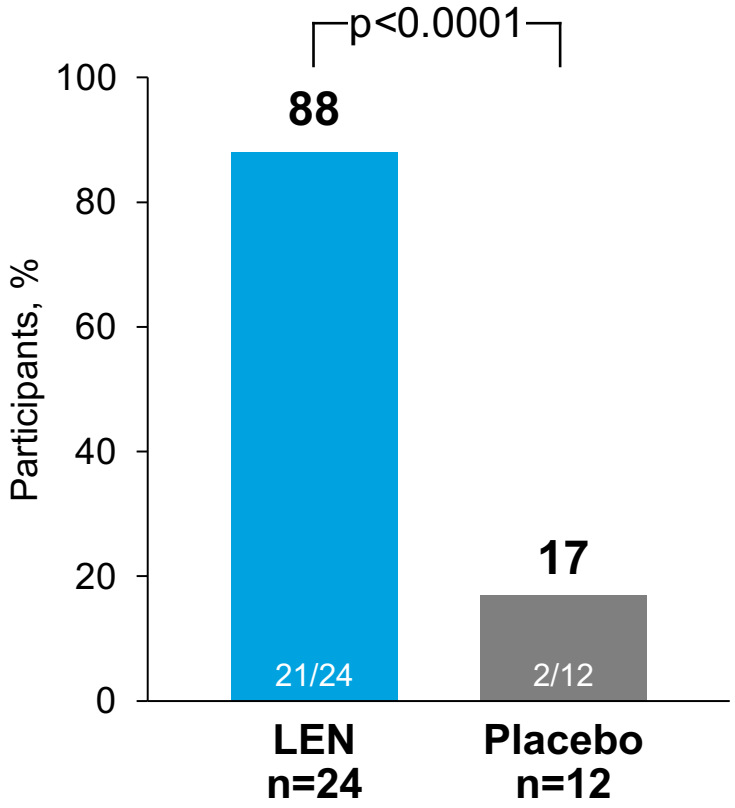
	Randomized		Nonrandomized	
	LEN n=24	Placebo n=12	LEN n=36	Total N=72
Age, median (range), years	55 (24 – 71)	54 (27 – 59)	49 (23 – 78)	52 (23 – 78)
Sex, % female at birth	29	25	22	25
Race, % Black	42	55	31	38
Ethnicity, % Hispanic or Latinx	25	36	14	21
HIV-1 RNA, median (range), log_{10} copies/mL	4.2 (2.3 – 5.4)	4.9 (4.3 – 5.3)	4.5 (1.3 – 5.7)	4.5 (1.3 – 5.7)
>75,000 copies/mL, %	17	50	28	28
CD4 count, median (range), cells/μL	172 (16 – 827)	85 (6 – 237)	195 (3 – 1296)	150 (3 – 1296)
≤200 cells/μL, %	67	92	53	64
Number of prior ARV agents, median (range)	9 (2 – 24)	9 (3 – 22)	13 (3 – 25)	11 (2 – 25)
Years since HIV diagnosis, median (range)	27 (13 – 39)	26 (14 – 35)	23 (9 – 44)	24 (9 – 44)
Prior ARV class exposure, %				
NRTI	96	92	97	96
NNRTI	92	83	92	90
PI	88	75	94	89
INSTI	100	92	83	90

Segal-Maurer, S. et al. CROI 2021. Virtual. Abstract 127.

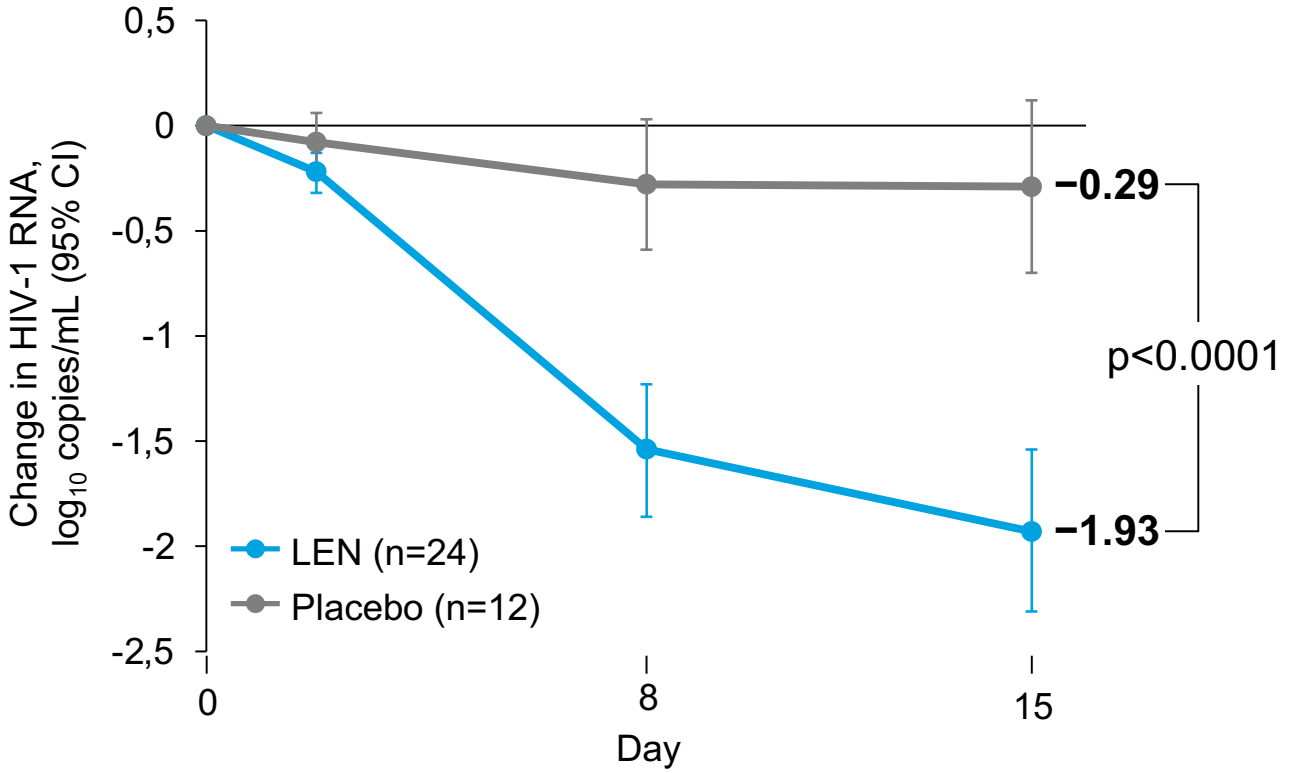
Antiviral Activity during Functional Monotherapy

Primary Endpoint

% Achieving HIV-1 RNA Decline ≥0.5 log_{10} copies/mL

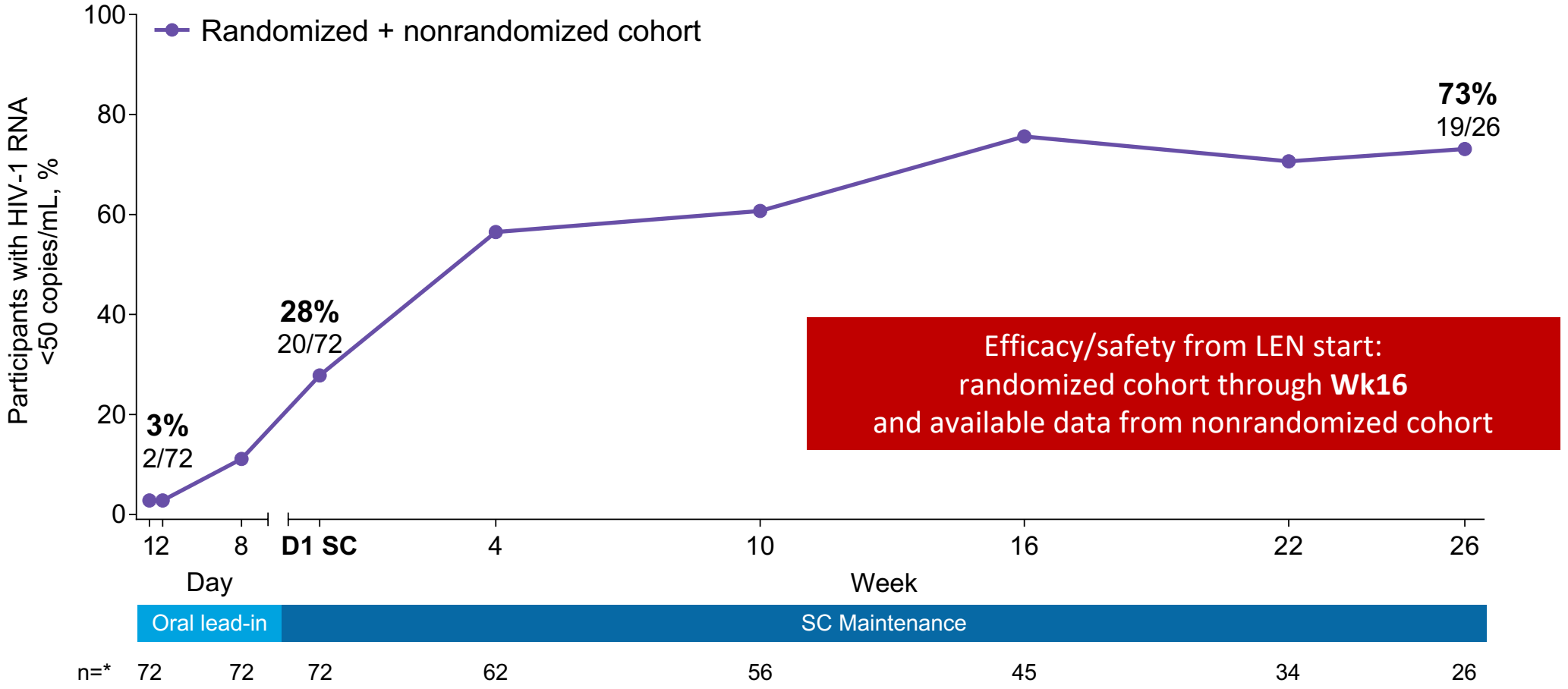


Mean Change in HIV-1 RNA by visit (95% CI)



Segal-Maurer, S. et al. CROI 2021. Virtual. Abstract 127.

Participants with HIV-1 RNA <50 copies/mL (M=F): To date (Feb2021) in those who received SC LEN (n=72)



*Denominators are those who received ≥1 dose of SC LEN and have available HIV-1 RNA at time of data cut, while study is still ongoing; D1 SC, the first day SC LEN was administered; 2 participants in Cohort 2 (nonrandomized cohort) had HIV-1 RNA <50 copies/mL on Day 1 but also >0.5 log reduction prior to Day 1 (presumably due to improved adherence).

Segal-Maurer, S. et al. CROI 2021. Virtual. Abstract 127.

Treatment-emergent Resistance

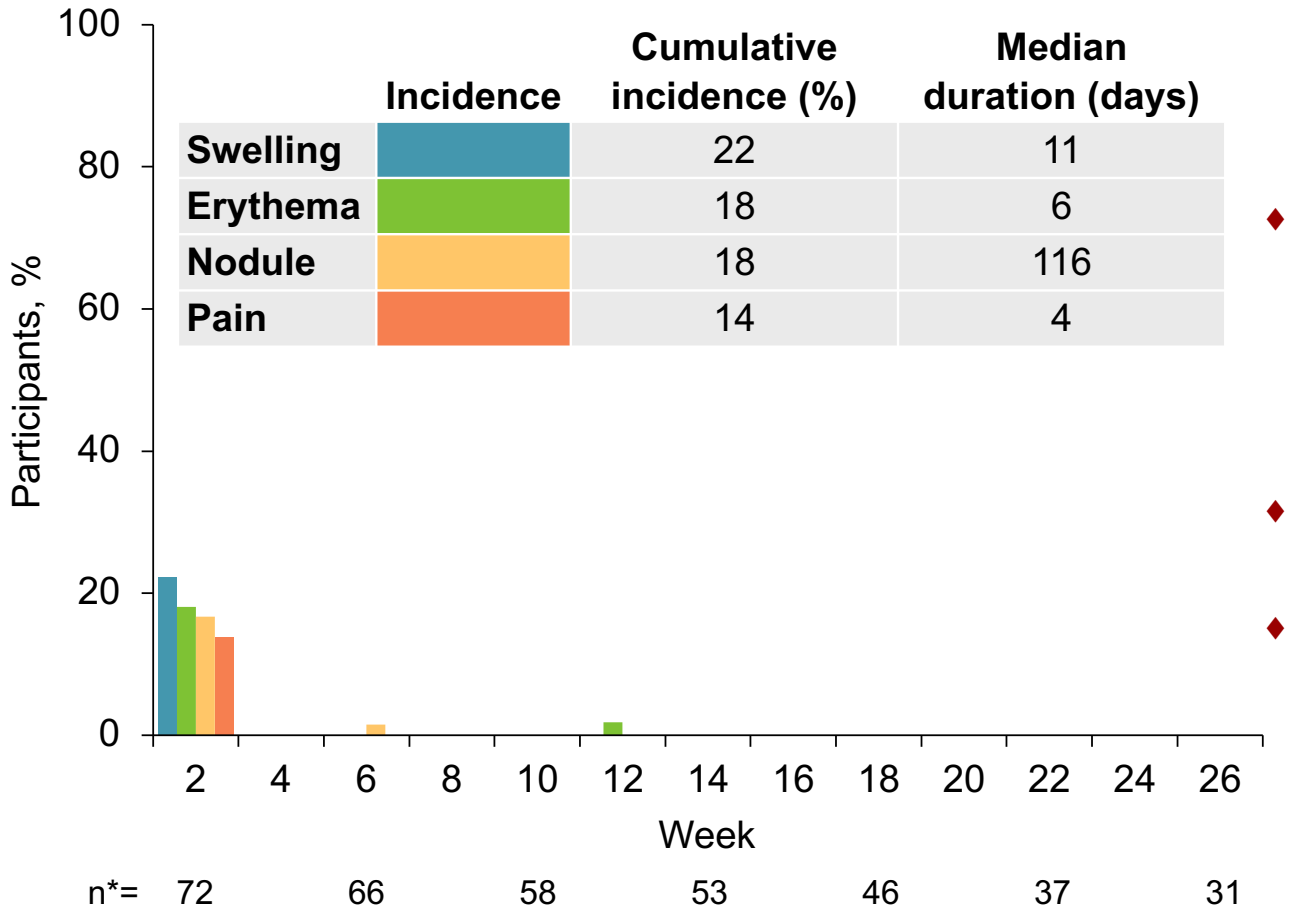
Participant	Fully active agents in OBR*	At Prior Visits while on LEN	Emergent Capsid Mutations	At Subsequent Visits while on LEN
#1	None	Suppressed	M66I, N74D (at Wk10: 2870 copies/mL)	Resuppressed with change in OBR
#2	DRV/COBI, DTG, RPV	Suppressed	M66I (at Wk26: 561 copies/mL)	Resuppressed with **no** change in OBR

- Among 72 heavily treatment-experienced participants with multidrug resistance and failing therapy at baseline who received SC LEN, 2 had emergent capsid mutations
  - The mutations conferred high level LEN resistance: >884 and 138 fold-change in EC_{50} (vs WT)
  - M66I mutation significantly impairs viral replication (1.5% replication capacity vs WT)
    - See oral presentation 1781: VanderVeen *et al* for additional information
- Further analyses are ongoing

*Other agents in the OBR:
- For participant #1: MVC, T20, DTG BID, DRV/COBI, 3TC.
- For participant #2: F/TAF; DRV/COBI and DTG were dosed BID.

Segal-Maurer, S. et al. CROI 2021. Virtual. Abstract 127.

Injection Site Reactions to SC LEN: Incidence



	Incidence	Cumulative incidence (%)	Median duration (days)
Swelling		22	11
Erythema		18	6
Nodule		18	116
Pain		14	4

- 46% (33/72) had ≥1 ISR related to LEN
  - Most ISRs were Grade 1 (82% [27/33]) and resolved within days
  - No Grade 4 ISRs occurred; one participant had Grade 3 swelling and erythema, which resolved in 4 and 8 days, respectively
- Nodules lasted a few months and were all Grade 1
- No participant discontinued due to ISRs

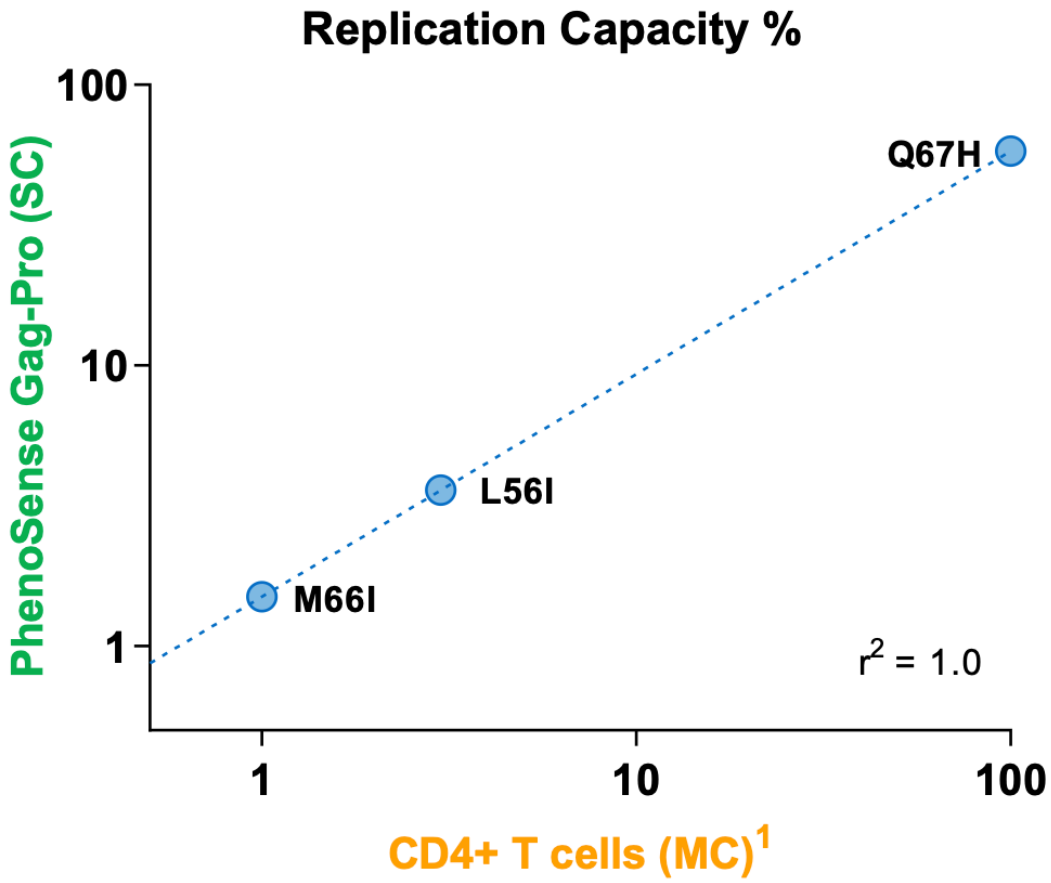
*Total n of participants on study or last study date in 2-week interval; only includes AE related to LEN and excludes those not related to it (e.g, T20).

Segal-Maurer, S. et al. CROI 2021. Virtual. Abstract 127.

LEN Resistance Mutations Are Associated with Reduced Viral Fitness

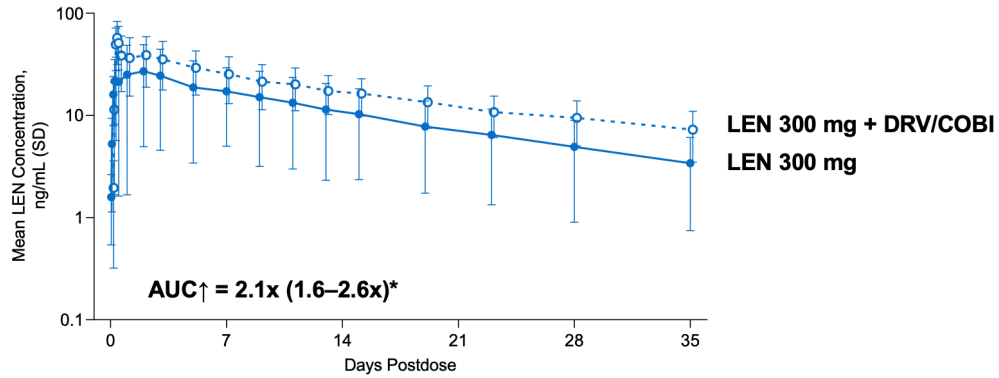
PhenoSense Gag-Pro (Single-cycle) vs. CD4+ T cell (Multi-cycle)

HIV-1 Capsid Sequence	PhenoSense Gag-Pro (SC)	
	LEN Fold-Resistance[a]	Replication capacity, % WT[b]
T107N	3.8	32
Q67H	4.8	58
N74D	16	ND
Q67H+N74S	20	15
Q67H+T107N	87	ND
L56I	204	3.6
Q67H+M66I	1,594	ND
Q67H+N74D	>2,700	ND
M66I	>2,700	1.5



MC, multi-cycle; ND, not determined; SC, single cycle.
a. Ratio of Mutant/WT EC_{50}, determined with SC reporter HIV-1 in PhenoSense Gag-Pro assay.
b. Percentage of reference strain, determined with SC reporter HIV-1 in PhenoSense Gag-Pro assay.
1. Link, Nature 2020; Yant, IAS 2019. Gag-Pro: overlapping data with CD4+ T cell MC assay available for 3 of 9 mutants.

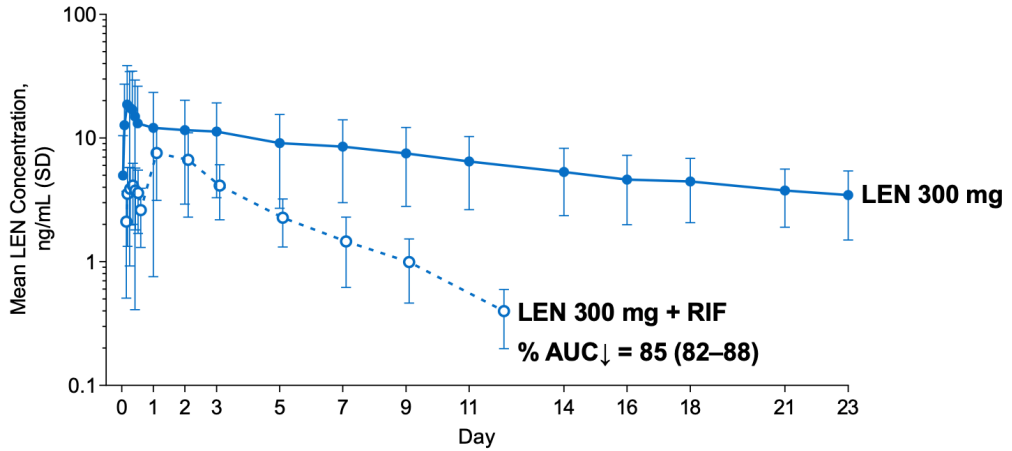
Strong CYP3A/P-gp Inhibition Increased LEN Exposure by ~ 2-fold



- Similar fold increase (2.3x [1.8 – 2.9x]) after COBI coadministration
- Deemed not clinically relevant based on available safety data
- **LEN can be co-administered with strong CYP3A/P-gp inhibitors, such as DRV/COBI**

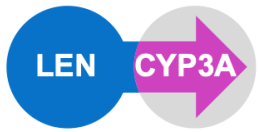
*Cmax increase was comparable

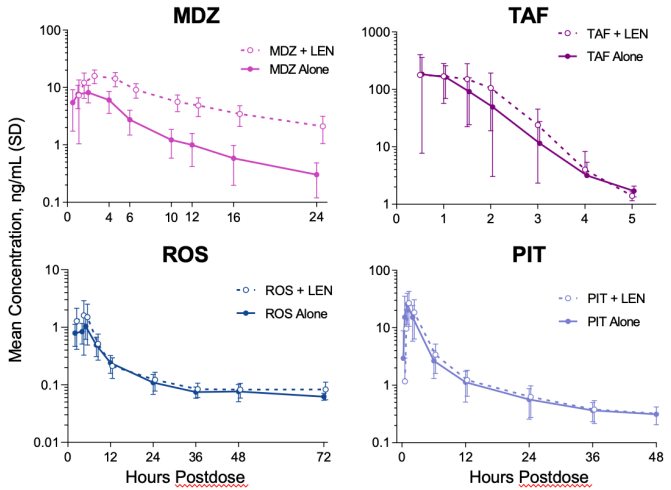
85% Decrease in LEN AUC by Strong CYP3A/P-gp/UGT Induction



- **LEN + RIF coadministration not advised**
- EFV (moderate inducer) results pending

LEN is a Moderate Inhibitor of CYP3A: 3.3x (3.1–3.6x) Increase in MDZ AUC



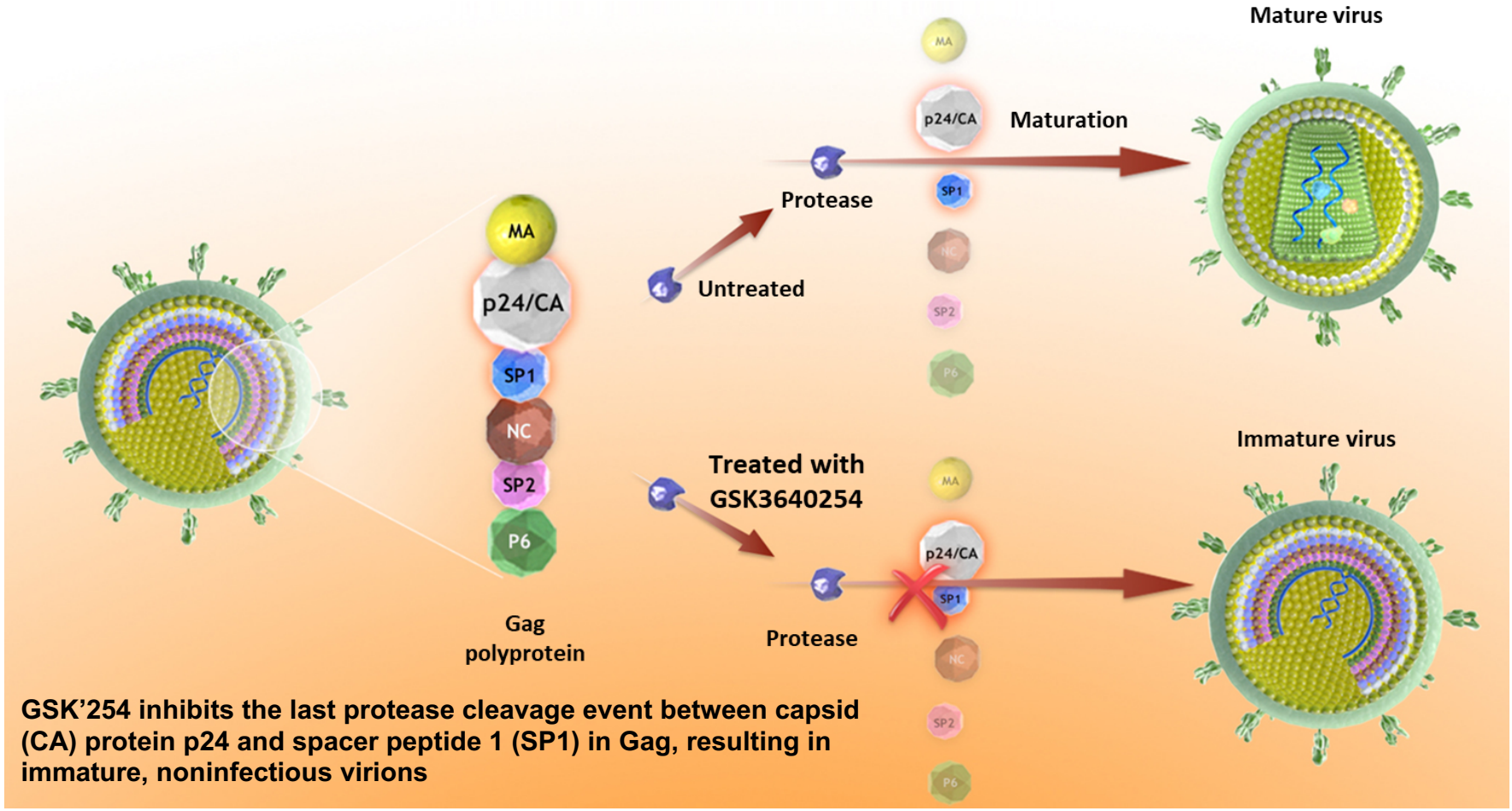


- Caution is advised with LEN coadministration with sensitive CYP3A substrates
- Minimal increase in TAF, ROS and PIT AUC* indicates that LEN can be administered with sensitive P-gp, BCRP or OATP substrates

***AUC↑:**
TAF = 1.5x (1.4–1.7x);
ROS = 1.3x (1.2–1.4x);
PIT = 1.1x (1.0–1.2x)

Begley R. et al. CROI 2021. Virtual. Abstract 89.

GSK'254 Proposed Mechanism of Action[1,2]

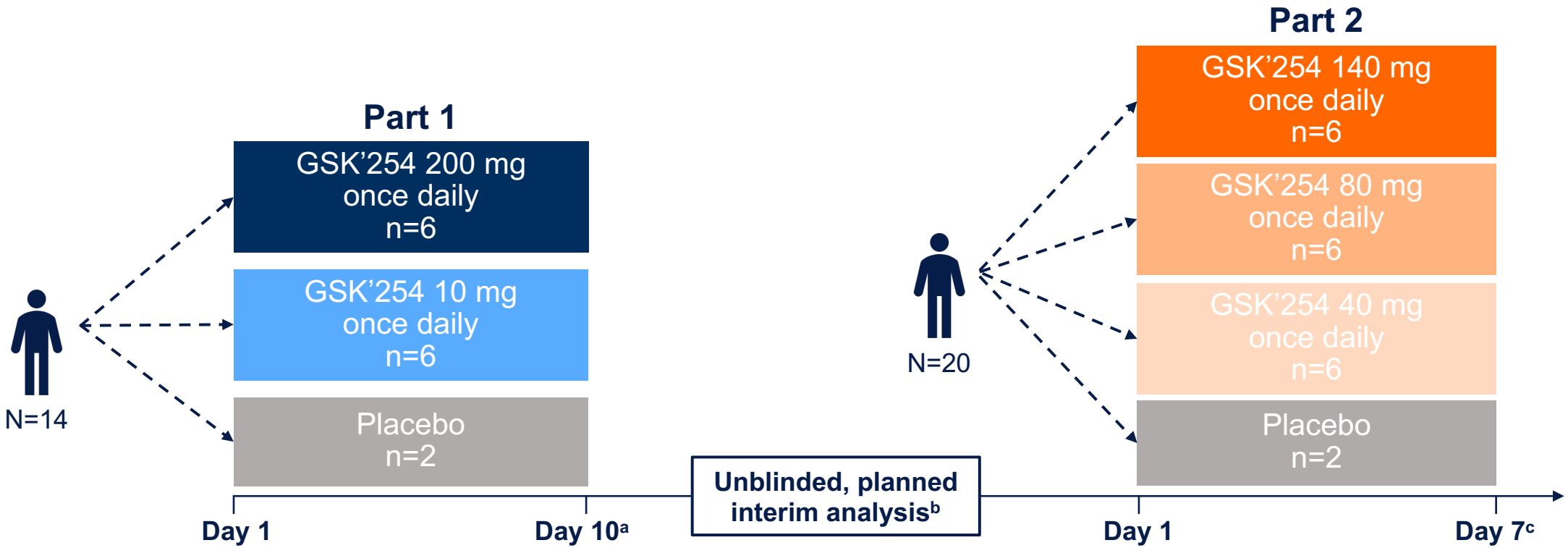


GSK'254 inhibits the last protease cleavage event between capsid (CA) protein p24 and spacer peptide 1 (SP1) in Gag, resulting in immature, noninfectious virions

Figure adapted from Lataillade et al. Conceptualization of HIV-1 maturation inhibition, and design of the mode of action of GSK3532795. In: 22nd CROI; February 22-26, 2015; Seattle, WA. Oral presentation 114LB.

1. Adamson et al. *Expert Opin Ther Targets*. 2009;13:895-908. **2.** Hwang et al. *Clin Infect Dis*. 2017;65:442-452.

Study Design: Double-blind (Sponsor-Unblinded), Randomized, Placebo-Controlled, Adaptive Study in ART-Naive Adults



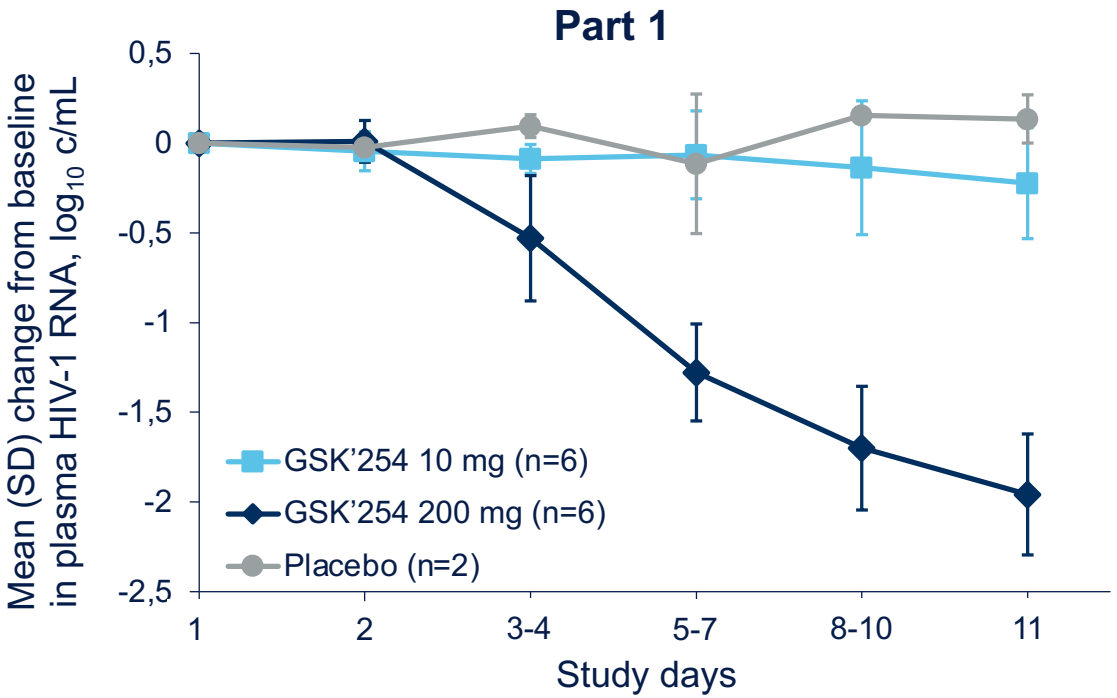
Primary endpoint: maximum change from Day 1 in plasma HIV-1 RNA during parts 1 and 2

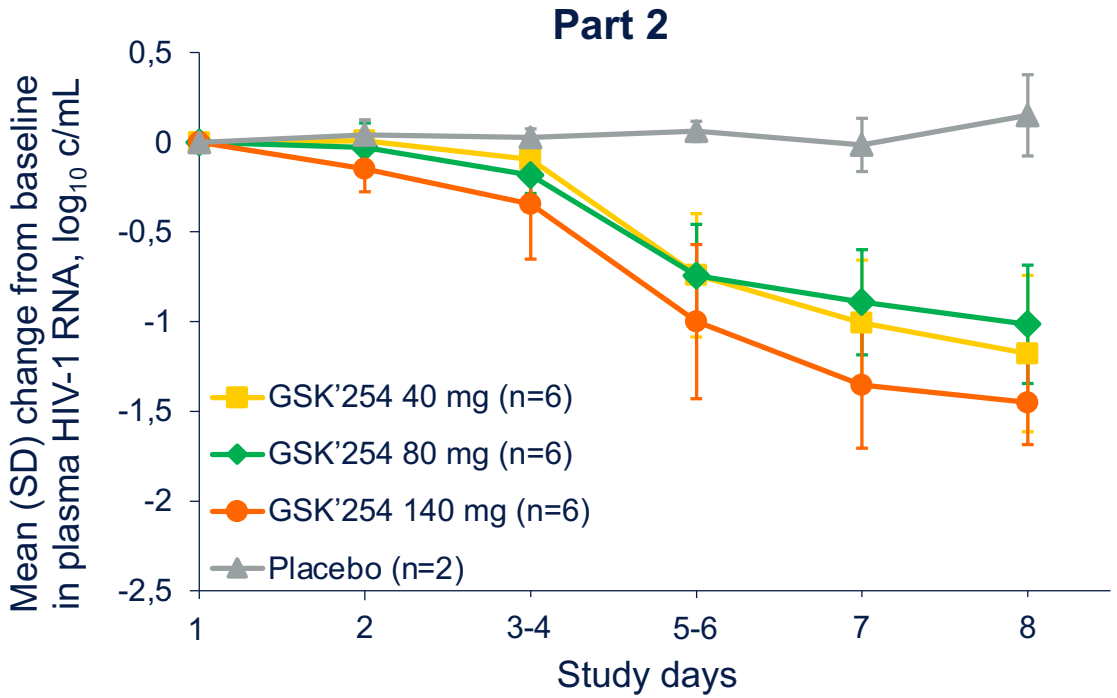
[a]Participants attended 1 follow-up visit during Days 11-17 and started combination ART after the final follow-up visit during Days 18-24.

[b]To determine whether to proceed to part 2. Treatment-emergent resistance-associated mutations were noted in the 200-mg group in part 1. Thus, the sponsor temporarily halted the study and conducted resistance analyses. A subsequent protocol amendment decreased monotherapy from 10 to 7 days in part 2 to reduce potential for treatment-emergent resistance mutations.

[c]Participants started combination ART at the follow-up visit on Day 8 and attended a final follow-up visit during Days 10-12.

Plasma HIV-1 RNA Decreased With All GSK'254 Doses in Parts 1 and 2

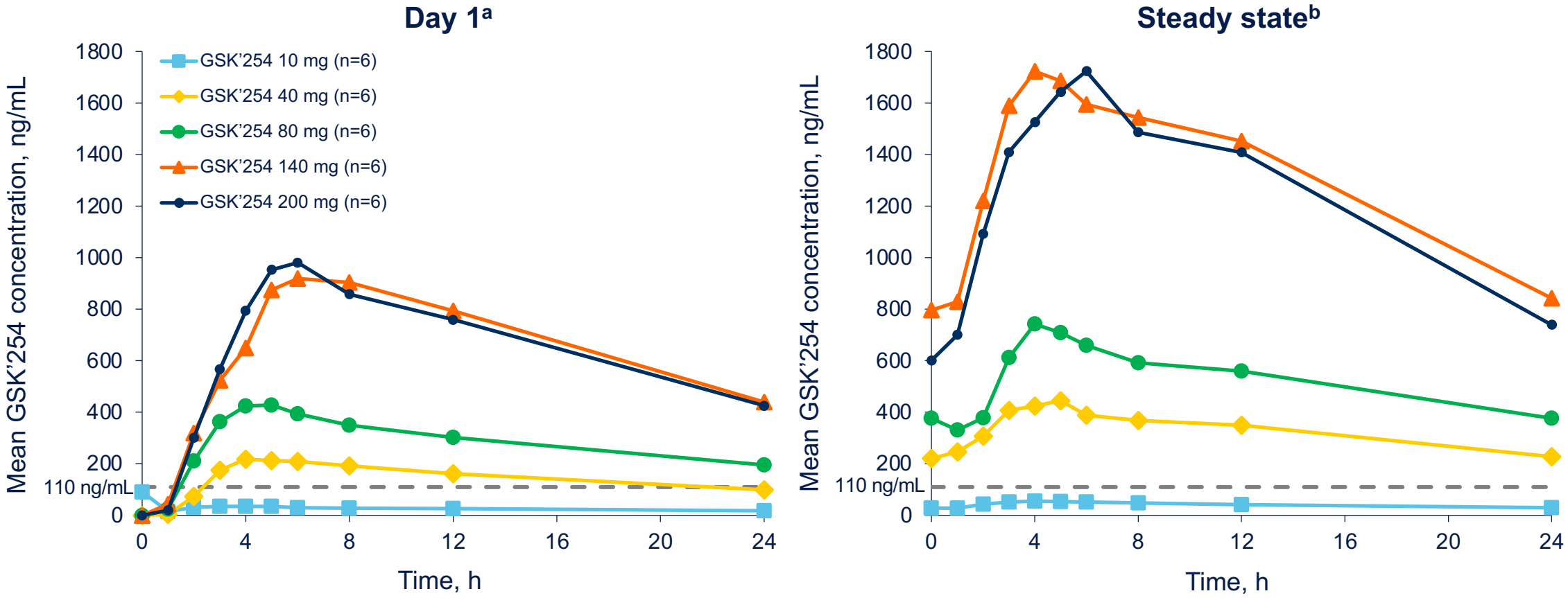




Plasma HIV-1 RNA change from baseline, mean (SD), log_{10} c/mL	Part 1 (Day 11)			Part 2 (Day 8)			
	GSK'254 10 mg (n=6)	GSK'254 200 mg (n=6)	Placebo (n=2)	GSK'254 40 mg (n=6)	GSK'254 80 mg (n=6)	GSK'254 140 mg (n=6)	Placebo (n=2)
Primary endpoint	−0.22 (0.309)	−1.96 (0.337)	0.14 (0.134)	−1.18 (0.436)	−1.02 (0.330)	−1.45 (0.235)	0.15 (0.226)
Maximum change	−0.36 (0.252)	−2.01 (0.329)	−0.21 (0.262)	−1.18 (0.436)	−1.02 (0.330)	−1.49 (0.267)	−0.03 (0.127)

Spinner et al. CROI 2021; Virtual. Slides 1975.

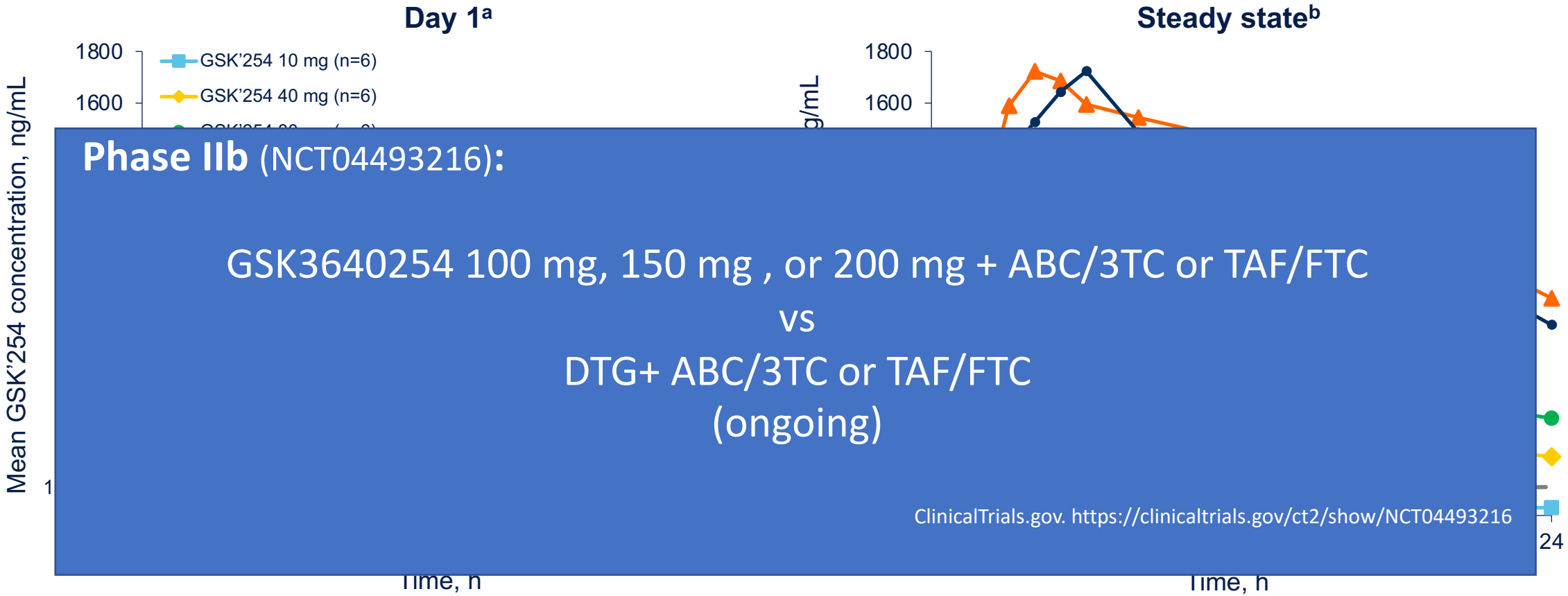
GSK'254 PK Results



- Mean GSK'254 concentrations were above the clinical efficacy target of 110 ng/mL[c] for the 40- to 200-mg GSK'254 doses

[a]One participant in the 10-mg group had a predose concentration that was inconsistent with the expected PK profile. One participant in the 200-mg group was excluded from PK analysis due to vomiting postdose ≤1 × tmax. [b]Steady state was measured at Days 8-9 in part 1 and Day 7 in part 2. [c]Value for which ≥95% of participants in a phase IIb study are projected to reach target trough concentrations.

GSK’254 PK Results



Phase IIb (NCT04493216)**:**

GSK3640254 100 mg, 150 mg , or 200 mg + ABC/3TC or TAF/FTC

vs

DTG+ ABC/3TC or TAF/FTC

(ongoing)

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04493216

- Mean GSK’254 concentrations were above the clinical efficacy target of 110 ng/mL[c] for the 40- to 200-mg GSK’254 doses

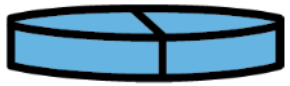
[a]One participant in the 10-mg group had a predose concentration that was inconsistent with the expected PK profile. One participant in the 200-mg group was excluded from PK analysis due to vomiting postdose ≤1 × tmax. [b]Steady state was measured at Days 8-9 in part 1 and Day 7 in part 2. [c]Value for which ≥95% of participants in a phase IIb study are projected to reach target trough concentrations.

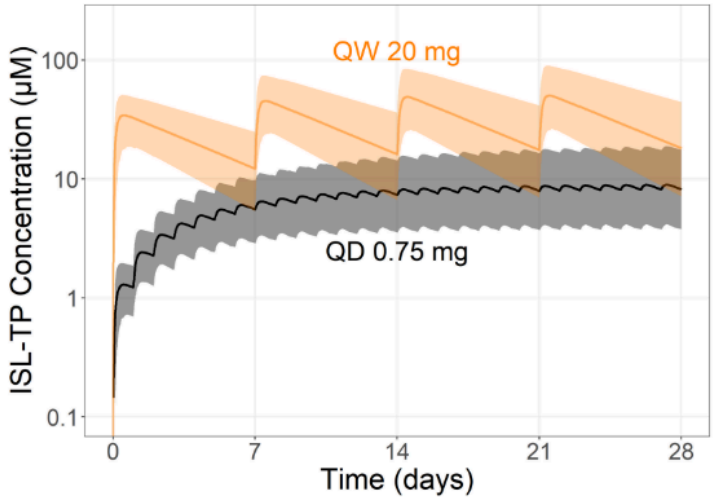
ISL/MK-8507 oral QW phase 2 dose-ranging study – dose selection framework

ISL

Islatravir

Benchmark ISL-TP
QD vs QW dosing
population PK model





HIV QW phase 2 doses
ISL 20 mg
MK-8507
100, 200, 400 mg

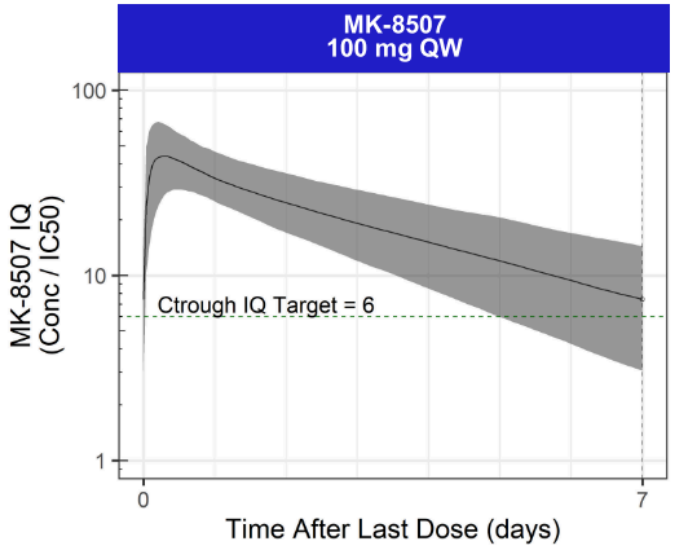
ISL+MK-8507
Viral dynamics modeling (VDM)
- PK (variability); PD (clinical IC_{50})
- IC_{50} shifts (resistance variants)
- Adherence to regimen

Simulations

Predict long-term efficacy
(Percentage of participants with HIV-1 RNA below 50 copies/mL at 48 weeks)

PK target
Population
PK model

MK-8507



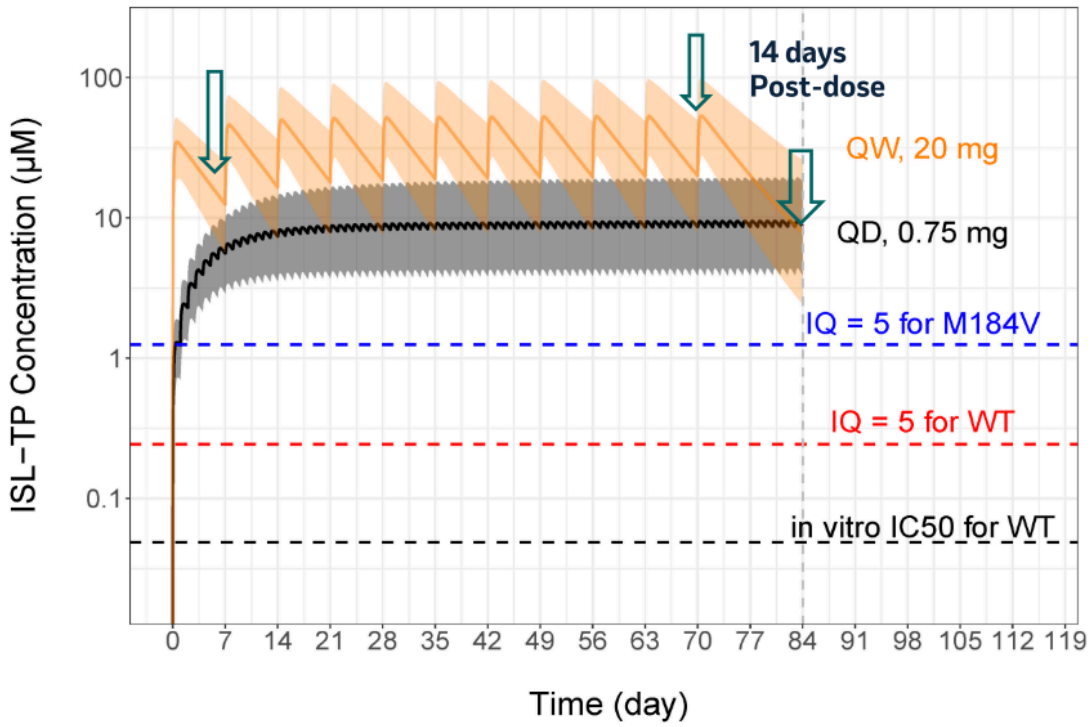
IQ – Inhibitory Quotient ; defined as $\frac{MK\text{–}8507\ Concentratio}{in\text{–}vitro\ IC50}$

Kandala, B. et al. CROI 2021. Virtual. Abstract 376. Science Spotlight

ISL 20 mg QW provides forgiveness for a missed/late dose

ISL

ISL 20 mg QW achieves **ISL-TP trough levels** after the first dose **comparable to ISL 0.75 mg QD** at steady state



ISL 20 mg QW provides ISL-TP concentrations above 0.75 mg QD out to **14 days post-dose,** providing a **full dosing interval of forgiveness**.

ISL 20 mg QW exceeds 5xIQ for M184V

IQ - Inhibitory Quotient ; defined as $\frac{ISL-TP\ Concentration}{in-vitro\ IC50}$

Grey line and shaded region: median (95% Prediction Interval) for 0.75 mg QD (efficacious Phase 2 dose)

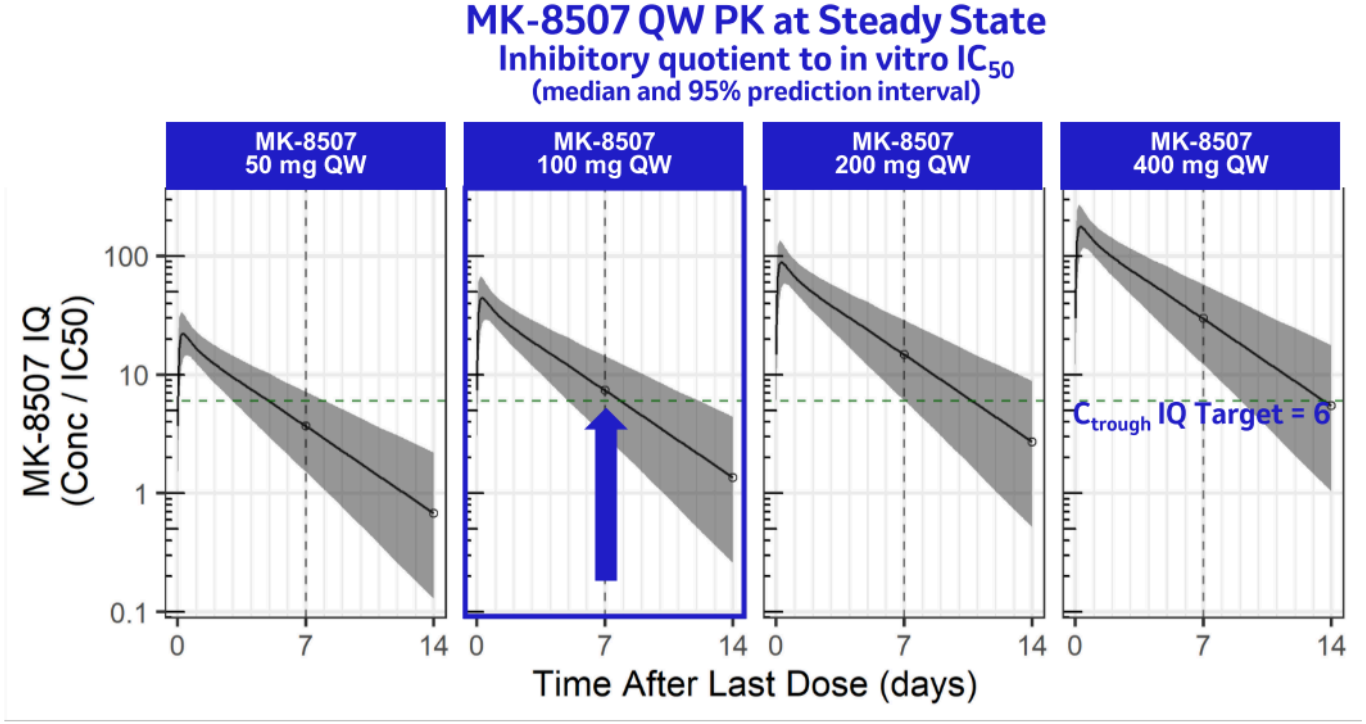
Orange line and shaded region: median (95% Prediction Interval) for 20 mg QW

Kandala, B. et al. CROI 2021. Virtual. Abstract 376. Science Spotlight

MK-8507: Doses ≥100 mg QW achieve target C_{trough}

MK-8507

Doses ≥100 mg QW Achieve PK target (IQ=6)



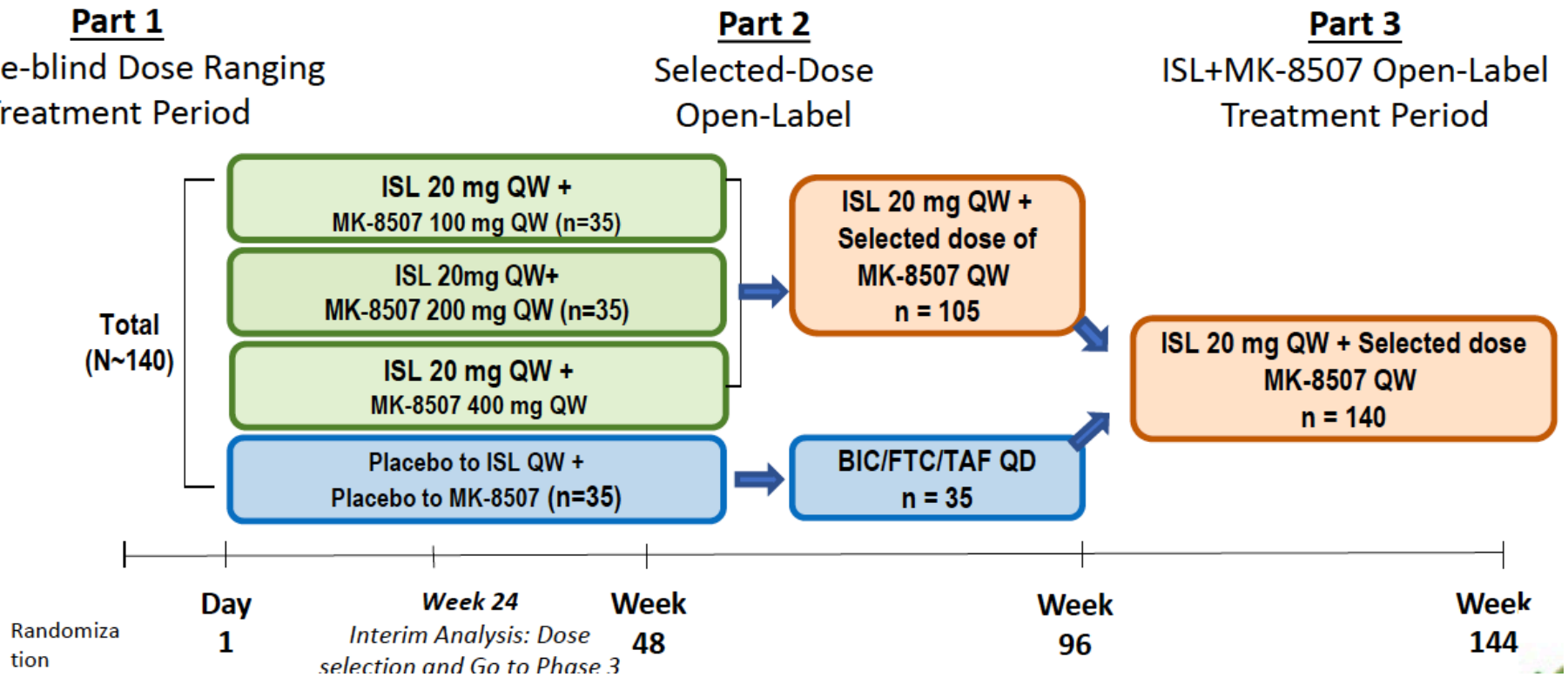
PK target at Day 7 (IQ=6) – Based on a model based meta-analysis[1] of marketed NNRTIs

- A 6-fold C_{trough}/IQ for NNRTI showed robust phase 3 efficacy without mutant breakthrough on the background of 2 NRTIs.
- IQ – Inhibitory Quotient ; defined as $\frac{MK{-}8507\ Plasma\ Concentration}{in{-}vitro\ IC50}$

1.Xu Y, et al. *Clin Transl Sci.* 2016;9.192–200.

Kandala, B. et al. CROI 2021. Virtual. Abstract 376. Science Spotlight

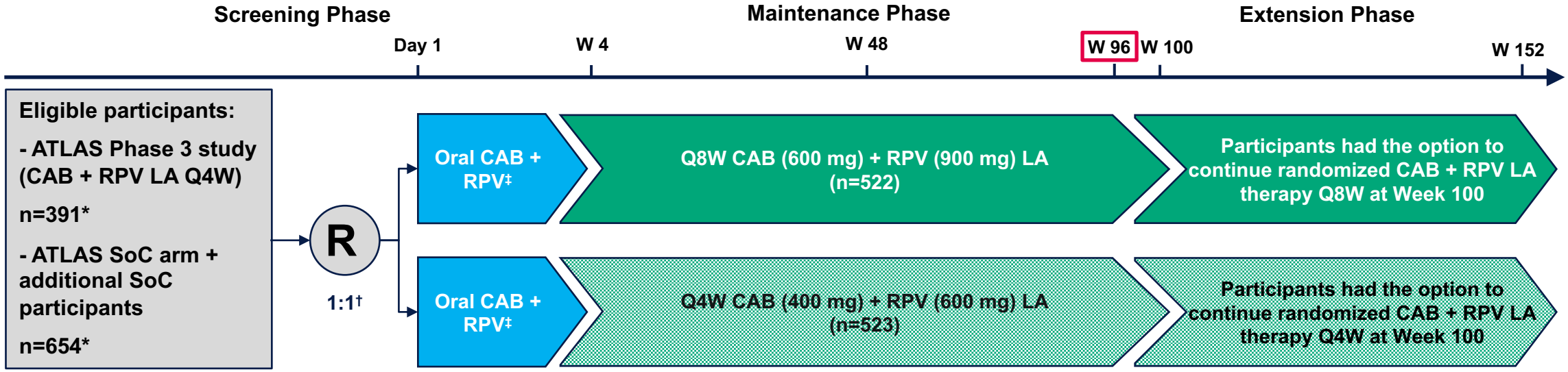
NCT04564547



https://www.clinicaltrials.gov

ATLAS-2M Week 96: 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 c/mL at Week 48 (Snapshot, ITT-E)
- Secondary endpoints included the proportion of participants with plasma HIV-1 RNA ≥50 or <50 c/mL at Week 96 (Snapshot, ITT-E)
- Other endpoints assessed at Week 96 included the incidence of CVF (two consecutive plasma HIV-1 RNA levels ≥200 c/mL), incidence of viral resistance in participants with CVF, and safety and tolerability

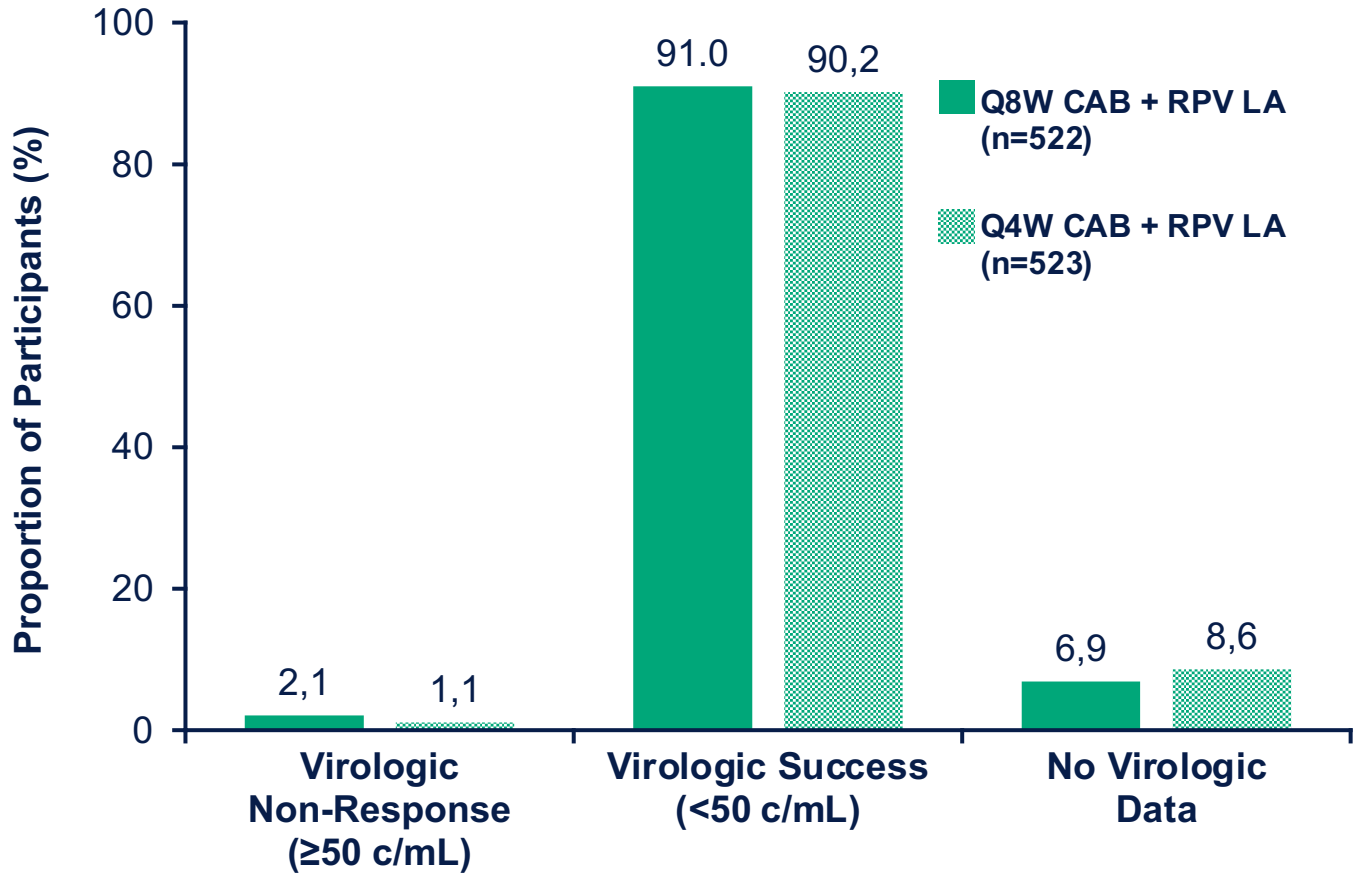
*ITT-E population. †Randomization was stratified by prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks). ‡Excluding participants with prior CAB + RPV exposure in ATLAS.

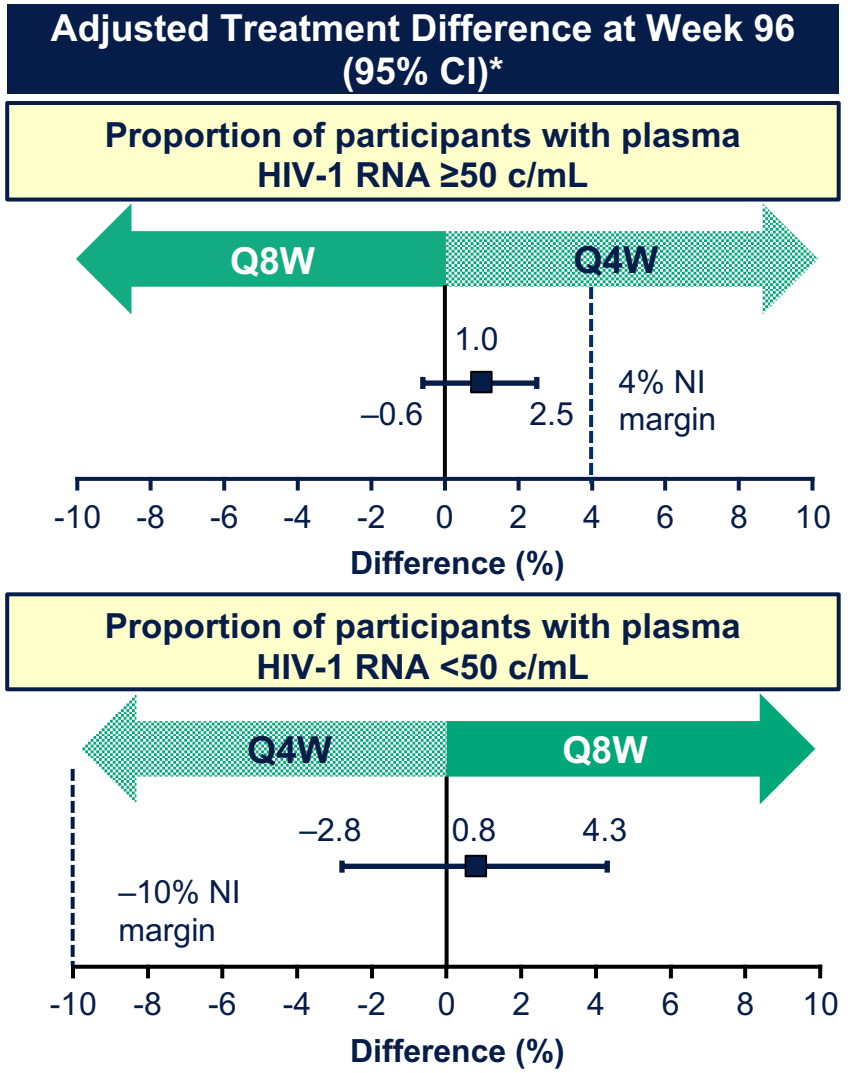
For further study design details, please see Overton et al. CROI 2020; Boston, MA. Presentation 3334.[1]

CAB, cabotegravir; CVF, confirmed virologic failure; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomized; RPV, rilpivirine; SoC, standard of care; W, week.

Overton ET, et al. Conference on Retroviruses and Opportunistic Infections 2020; Boston, MA; March 8–11, 2020. Presentation 3334. Available from: www.croiwebcasts.org/p/2020croi/croi/34

ATLAS-2M Week 96: Virologic Snapshot Outcomes for ITT-E: CAB + RPV LA Continued to Maintain High Levels of Viral Suppression





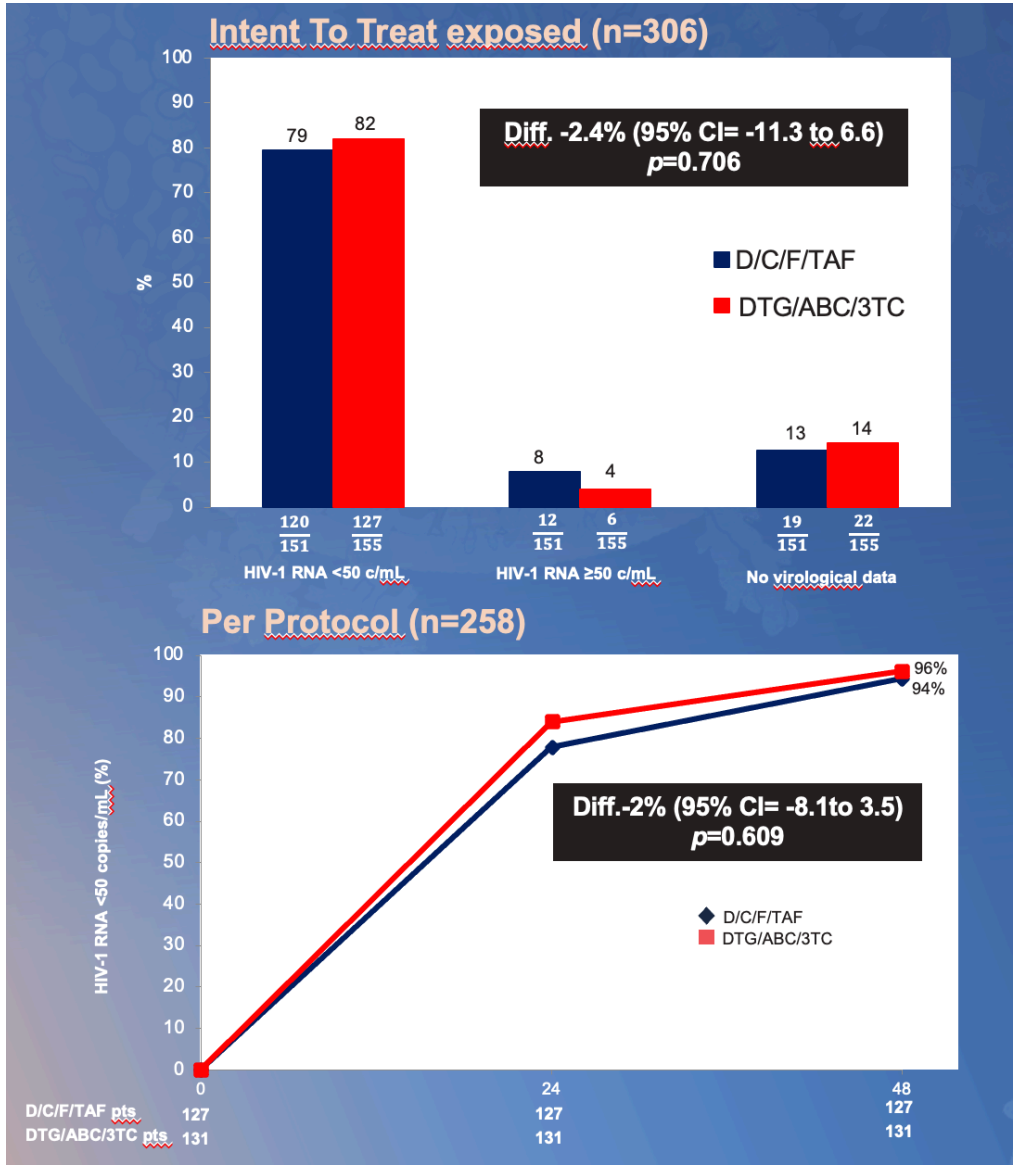
*Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks).
CAB, cabotegravir; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority;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

Jaeger et al. CROI 2021; Virtual. Science Spotlight 1753.

D/C/F/TAF vs DTG/ABC/3TC FOR INITIAL TREATMENT IN HIV+ ADULTS: A RANDOMIZED STUDY

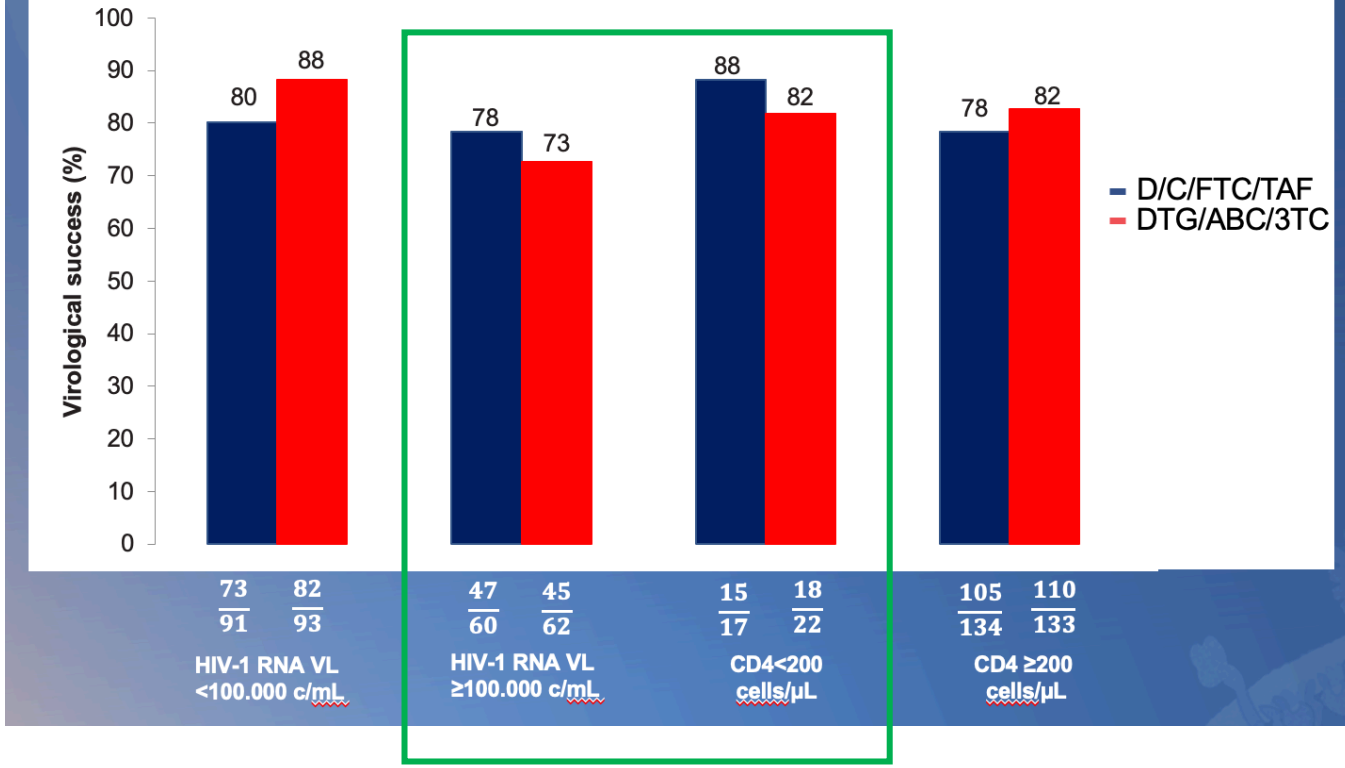
SYMTRI Study

		D/C/FTC/TAF (n=151)	DTG/ABC/3TC (n=155)
Median age, years		34 (27-41)	36 (31-43)
Gender (male) (n, %)		146 (97%)	142 (92%)
Risk practice (n, %)	MSM	127 (84%)	115 (74%)
	Heterosexuals	16 (11%)	31 (20%)
	Intravenous drug use	2 (1%)	2 (1%)
	Others | Unknown	6 (4%)	7 (4%)
AIDS (opportunistic diseases) (n, %)		0 (0%)	0 (0%)
Median CD4+ cell count (x10E6/µL)		420 (286-608)	383 (247-569)
CD4+ cell count (n, %)	<200 /µL	17 (11%)	22 (14%)
	200-350 /µL	40 (26%)	44 (28%)
	>350 /µL	94 (62%)	89 (57%)
Median HIV-1 RNA (copies/mL)		63096 (13534-233000)	65900 (24786-212000)
HIV-1 RNA concentration (n, %)	<100000 c/mL	91 (60%)	93 (60%)
	≥100000 c/mL	60 (40%)	62 (40%)
Hepatitis C virus infection (n, %)		5 (3%)	5 (3%)
Median weight (kg)		72.95 (64-79.97)	72.75 (64.5-80)
Median Body Mass Index (kg/m^2)		23.78 (21.77-26.3)	23.81 (22.04-26.08)

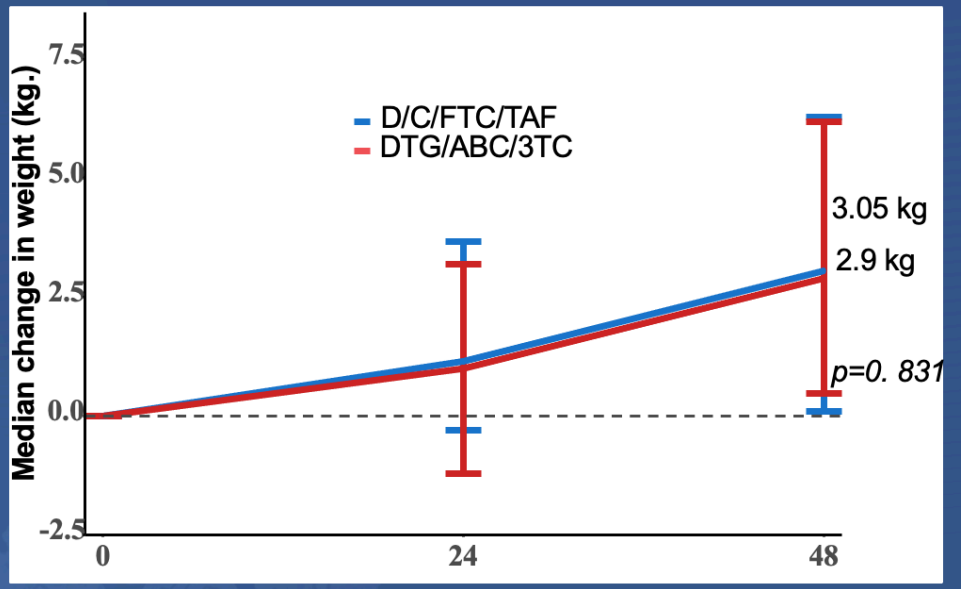


Podzamczer D, et al. CROI 2021 Virtual. Abstract 413. Science Spotlight

% of VL < 50 c/mL according to BL VL and CD4



Weight change*



- *Similar changes for BMI were observed*

Podzamczer D, et al. CROI 2021 Virtual. Abstract 413. Science Spotlight

DOLUTEGRAVIR VS. DARUNAVIR/r-BASED ART IN VERY ADVANZED PATIENTS: 48-WEEK RESULTS

ADVANZ-4 Study

Objectives

- The objective was to study the immune reconstitution in very immunosuppressed antiretroviral-naive, HIV-1–infected individuals by comparing a DTG-based regimen with a **Darunavir/ritonavir** (**DRV/r**)-boosted protease inhibitor regimen.
- To assess the impact of these ART regimens on bacterial translocation, inflammation and immune activation in antiretroviral-naïve individuals with very advanced HIV-1-infection.

- The **Advanz-4 trial** (NCT02337322) is a multicenter RCT with 104 HIV-1-infected **ART-naïve** patients with **<100 CD4+ cells/mm3** randomly assigned 1:1 to **DTG** (N=52) or **DRV/r** (N=52) plus **abacavir and lamivudine** at standard doses.
- The **primary end point** was median increase in CD4 cell count at week 48. **Secondary end points** were the proportion of patients with plasma HIV-1 RNA viral load (VL) <50 copies/mm3, bacterial translocation, inflammation, immune activation, adverse events, IRIS, HIV disease progression and death.

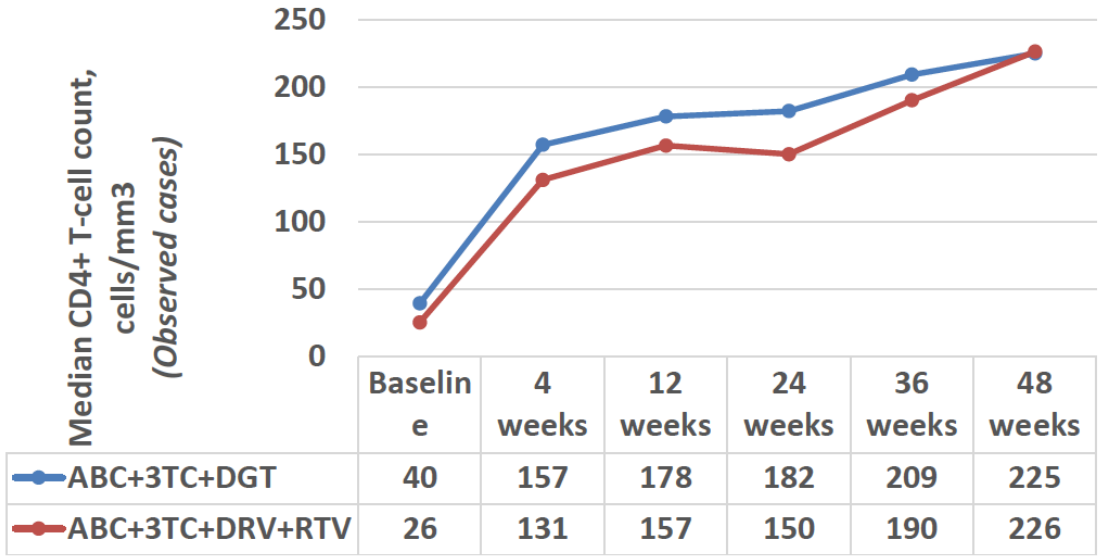
Miró JM, et al. CROI 2021 Virtual. Abstract 412. Science Spotlight

Results (II): mITT analysis

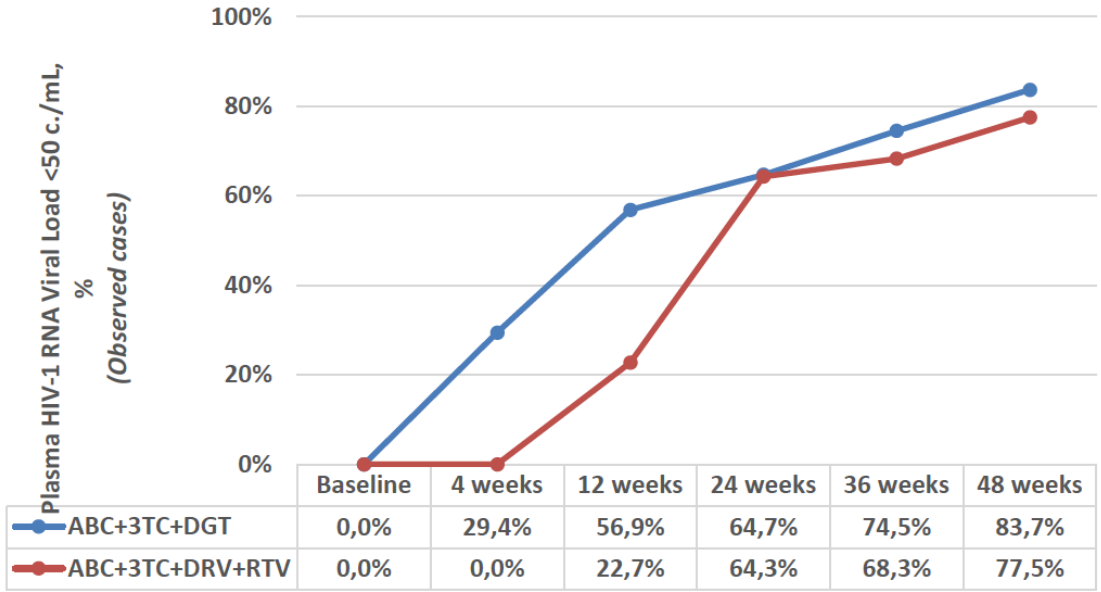
	Dolutegravir N=52	Darunavir/rtv N=49	p-value
• Age, yr., median (IQR)	40 (30;48)	41 (34;46)	NA*
• Male gender, n (%)	44 (87)	46 (88.5)	
• Men who have sex with men (MSM), n (%)	31 (60)	25 (51)	
• Baseline AIDS-defining events (ADE), n (%)	22 (42)	24 (46)	
• Baseline RNA HIV VL, median (IQR) log10/mL	5.47 (4.79;6.10)	5.67 (5.14;6.12)	
• Baseline CD4, median (IQR) cells/mm^3	41 (18; 67)	30 (11; 54)	
• **48-wk CD4 increase (median delta, IQR)**	**172.50 (118; 255)**	**157 (66; 277)**	**0.430**
• **48-wk RNA HIV VL <50 copies/ml, n (%)**	**40 (77)**	**31 (63)**	**0.191**
• **IRIS, n (%)**	**5 (10)**	**6 (12)**	**0.911**
• **New ADEs/death, n (%)**	**4 (8)**	**6 (12)**	**0.666**
• **Treatment discontinuation (any reason), n (%)****	**4 (8)**	**12 (24.5%)**	**0.029**

Miró JM, et al. CROI 2021 Virtual. Abstract 412. Science Spotlight

Results (III): mITT analysis



	Baseline	4 weeks	12 weeks	24 weeks	36 weeks	48 weeks
ABC+3TC+DGT	40	157	178	182	209	225
ABC+3TC+DRV+RTV	26	131	157	150	190	226



	Baseline	4 weeks	12 weeks	24 weeks	36 weeks	48 weeks
ABC+3TC+DGT	0,0%	29,4%	56,9%	64,7%	74,5%	83,7%
ABC+3TC+DRV+RTV	0,0%	0,0%	22,7%	64,3%	68,3%	77,5%

- **Median (IQR) increase in the CD4** count after 48 weeks by mITT analysis was +172 (118; 255) and 157 (66; 277) cells/mm^3 in the **DTG** and **DRV/r** arms, respectively (p=0.430).
- **Plasma HIV-1 RNA VL suppression** (<50 copies/ml) was significatively faster in the **DTG** arm at 4 and 12 weeks. **At 48 weeks**, the rate of suppressed patients by mITT analysis was similar (**77% vs. 63%; p=0.191**).
- **Inflammation** (TNF-alpha, IL-6, hsCRP), **immune activation** (CD8+CD38+ T cells, CD8+CD38+DR+) and **apoptotic** (annexin-V) **markers** were similar at baseline and declined significantly and similarly in both ART arms (P>0.05 for all comparisons).
- A greater reduction in **bacterial translocation** (srCD14) marker in patients treated with **DTG** was found (-802 [-1302; -398] vs. -396 [-924, 0.00] ng/mL; p=0.011).

Miró JM, et al. CROI 2021 Virtual. Abstract 412. Science Spotlight

ODYSSEY

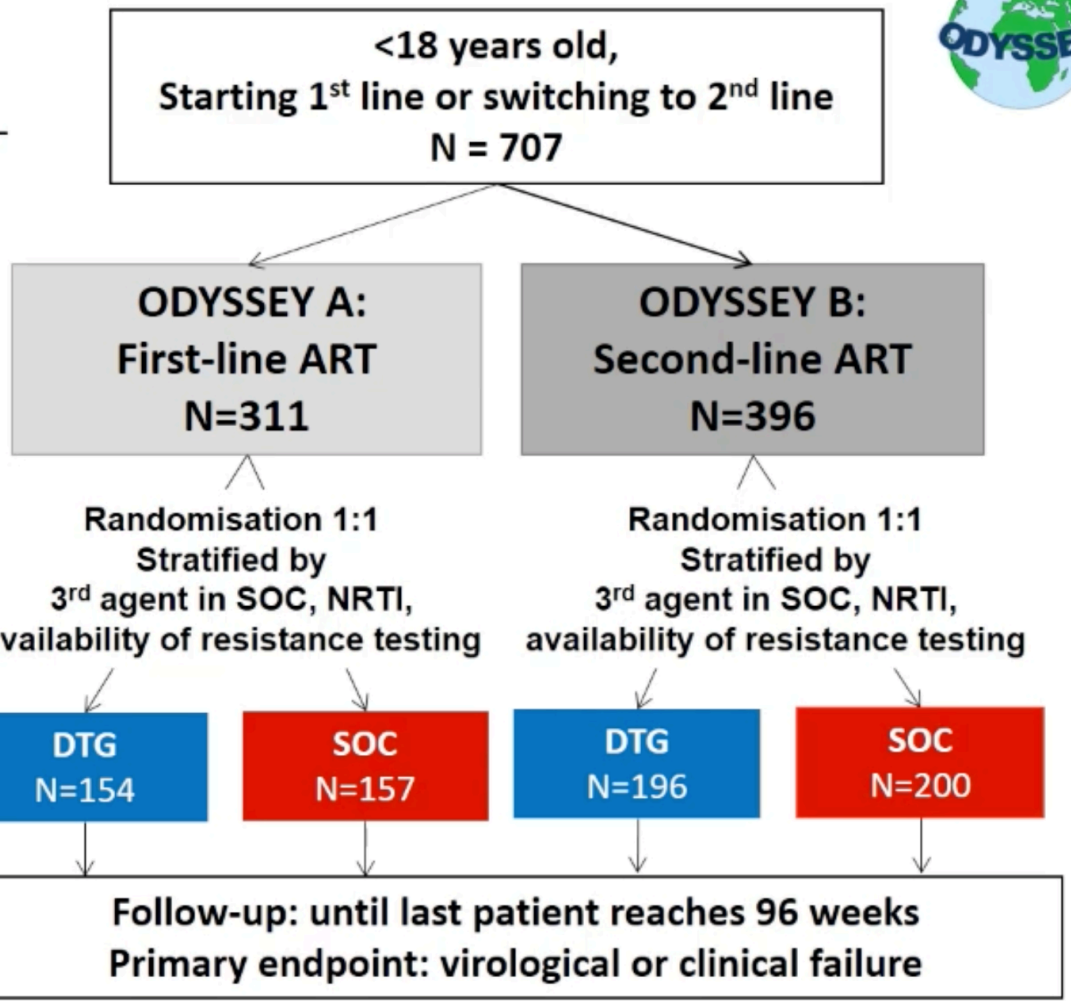
- International multi-centre, randomised 96-week non-inferiority trial
- **Aim:** compare **efficacy and safety** of Dolutegravir (DTG) with standard-of-care across different settings in children **starting first- or second-line ART**
- **Main trial: children ≥14 kg**
- **Sample size assumptions**

  Total ODYSSEY population (A & B): N ≥700
  - Failure 18%, 10% Non-inferiority (NI) margin
  - 10% LTFU, 90% power, 5% two-sided α

  ODYSSEY A: N ≥310 children
  - Failure 15%, 12% NI

  ODYSSEY B: N ≥390 children
  - Failure 20% 12% NI

  For each of A and B: 80% power



Penta

SOC= standard of care

Turkova A, et al. CROI 2021 Virtual. Abstract 174.

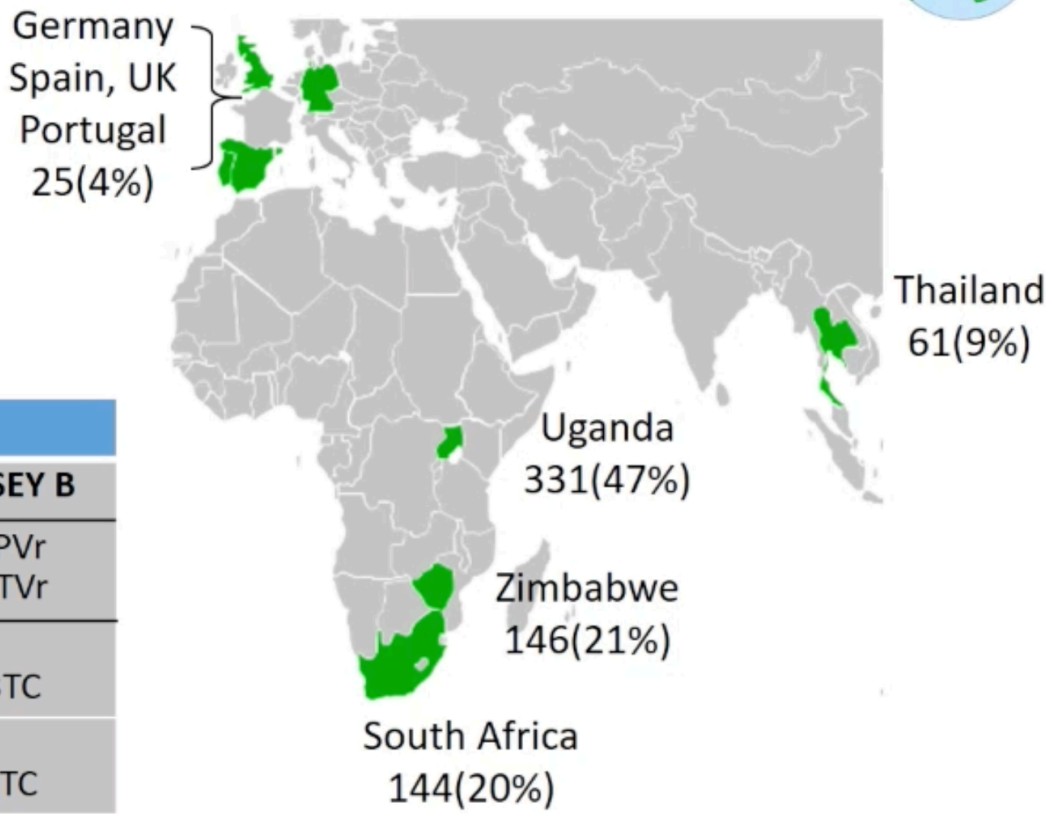
Population at baseline (n=707)

Characteristics

- Age, median [range]: 12.2 years [2.9-18]
- 49% female
- 27% WHO stage 3/4
- 22% CD4 <200 cells/mm^3
- 88% African

Baseline ART in ODYSSEY from randomisation

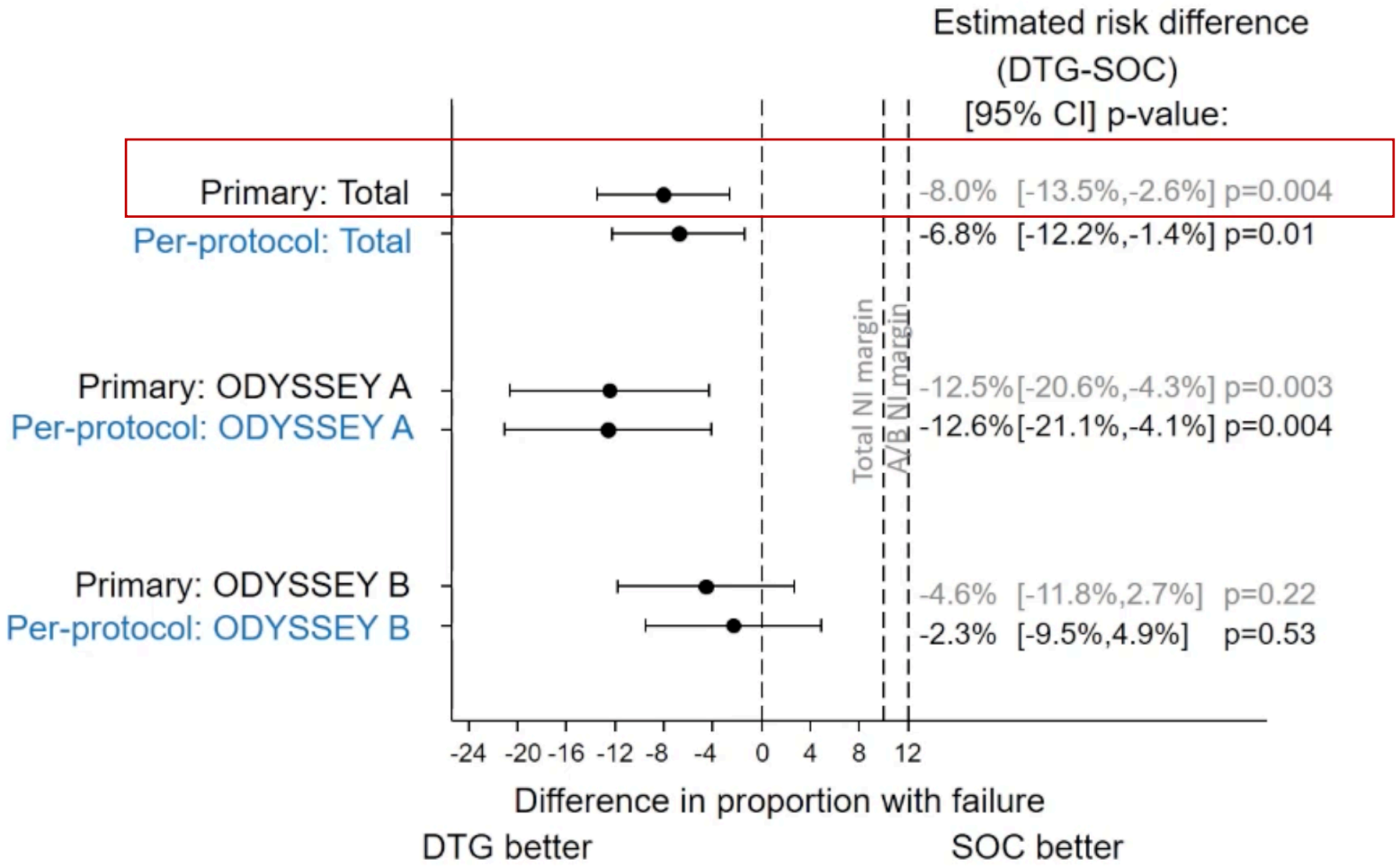
	DTG		SOC	
	ODYSSEY A	**ODYSSEY B**	**ODYSSEY A**	**ODYSSEY B**
3rd agent	DTG	DTG	92% EFV	72% LPVr 25% ATVr
NRTI	82% ABC+3TC	54% ABC+3TC	78% ABC+3TC	55% ABC+3TC
	18% TDF+XTC	27% TDF+XTC	20% TDF+XTC	26% TDF+XTC
		19% ZDV+3TC		19% ZDV+3TC



Penta

Turkova A, et al. CROI 2021 Virtual. Abstract 174.

Per protocol analysis over 96 weeks



No significant difference in treatment effects by sex, weight, age, stratification factors, baseline VL or baseline CD4

Penta

$ Excluding all patients who did not meet eligibility criteria & censoring follow-up in both arms for switch to 3rd agent for protocol deviation, toxicity or pregnancy, or stop of ART for >31 days

Turkova A, et al. CROI 2021 Virtual. Abstract 174.


PrEP
Pre-Exposure Prophylaxis

Islatravir implants

- Islatravir implant uses Nexplanon® applicator
  - Nexplanon® is an implantable contraceptive placed subdermally

- Initial trial (P007) with prototype implants had encouraging results[1]
  - Prototype implants (polymer and ISL only)
  - 12 weeks of placement, double-blind placebo-controlled trial of 54 mg and 62 mg implants in low-risk HIV-negative participants
  - Implants generally well tolerated, with higher dose implant (62 mg) projected to have sufficient ISL-TP levels for at least a year

- Next generation implants (P008) are radiopaque
- Contain additional excipients that facilitate manufacture

- Release rate dynamics of ISL from the next generation implants are different than those of the implants in the initial trial
  - 62 mg P007 implant ≈ 56 mg P008 implant
  - 54 mg P007 implant ≈ 48 mg P008 implant

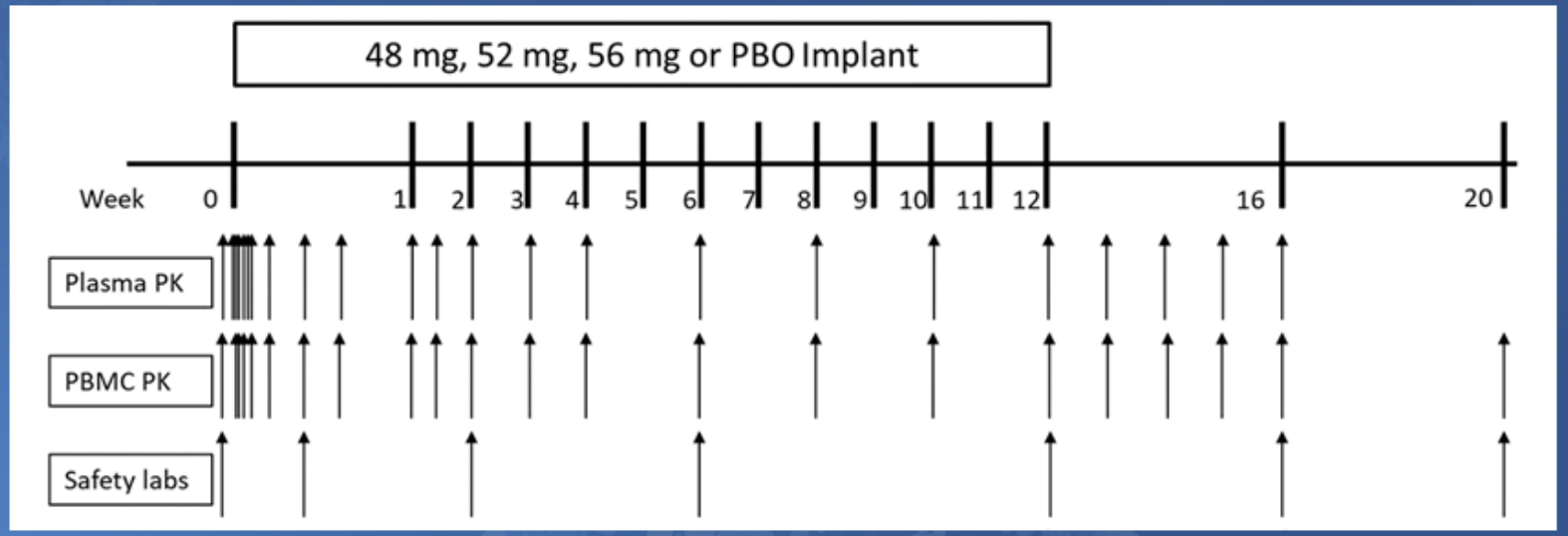
- In the current study (P008), next generation radiopaque islatravir implants were evaluated for tolerability and PK relative to a threshold level

Mathews RP, et al. CROI 2021 Virtual. Abstract 88.

[1]Matthews RP et al. IAS 2019

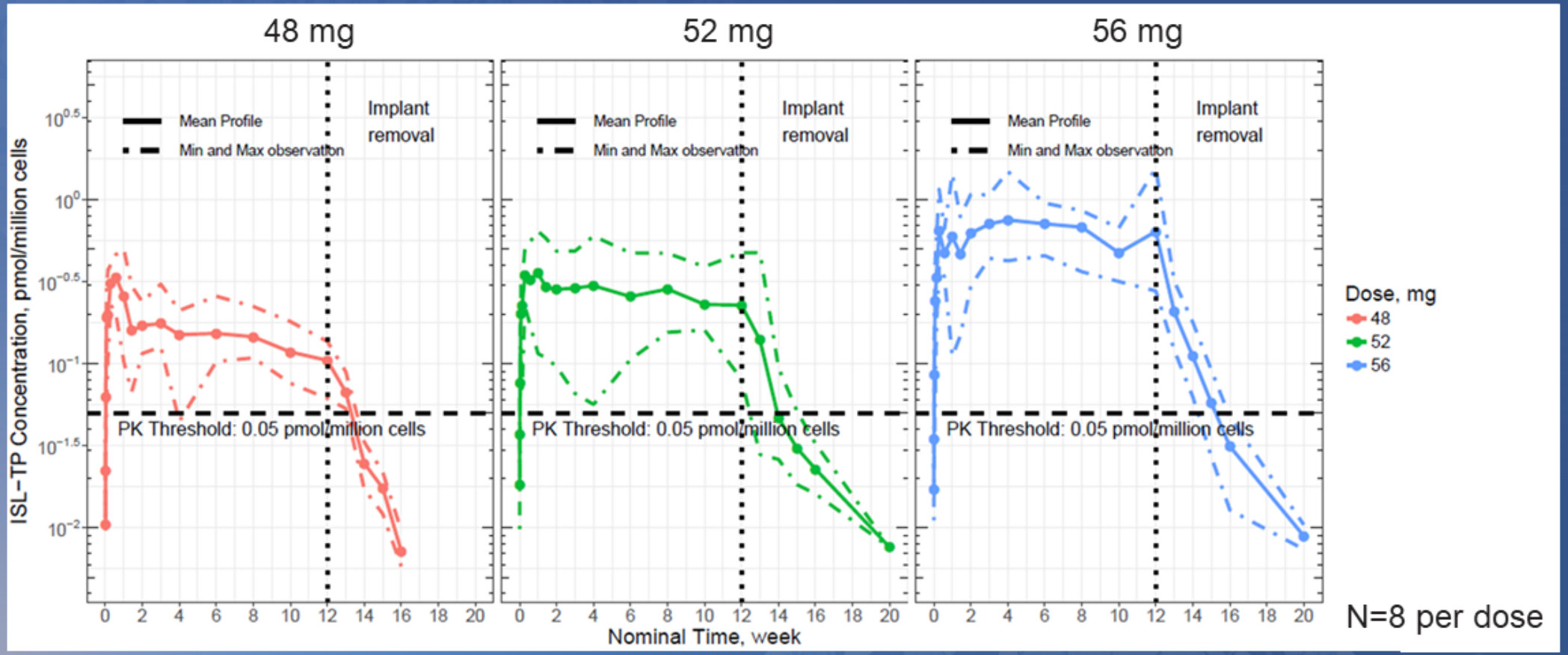
Protocol 008 Phase 1 next-generation implant study design

- Double-blind, placebo-controlled multisite trial in low-risk HIV-negative men and women
  - Panel A: 48 mg
  - Panel B: 52 mg
  - Panel C: 56 mg
- Twelve (8 + 4 design) per panel
- Subdermal placement in upper arm of nondominant hand
- Implant in place 12 weeks, followed by 8 weeks post-removal
- PK (plasma and PBMC), ECGs, vital signs, safety labs collected throughout



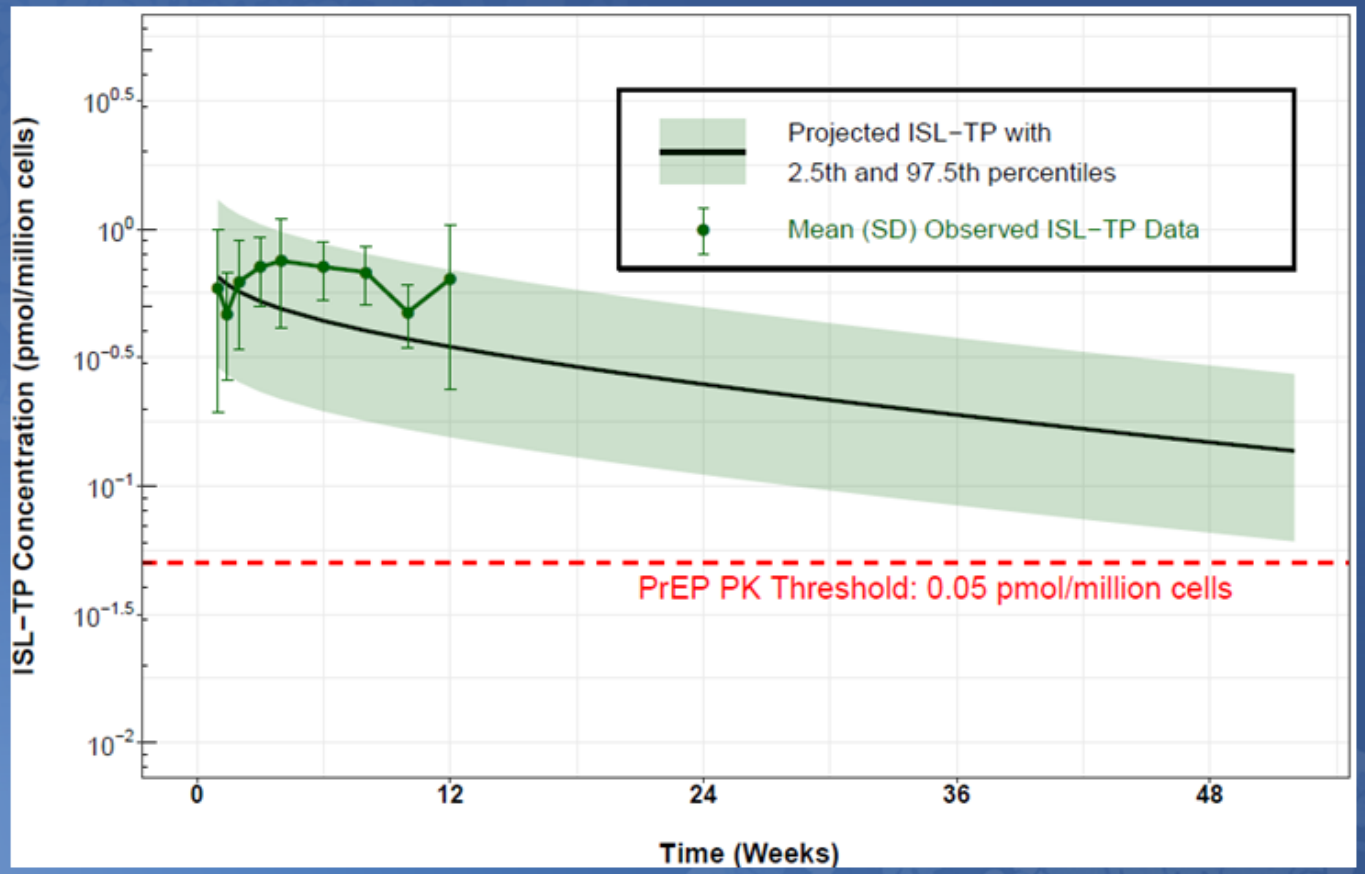
Mathews RP, et al. CROI 2021 Virtual. Abstract 88.

Intracellular ISL-TP PK threshold of 0.05 pmol/10^6 cells maintained throughout placement for two highest doses



- 56 mg implant ISL-TP concentrations comparable to 62 mg from previous study
- Half-life after removal of implant similar to half-life of orally dosed ISL ($t_{1/2}$ for 56 mg is ~198 hr)

56 mg implant projected to lead to concentrations above threshold for 52 weeks



- 56 mg implant projected to release adequate ISL-TP (above the PK threshold) for almost all individuals for >52 weeks

Mathews RP, et al. CROI 2021 Virtual. Abstract 88.

Safety Summary
Generally Mild Local Tolerability Effects

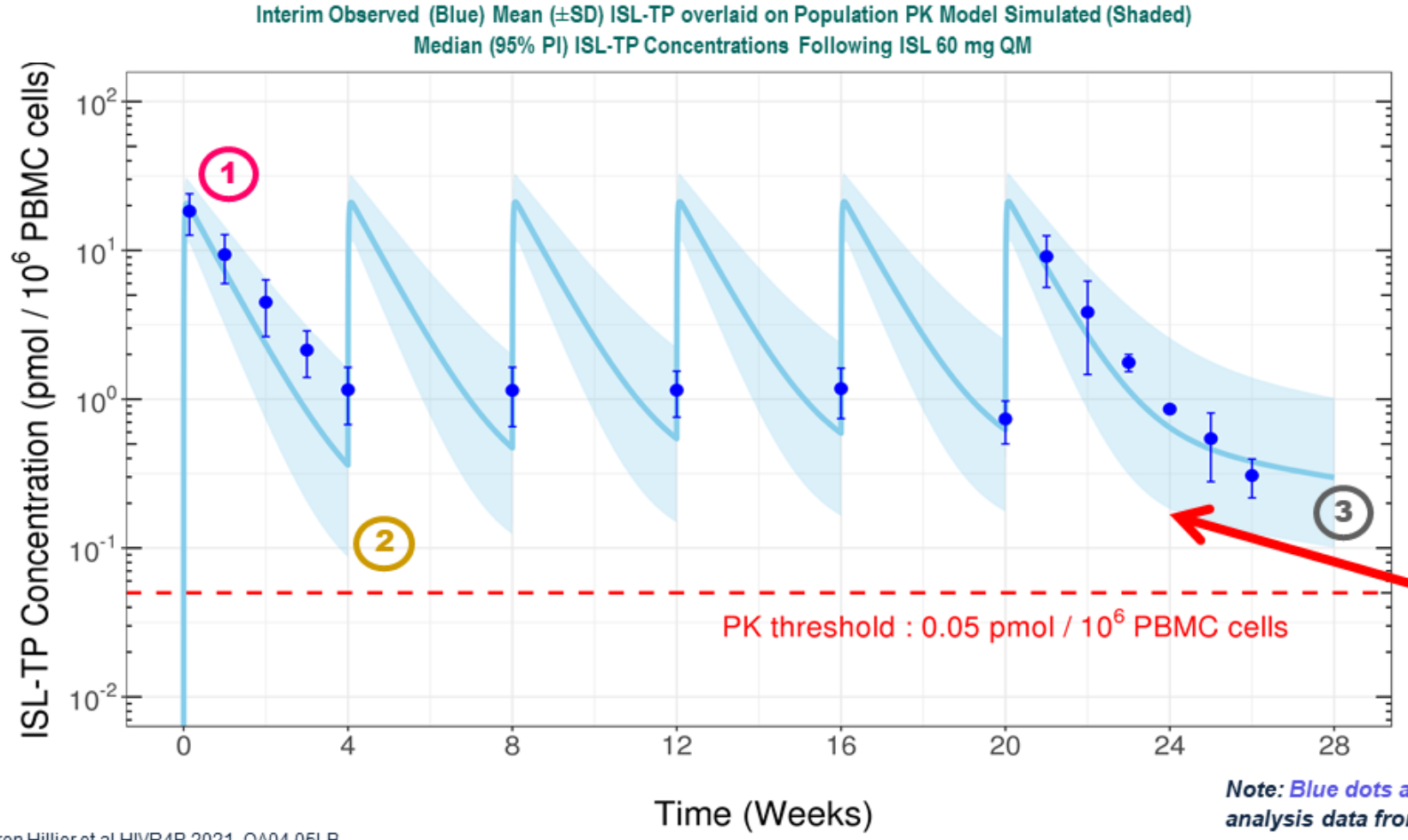
- Review of implant site adverse events (AEs) suggests that implants were generally well tolerated
  - 22/36 (61%) participants reported at least 1 implant site AE (not including hematoma)
  - All AEs were mild or moderate in severity
  - No serious AEs and no discontinuations due to an AE
  - Types of AEs observed consistent with those observed with other implants

	Number (percent) of individuals reporting AE during study N=8 active/dose, 12 PBO (placebo; mod=moderate)			
	PBO	48 mg	52 mg	56 mg
TOTAL	6 (50)	6 (75)	4 (50)	6 (75)
Erythema	3 (25)	4 (50) 2/4 mod	2 (25)	4 (50) 1/4 mod
Tenderness/pain	4 (33)	2 (25)	4 (50)	4 (50)
Pruritis	3 (25)	5 (63) 1/5 mod	2 (25)	6 (75)
Induration	2 (17)	4 (50)	4 (50)	4 (50)

- No clear relationship between dose and AE frequency/severity
- Most common AE not related to implant was headache, with no clear dose relationship
- No effects on laboratory studies, ECGs, vital signs

Mathews RP, et al. CROI 2021 Virtual. Abstract 88.

Monthly oral dose of ISL 60 mg is expected to maintain systemic ISL-TP concentrations above the PK threshold

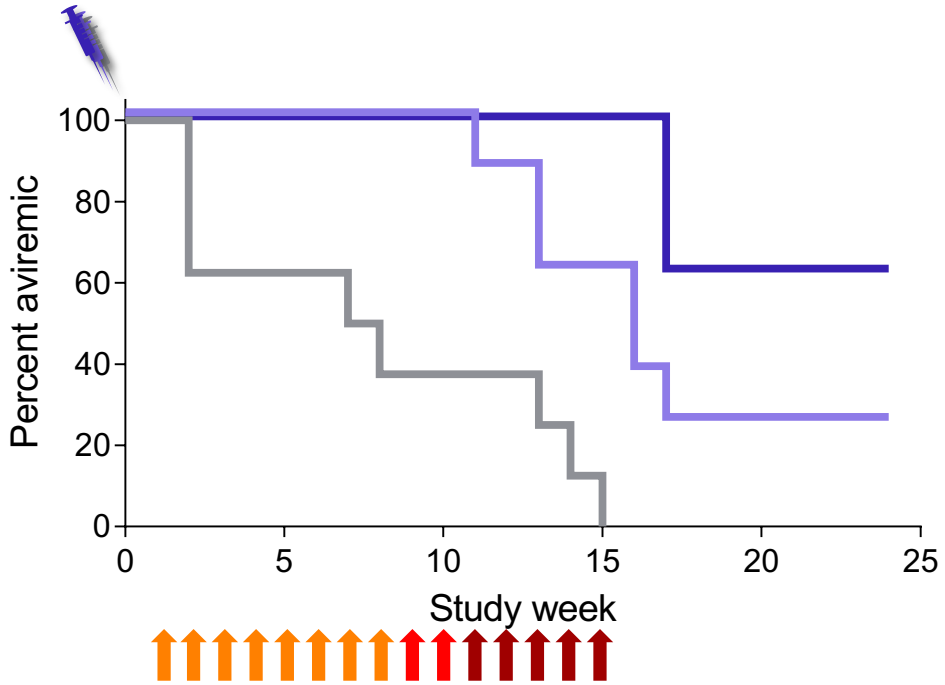


All participants are predicted to be above the PK threshold with the lower 2.5th % prediction interval having an IQ of ≥ ~17

Note: Blue dots and error bars represent observed Interim analysis data from an ongoing Protocol 016 Phase2a trial[1]

1. Sharon Hillier et al,HIVR4P 2021, OA04.05LB
Note: Shaded area represents 95% Prediction Interval (N=1000); Solid line represent the population PK model predicted median concentration; Blue filled circles represent mean of Protocol 016 interim observed data; Blue error bars represent standard deviation of Protocol 016 interim observed data; Previously built Population PK model of ISL was leveraged for population PK simulations (CROI 2020, Abstract 462)

GS-CA1 Protects from Repeat Intrarectal SHIV Challenges



	No. Protected	Median Weeks to Infection (95% CIs)	Hazard Ratio	p-value
GS-CA1 300 mg/kg	5 / 8	Not reached (17, –)	0.038	**0.0002**
GS-CA1 150 mg/kg	2 / 8	16 (11, –)	0.141	**0.0061**
Placebo	0 / 8	7.5 (2,14)	1	

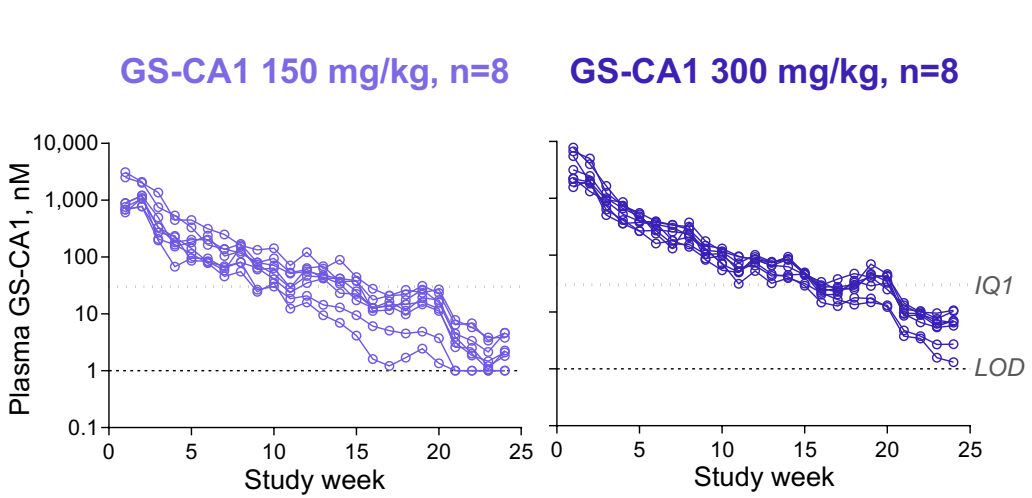
Hazard ratios, p-values calculated using Cox regression model.

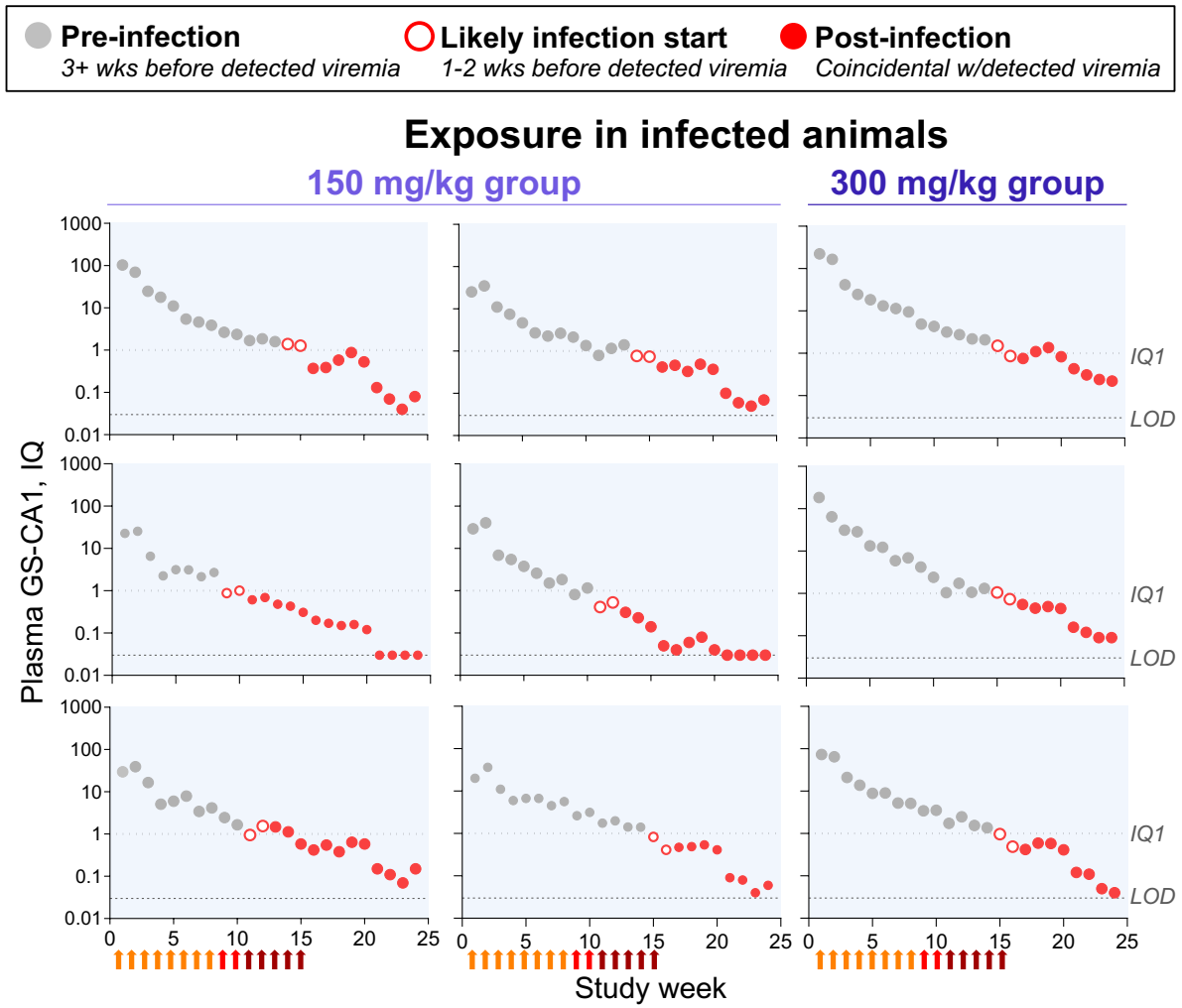
- 100% infection of placebo controls within 15 challenges
- Significant infection risk reduction with GS-CA1 vs placebo (86% and 96% for low- and high-dose groups, respectively)
- Infections in GS-CA1-dosed groups occurred only after marked compound washout (9+ weeks post dose*)

CI, confidence interval. *Assumes 2-week infection-detection window.

Bekerman E, et al. CROI 2021 Virtual. Abstract 717. Science Spotlight

Protection Correlates with GS-CA1 Exposure





Main conclusions:

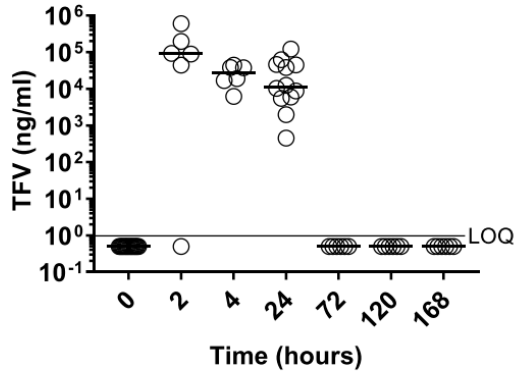
- Single GS-CA1 dose achieved long-acting exposure (>IQ1 for 2-4 months) in macaques
- Mean IQ at time of infection was 1* (0.41-1.5 range)
- Complete protection from infection observed with GS-CA1 exposures above IQ1.5 (1.5x paEC95)
- GS-CA1 preclinical data support clinical evaluation of capsid inhibitors for HIV prevention

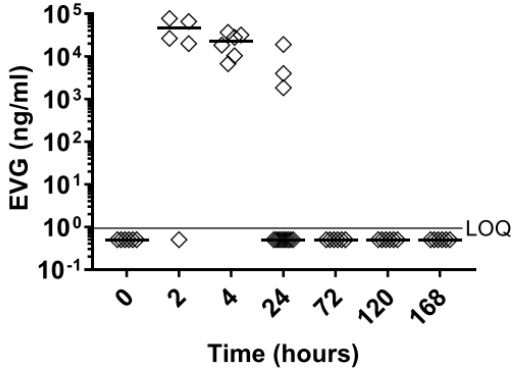
IQ, inhibitory quotient (protein-adjusted 95% effective concentration). LOD, limit of detection. *Assumes 2-week infection-detection window.

Bekerman E, et al. CROI 2021 Virtual. Abstract 717. Science Spotlight

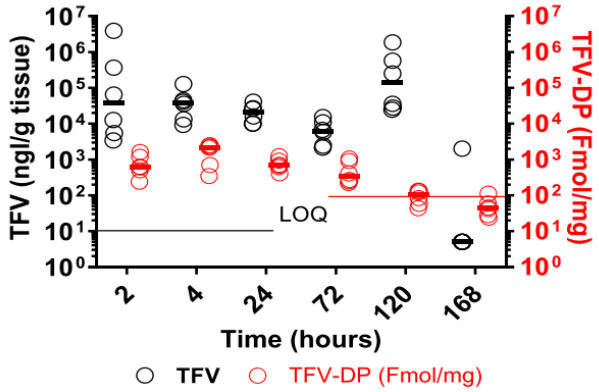
Accumulation of TFV, TFV-DP, and EVG in rectal fluids and tissue after single dose insert administration

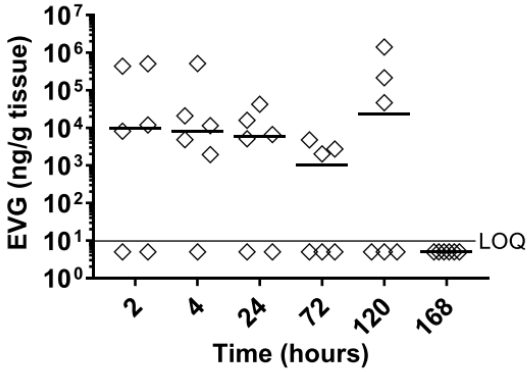
Rectal Fluids



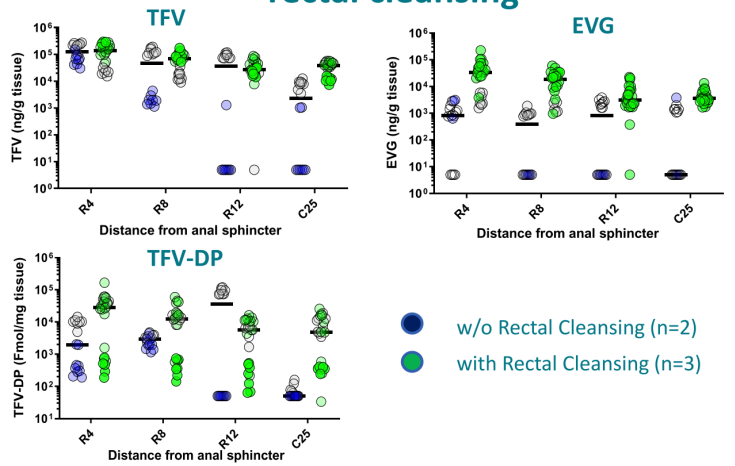


Rectal tissue

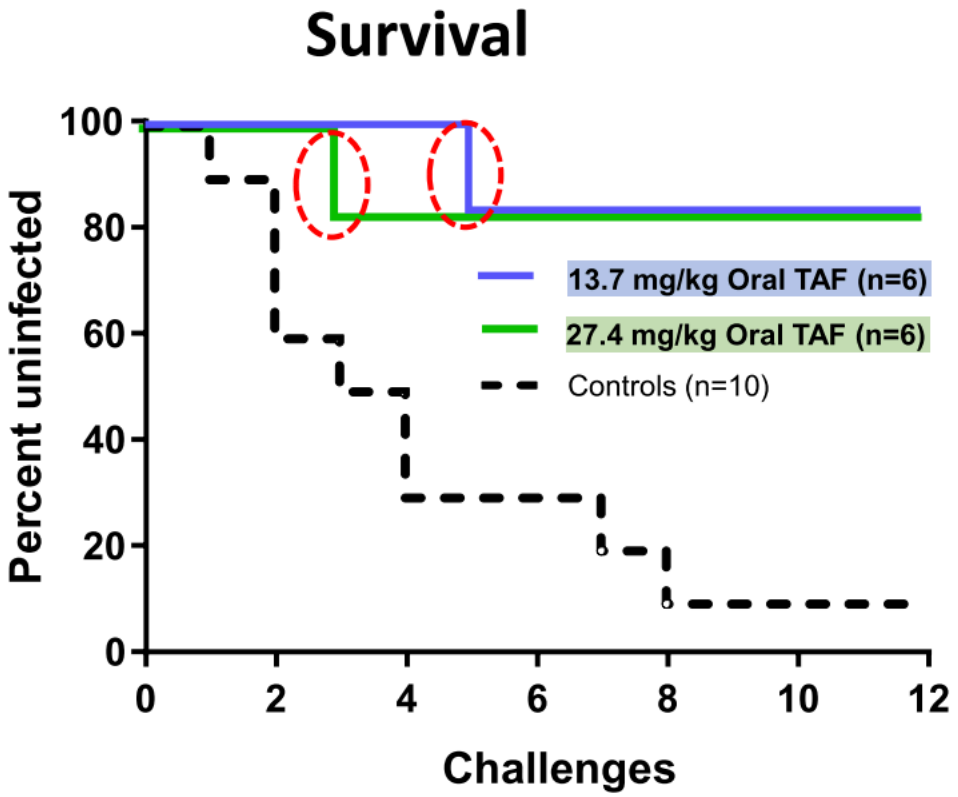




Drug distribution in rectal tissue improves with rectal cleansing



High efficacy of weekly oral TAF against SHIV vaginal infection



Efficacy = 92.1% [95%CI=39.6%, 99.0%]

Efficacy = 92.3% [95%CI=41.4%, 99.0%]

TFV-DP in PBMCs

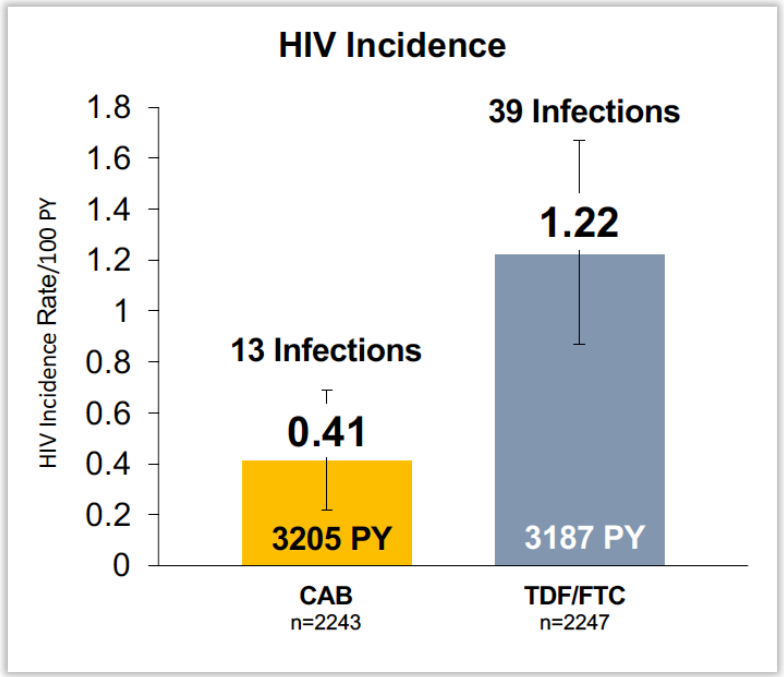
Study arm	TFV-DP at day 3 (fmols/10^6 cells)	TFV-DP at day 6 (fmols/10^6 cells)	TFV-DP in breakthrough infection (fmols/10^6 cells)
27.4 mg/kg	6,095	3,290	**405**
13.7 mg/kg	3,454	1,321	**3,457**

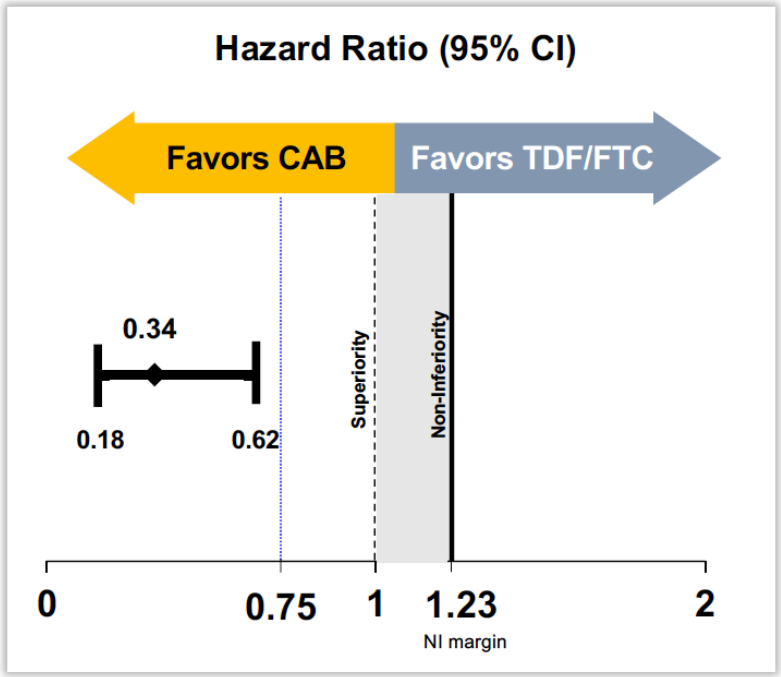
Low TFV exposures in plasma

Study arm	TFV at day 3 (ng/ml)	TFV-DP at day 6 (ng/ml)
27.4 mg/kg	**12.6 [BLOD-72.1]**	**BLOD [BLOD-10.9]**
13.7 mg/kg	BLOD	BLOD

I Massud, et al. CROI 2021 Virtual. Abstract 714. Science Spotlight

HIV Incidence: CAB vs. TDF/FTC





CI, confidence interval

Landovitz RJ et al. AIDS 2020, #OAXLB01

Extended HPTN LC Testing

HIV testing

Back-testing

qual RNA — **CAB arm:** All visits
TDF/FTC arm: Enrollment, weeks 2, 4, 5

Ag Ab — **CAB arm:** Enrollment plus three visits prior to the first RNA pos visit
TDF/FTC arm: Enrollment plus one visit prior to the first RNA pos visit

↓

Ab — If Ag/Ab test reactive

VL — If qualitative RNA test reactive

SC RNA — Selected cases/visits

HIV genotyping (VL >500 c/mL)

CAB arm

- All study visits

TDF/FTC arm

- First HIV positive visit
- First site positive visit

Ag Ab — ARCHITECT antigen/antibody test

qual RNA — APTIMA qualitative RNA test

Ab — Geenius discriminatory antibody test

VL — Viral load test

SC RNA — Single copy RNA test

Pharmacology testing

CAB concentrations

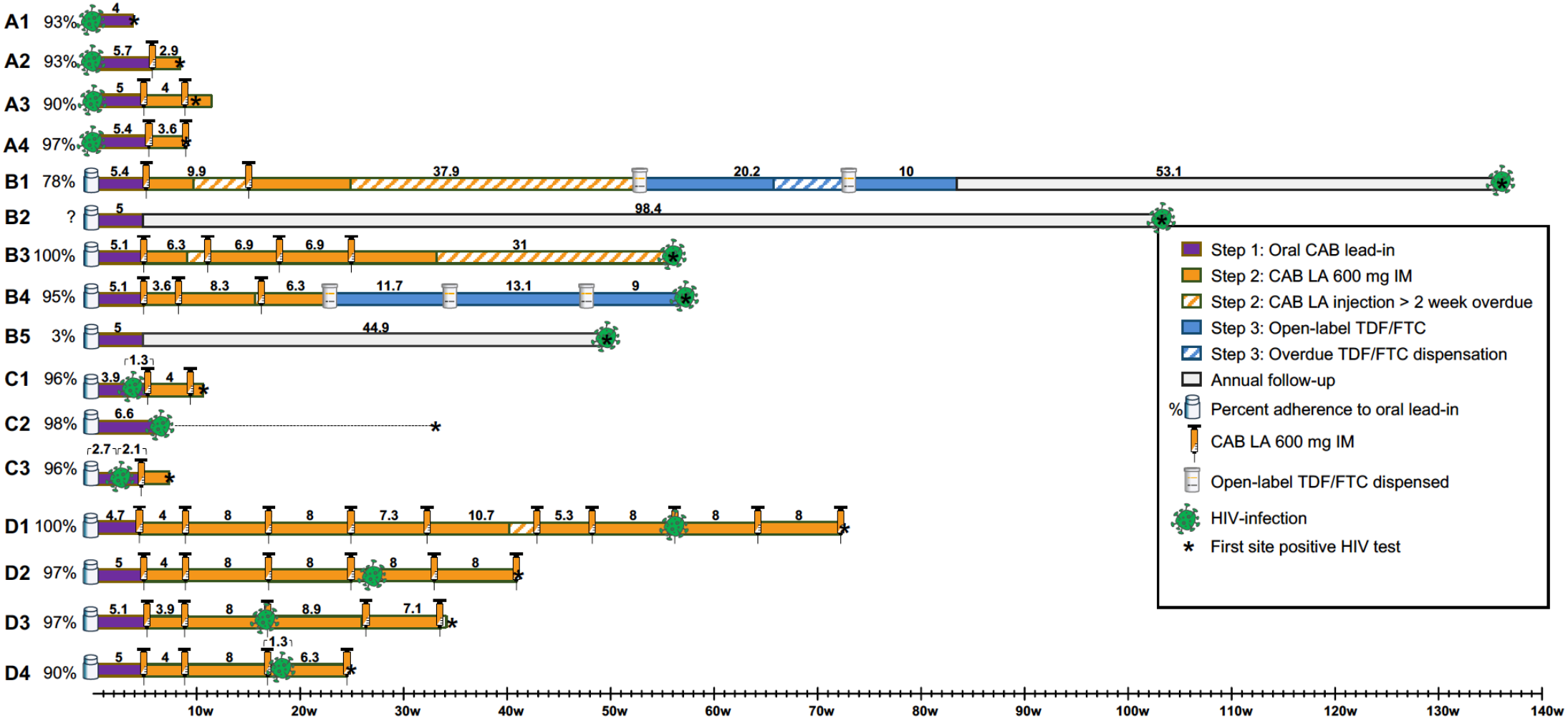
CAB arm
Plasma [CAB]: all study visits
Plasma [TFV]: baseline infections, step 3 infections
DBS [TFV-DP]: step 3 infections

TDF/FTC concentrations

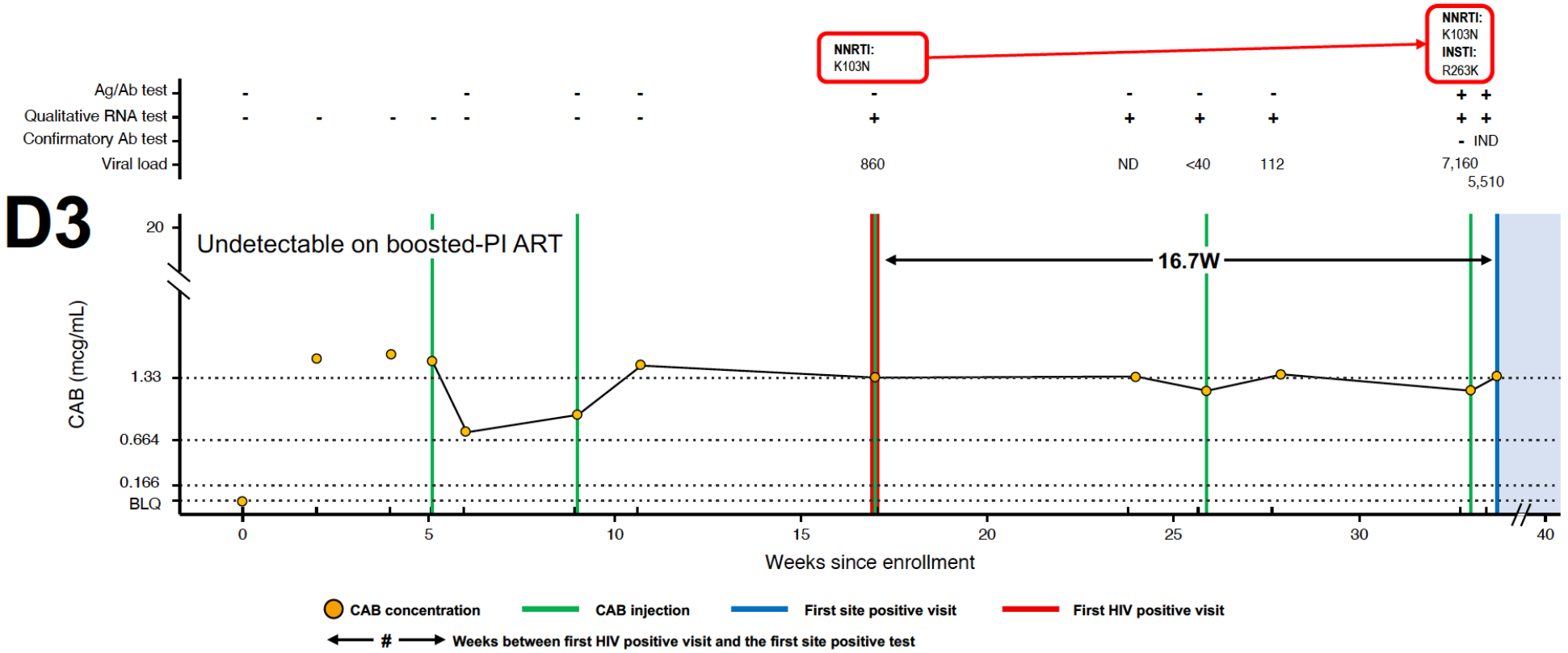
Plasma [TFV]: first site pos, first HIV pos, 3 prior visits
DBS [TFV-DP]: first site pos,1 prior visit

Landovitz R, et al. CROI 2021 Virtual. Abstract 153.

13 Incident, 4 baseline Infections: Cabotegravir



Landovitz R, et al. CROI 2021 Virtual. Abstract 153.



The shaded area represents time on ART.

Agradecimientos:

Imma Clotet
Raphael Landovitz
Daniel Podzamczer
Marta Rosell
Eva Xicola

¡MUCHAS GRACIAS!

aimaz@bellvitgehospital.cat

Unitat de VIH i ITS
Hospital Universitari de Bellvitge

web http://www.vihhub.cat

@VIHHUB

Unitat_vihmts@bellvitgehospital.cat