UNIVERSITÀ DI PISA

PIPELINE SVILUPPO TERAPIE A LUNGA DURATA

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Milano 28.04.2025

Outline

- **What's new on the horizon?**
- **Oral options**
- **Parenteral options**
- **A reflection on the future of ART**

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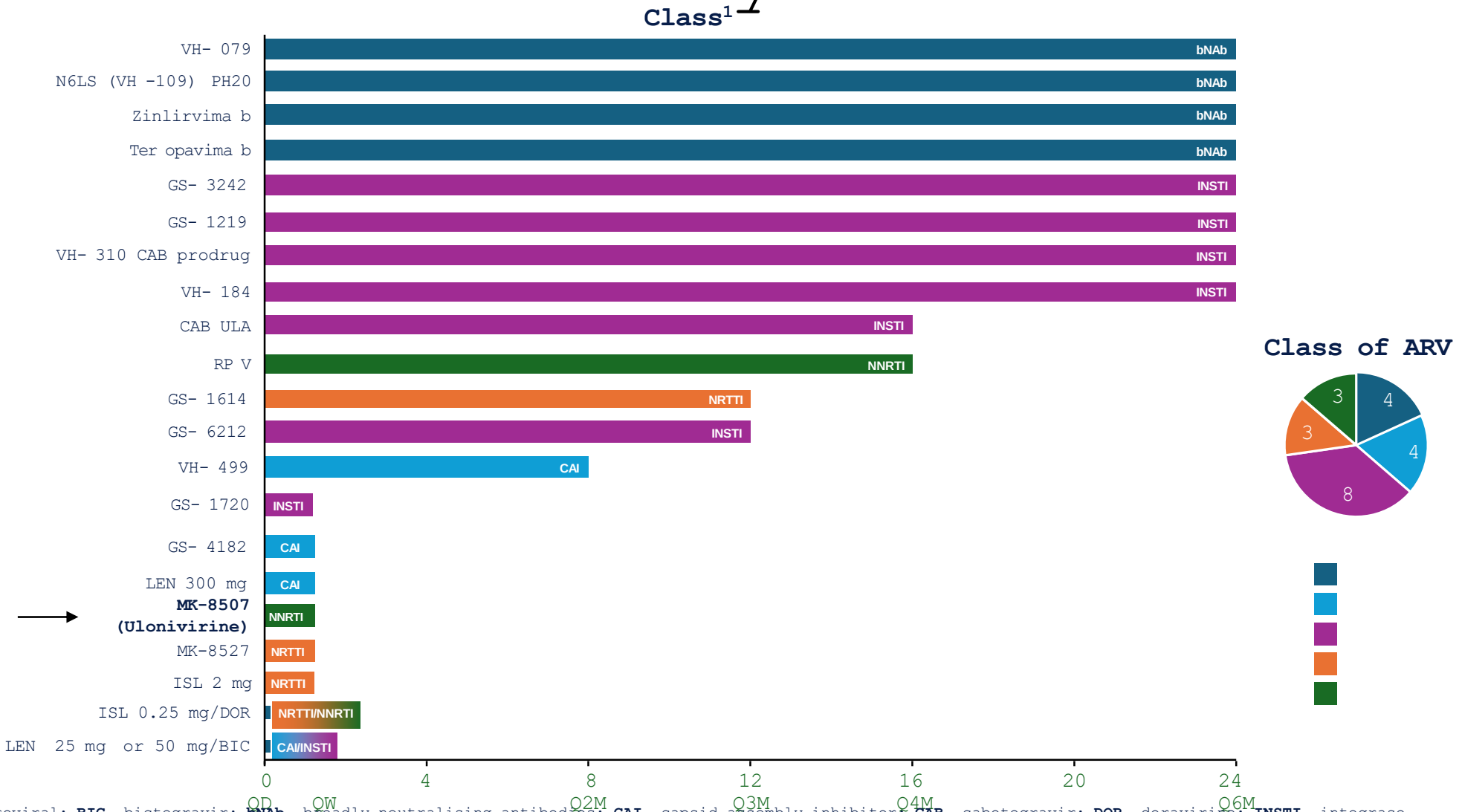
The pipeline by 'planned' administration and by class



ARV, antiretroviral; **BIC**, bictegravir; **bNAb**, broadly neutralising antibodies; **CAI**, capsid assembly inhibitor; **CAB**, cabotegravir; **DOR**, doravirine; **INSTI**, integrase strand transfer inhibitor; **ISL**, islatravir
LEN, lenacapavir; **NNRTI**, non-nucleoside reverse transcriptase inhibitor; **NRTTI**, nucleoside reverse transcriptase translocation inhibitor; **RPV**, rilpivirine; **QD**, once daily; **QW**, once weekly; **QXM**, every X months
ULA, ultra-long acting. **1.** Arribas J, et al. HIV Glasgow 2024. New treatments and future combinations; **2.** Merck. Merck Provides Update on Phase 2 Clinical Trial of Once-Weekly Investigational Combination of MK-8507 and Islatravir for the Treatment of People Living with HIV-1. Available at: https://www.merck.com/news/merck-provides-update-on-phase-2-clinical-trial-of-once-weekly-investigational-combination-of-mk-8507-and-islatravir-for-the-treatment-of-people-living-with-hiv-1/. Accessed February 2025

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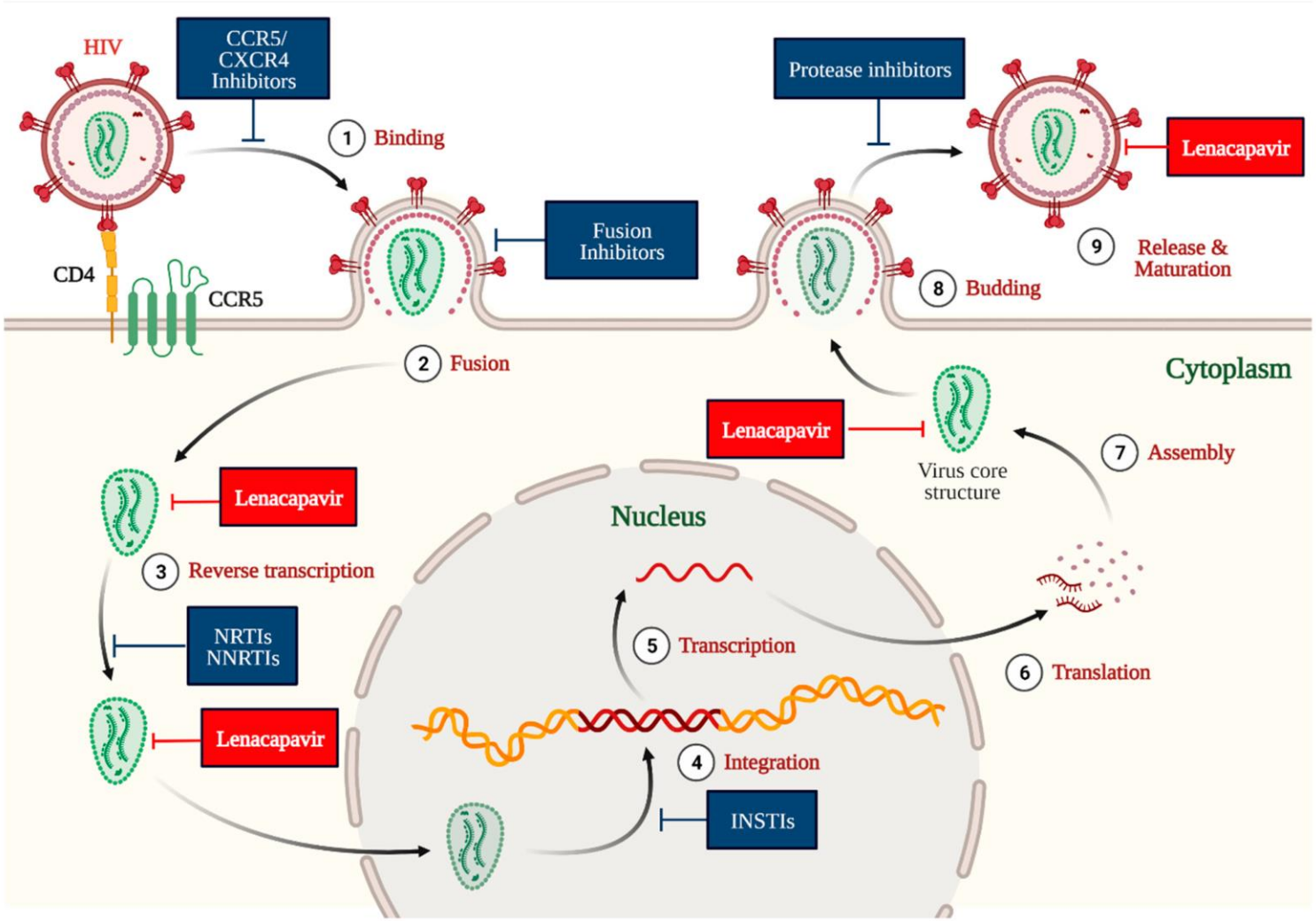
New drug combinations



LEN interferes at multiple stages of the HIV-1 life cycle, including capsid-mediated nuclear uptake of HIV-1, virus assembly and release, and capsid core formation.

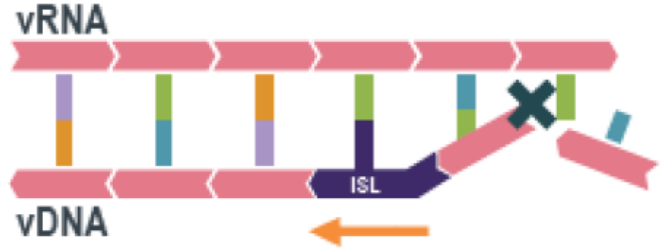
Islatravir: A NRTTI With Multiple Mechanisms of Action

- Islatravir (ISL) is a nucleoside reverse transcriptase translocation inhibitor (NRTTI) being studied for HIV-1 treatment

Translocation Inhibition

- Translocation inhibition prevents opening of the RT nucleotide binding site
- Nucleotides cannot be incorporated into vDNA
- **Viral replication is inhibited**

Delayed Chain Termination



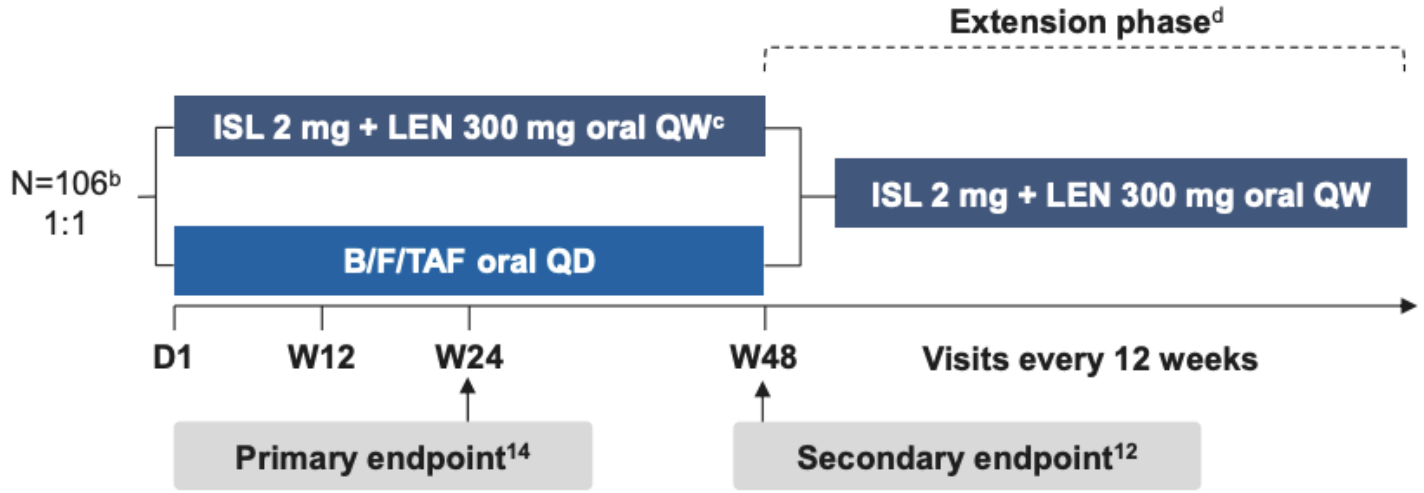
- ISL changes vDNA structure such that nucleotide incorporation is prevented
- As ISL is not in the RT active site, it is not susceptible to resistance-conferring mutations
- **Viral replication is inhibited**

Multiple mechanisms contribute to the high potency of ISL against HIV-1 (including drug-resistant variants) and its high barrier to resistance

QW: ISL 2 mg + LEN 300 mg, Week 48

Key eligibility criteria

- Aged ≥18 years
- On B/F/TAF for >6 months
- HIV-1 RNA <50 copies/mL for >6 months
- No history of virologic failure
- CD4+ T-cell count ≥350 cells/µL
- Lymphocyte count ≥900 cells/µL
- No HBV infection
- No NRTI or NNRTI resistance[a]



[a]The ongoing Phase 3 clinical trials do not have this resistance exclusion criteria.[1,2] [b]Randomized, N=106; dosed, n=104 (n=52 per group). [c]600 mg of LEN was given on D1 and D2 for pharmacologic loading. [d]Participants could elect to continue the study in post-W48 extension phase.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; D, Day; HBV, hepatitis B virus; ISL, islatravir; LEN, lenacapavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; QD, once daily; QW, once weekly; W, Week.

Endpoints included virologic outcomes, safety, changes in lymphocyte counts, weight, BMI
and adherence (by pill count)

Note: AEs leading to study treatment discontinuation included large intestinal perforation and renal colic (n=1), acute hepatitis B infection (n=1)
***Last VL under treatment <50 c/mL**
BMI, body mass index
Colson AE, et al. HIV Glasgow 2024. Oral presentation 21

Virological results at Week 48 (FDA Snapshot)

Weekly oral ISL + LEN maintained a high rate of virologic suppression at Week 48

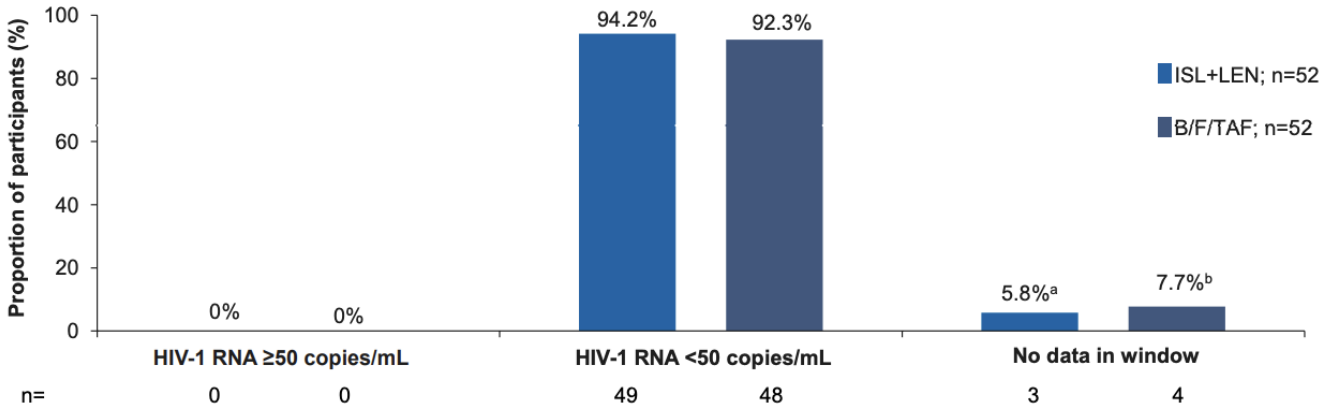


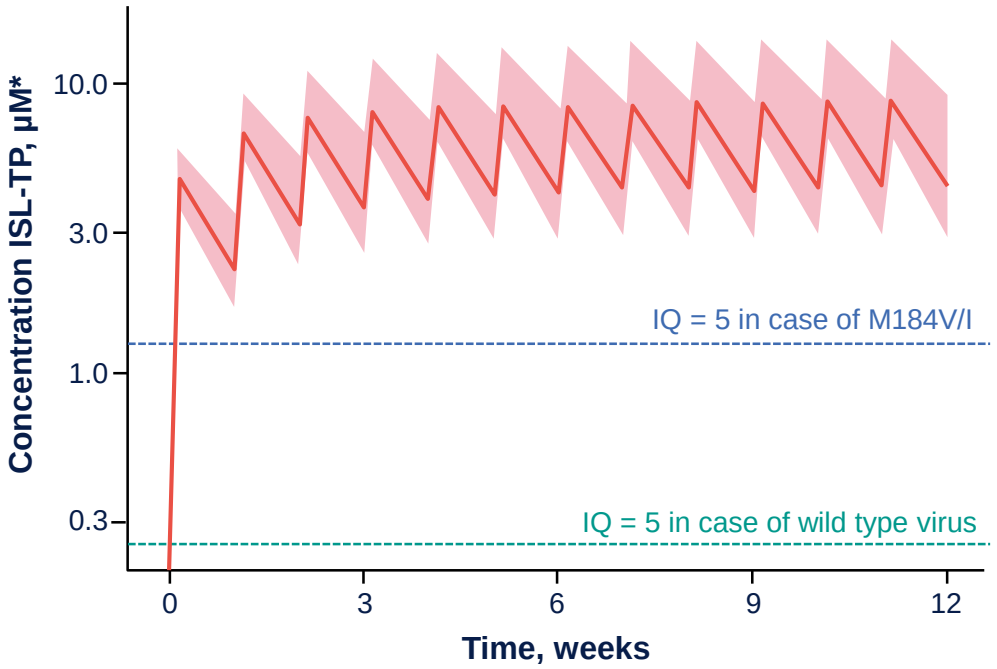
Figure adapted from Colson A, et al. IDWeek 2024.
[a]Two participants discontinued due to adverse events not related to study drug and one participant discontinued due to other reasons not related to study drug; all participants had HIV-1 RNA <50 copies/mL at study discontinuation. [b]Three participants discontinued due to other reasons not related to study drug and had HIV-1 RNA <50 copies/mL at study discontinuation; one participant had missing data during window but remained on study drug.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; FDA, Food and Drug Administration; ISL, islatravir; LEN, lenacapavir.

Participants, n (%)	ISL + LEN (n=52)	BIC/FTC/TAF (n=52)
VL <50 c/mL	49 (94.2)	48 (92.3)
VL ≥50 c/mL	0	0
Absence of virological data at Week 48	3 (5.8)	4 (7.7)
Discontinuation due to AEs not related to study drug	2 (3.8)*	0
Discontinuation due to other reasons not related to study drug	1 (1.9)*	3 (5.8)*
Missing data in window but still under study processing	0	1 (1.9)

Colson A, et al. IDWeek 2024; Presentation 577. 13. Colson A, et al. HIV Drug Therapy Glasgow 2024; Presentation O21.

QW: ISL 2 mg + LEN 300 mg QW, pharmacological data

Simulations of ISL-TP concentration-time series following ISL 2 mg QW dosing (n=52)



→ **The observed PKs suggest that ISL 2 mg QW is predicated to provide sufficient exposure to ISL-TP to cover wild-type and M184V/I HIV-1 variants, without negatively impacting CD4⁺ T-cell or lymphocyte counts**

→ **LEN 300 mg QW provided effective exposure to LEN consistent with approved subcutaneous administration**

→ **ISL + LEN once weekly maintains viral suppression, with good tolerability**

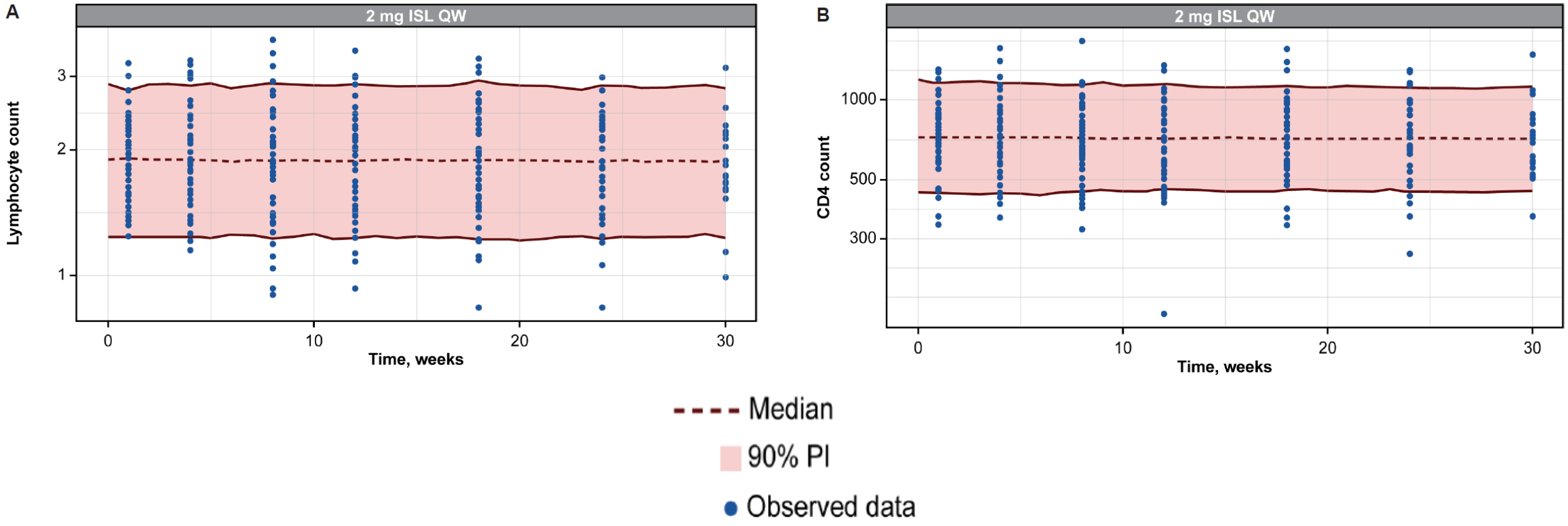
→ **Phase III trials in preparation (ISLEND-1 and ISLEND-2)**

/ Solid lines: median prediction; coloured bands: 95% CI of individual prediction
/ Based on a popPK prediction model, mean steady-state ISL-TP C_{trough} (5.60 µM) remained above the IQ of 5 (IQ5; 1.25 µM) for M184V/I variants and the IQ5 (0.25 µM) for wild-type HIV-1
/ PK/PD simulations demonstrated a lack of ISL-TP exposure-related decreases in CD4⁺ T-cell lymphocyte counts in ISL + LEN-treated participants

***Solid lines indicate median predication; coloured bands indicate 95% individual predication interval
ISL-TP, islatravir triphosphate
Longo D, et al. HIV Glasgow 2024. Poster 224

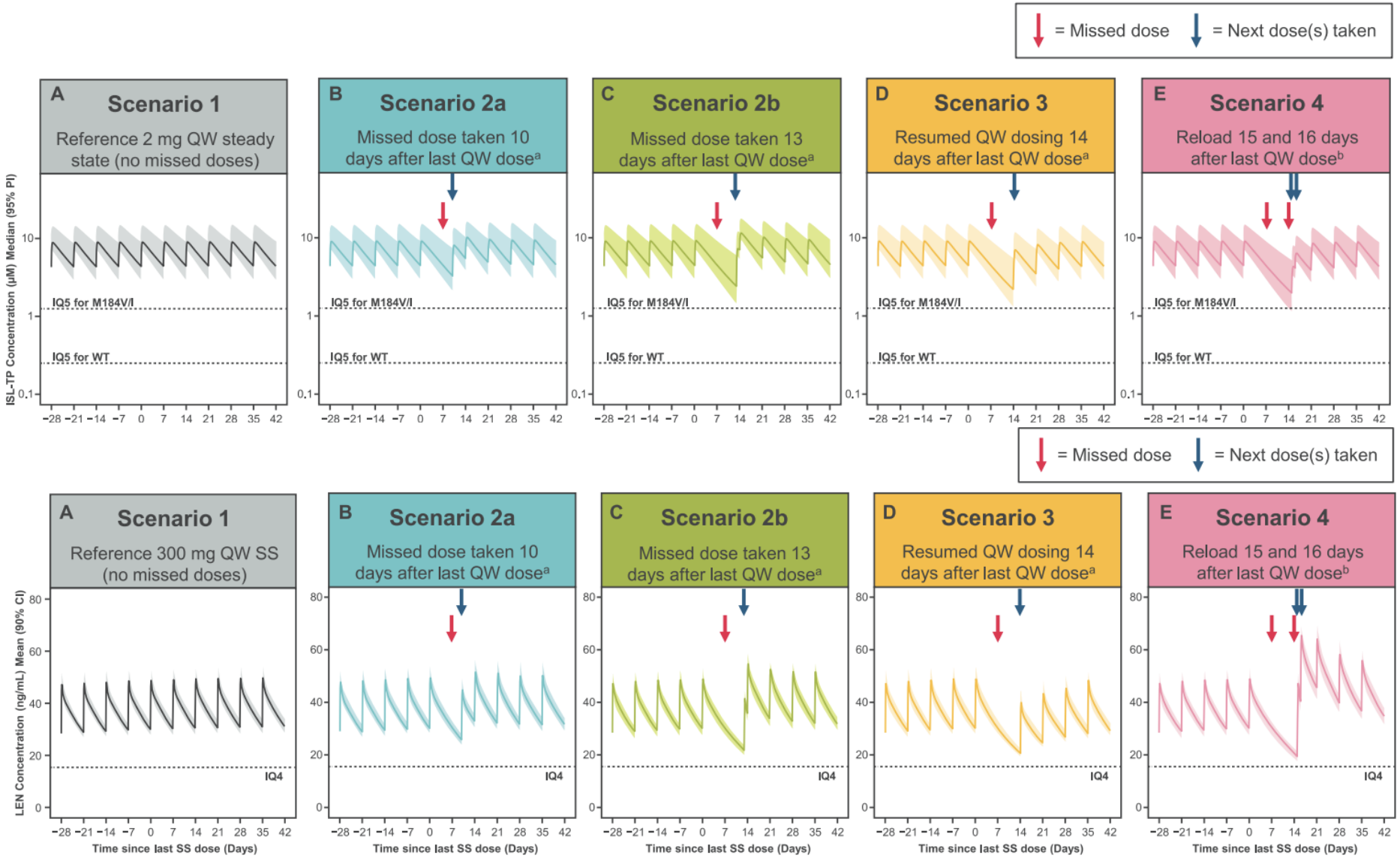
Predicted and Observed (A) Lymphocyte Counts and (B) CD4+ T-cell Counts Following ISL 2 mg QW

- As previously predicted[1], lymphocyte and CD4+ T-cell counts showed no decline in ISL+LEN-treated participants



ISL, islatravir; PI, prediction interval; QW, once weekly; n = 1000*, reps = 100; *1000 sampled from the GS-US-563-6041 population (n = 52); lymphocyte cell count = 103 cells/mm^3; CD4+ T-cell count = cells/mm^3; **1**. Vargo RC et al. Presented at Conference on Retroviruses and Opportunistic Infections (CROI); February 19-22, 2023; Seattle, Washington. Abstract 497.

Pharmacokinetic Modeling of Missed Dose Scenario of Oral Weekly Islatravir Plus Lenacapavir



Simulations demonstrated that both ISL-TP and LEN maintained optimal concentrations one week after a missed dose at steady state.

Marathe et al. CROI 2025, Abstract 642

Resistance Analysis of Weekly Islatravir Plus Lenacapavir in People With HIV at 48 Weeks

Pre-Existing (Baseline) Primary Resistance to four main ARV Classes

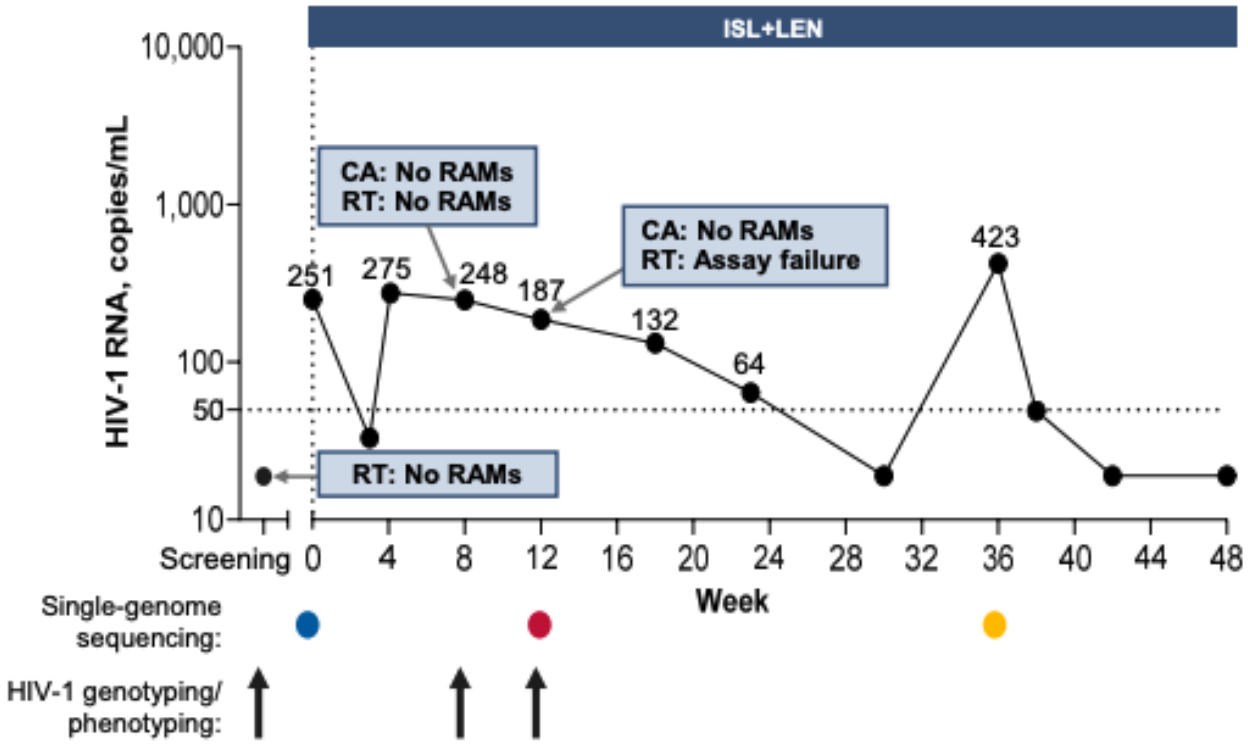
Pre-existing primary resistance substitutions, n/N (%)	ISL+LEN (n=52)	B/F/TAF (n=52)	All (N=104)
NRTI resistance	2/52 (3.8)	2/52 (3.8)	4/104 (3.8)
Any TAM[a]	1/52 (1.9)	1/52 (1.9)	2/104 (1.9)
M41L	1/52 (1.9)	0/52	1/104 (1.0)
L74V	1/52 (1.9)	0/52	1/104 (1.0)
M184V/I	1/52 (1.9)	1/52 (1.9)	2/104 (1.9)
K219R	0/52	1/52 (1.9)	1/104 (1.0)
NNRTI resistance	2/52 (3.8)	0/52	2/104 (1.9)
K103N	1/52 (1.9)	0/52	1/104 (1.0)
V108I	1/52 (1.9)	0/52	1/104 (1.0)
PI resistance	4/52 (7.7)	2/52 (3.8)	6/104 (5.8)
M46I/L	3/52 (5.8)	2/52 (3.8)	5/104 (4.8)
I84V	1/52 (1.9)	0/52	1/104 (1.0)
INSTI resistance	0/51	2/49 (4.1)	2/100 (2.0)
T66A	0/51	2/49 (4.1)	2/100 (2.0)

[a]TAMs are M41L, D67N, K70R, L210W, T215F/Y, K219E/N/Q/R in RT.
ARV, antiretroviral; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; INSTI, integrase strand transfer inhibitor; ISL, islatravir; LEN, lenacapavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RT, reverse transcriptase; TAM, thymidine analog mutation.

Resistance mutations

One participant in the ISL+LEN group met criteria for post-baseline resistance analysis:

- The participant had no pre-existing primary NRTI or NNRTI RAMs and was viremic at Day 1 (HIV-1 RNA 251 copies/mL)
- The participant did not have treatment-emergent drug resistance and achieved sustained viral suppression after Week 36 while maintaining ISL+LEN
- The participant demonstrated adequate plasma ISL and LEN levels
- Single-genome analysis of longitudinal plasma sequences identified 15% (7/47) identical HIV-1 RNA sequences, suggesting clonal T-cell expansion may have contributed to low-level viremia



Resistance Analysis of Weekly Islatravir Plus Lenacapavir in People With HIV at 48 Weeks. CROI 2025. abstract 736

Conclusions

- In virologically suppressed adults with HIV-1 treated with oral once-weekly (QW) islatravir (ISL) plus lenacapavir (LEN) for 48 weeks:
  - High rates of virologic suppression were maintained
  - One participant with pre-existing M184V/I also maintained virologic suppression
  - No participant developed treatment-emergent HIV-1 drug resistance

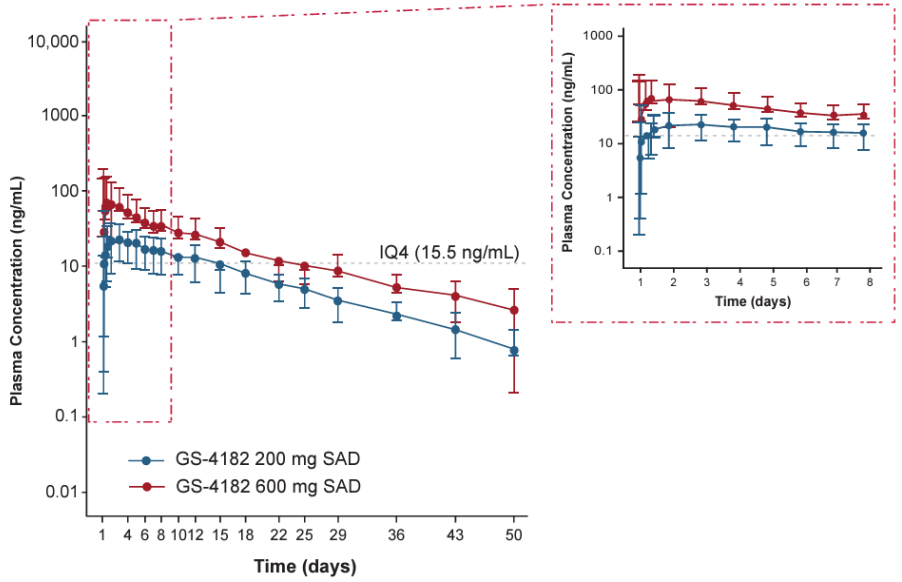
- No concerns signal emerged about lymphocytes and CD4 count;

- PK profile supports QW dosing with apparently adequate forgiveness window

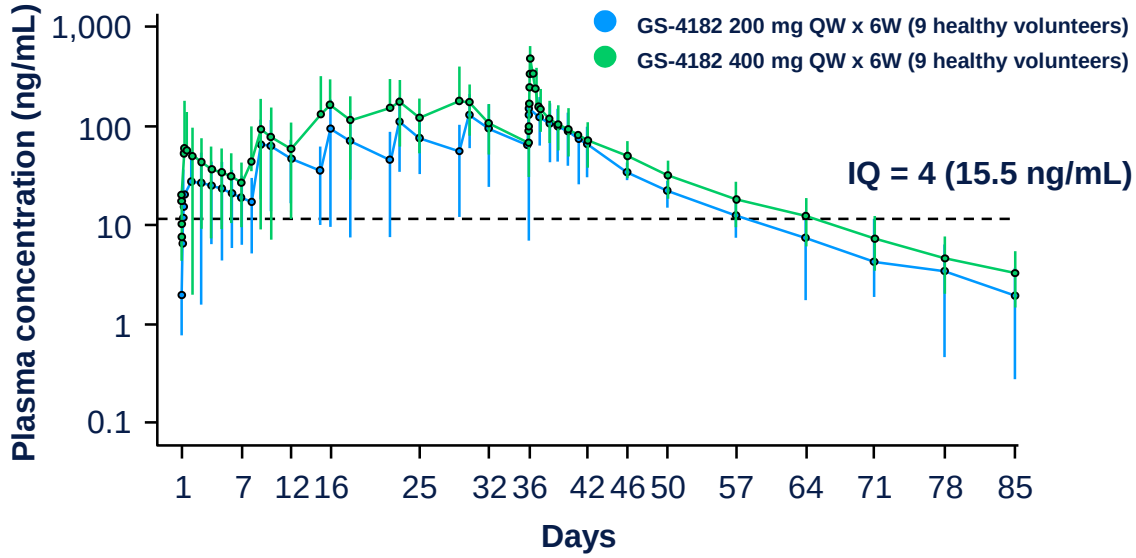
QW: GS-4182, an oral prodrug of LEN

- Phase Ia, randomised, blinded, placebo-controlled study evaluating safety and PKs:
  - In SAD cohorts, participants received a single dose of GS-4182 200 mg or 600 mg (for each dose: active treatment n=8, placebo n=2)
  - In MAD cohorts, participants received repeated doses of GS-4182 200 mg or 400 mg QW for 6 weeks (for each dose: active treatment n=9, placebo n=3) in adults (aged 18–45 years) without HIV-1

LEN plasma concentration-time profile following single oral administration of GS-4182



LEN plasma concentration-time profile following QW oral administration of GS-4182 for 6 weeks



- ~2X higher LEN relative bioavailability was observed for GS-4182 compared with historic data for direct oral LEN administration (**19% and 15% for GS-4182** 200 mg and 600 mg, respectively; **10% and 5% for LEN** 300 mg and 600 mg, respectively)

→ **Mean LEN concentrations on Day 7 following single doses of GS-4182 200 mg or 600 mg were above IQ4 (efficacy target)**

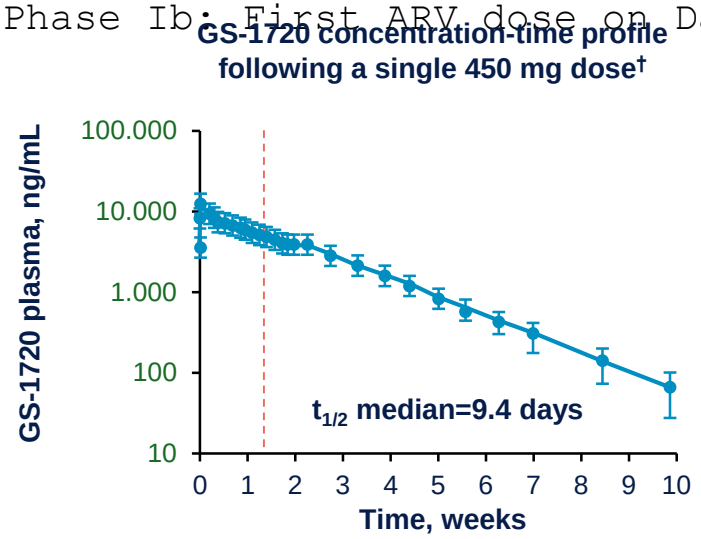
IQ, inhibitory quotient; **MAD,** multiple ascending dose; **SAD,** single ascending dose

Shaik N, et al. AIDS 2024. Abstract WEPEB117

QW: GS-1720, new oral INSTI taken weekly

- Phase Ia trial in adults without HIV-1; Phase Ib in adults with HIV-1* (VL 5,000–400,000 c/mL, $CD4^+$ T-cells >200 cells/uL)
- Objectives: Phase Ia - PK, safety and tolerability; Phase Ib - antiviral activity (plasma HIV-1 RNA change from BL to Day 11 relative to historical placebo), safety and PK
- Phase Ib: First ARV dose on Day 1, second dose on Day 2

A



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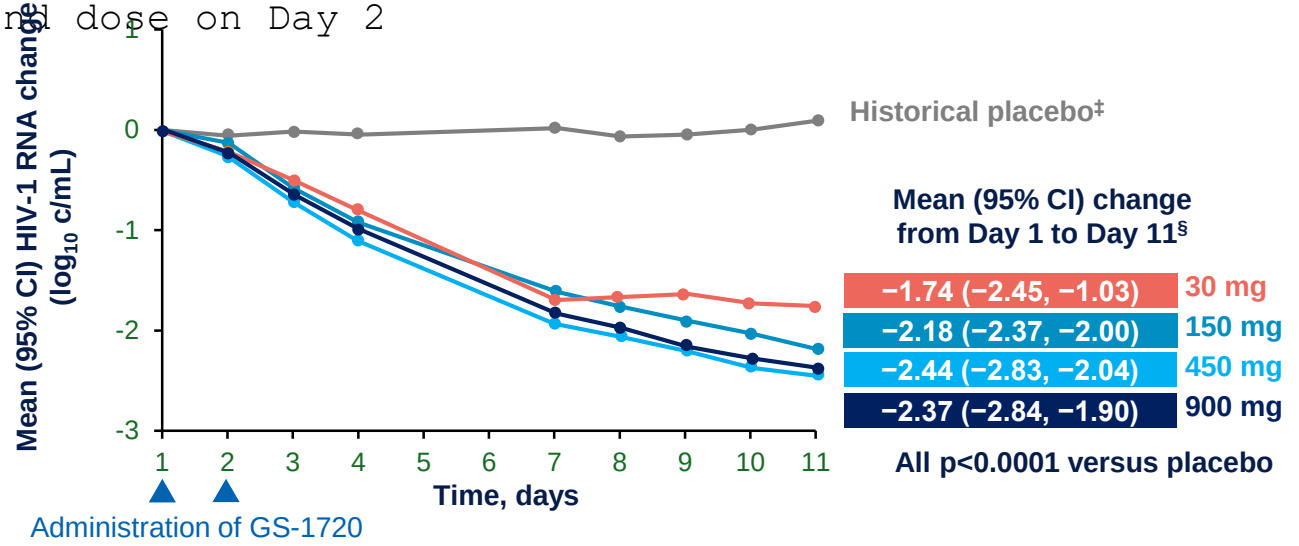


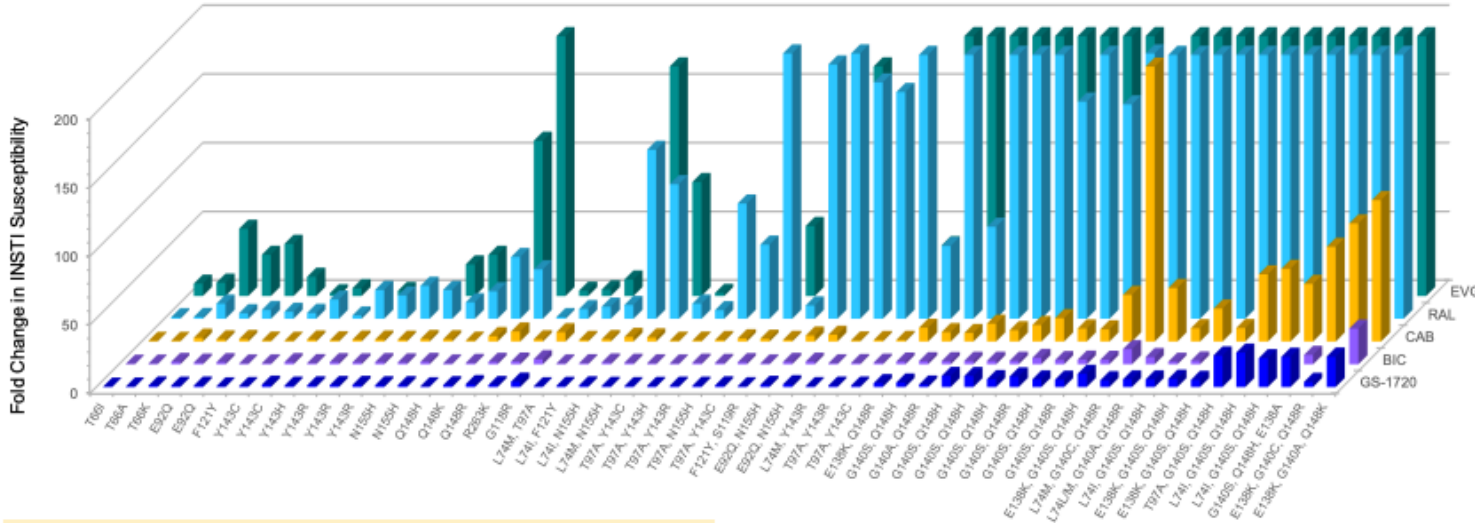
- **PK profile suitable for weekly administration**
- **Potent antiviral activity with a mean >2 log_{10} c/mL decline in HIV-1 RNA (highest dose cohorts), comparable to currently approved QD INSTIs**
- **No treatment-emergent INSTI resistance was observed at Day 11; well-tolerated with a favourable safety profile**

*Treatment-naïve OR treatment-experienced and naïve to INSTIs and off ART for >12 weeks; †GS-1720 (n=8) and matched placebo (n=2) was administered under fasting conditions as a single 450 mg oral dose ‡Historical placebo (HIV-1 RNA change from Day 1 = +0.01 log_{10} c/mL) includes placebo-treated participants from three previous Gilead-sponsored studies; for historical studies without Day 11 HIV-1 RNA,
Day 10 values were used for Day 11; §n=7 per cohort
PK, pharmacokinetic; **$t_{1/2}$,** terminal half life. Fichtenbaum CJ, et al. CROI 2024. Oral presentation 1903

In Vitro Resistance Profile for GS-1720, a Potent Once-Weekly Oral InSTI in Clinical Development

METHODS

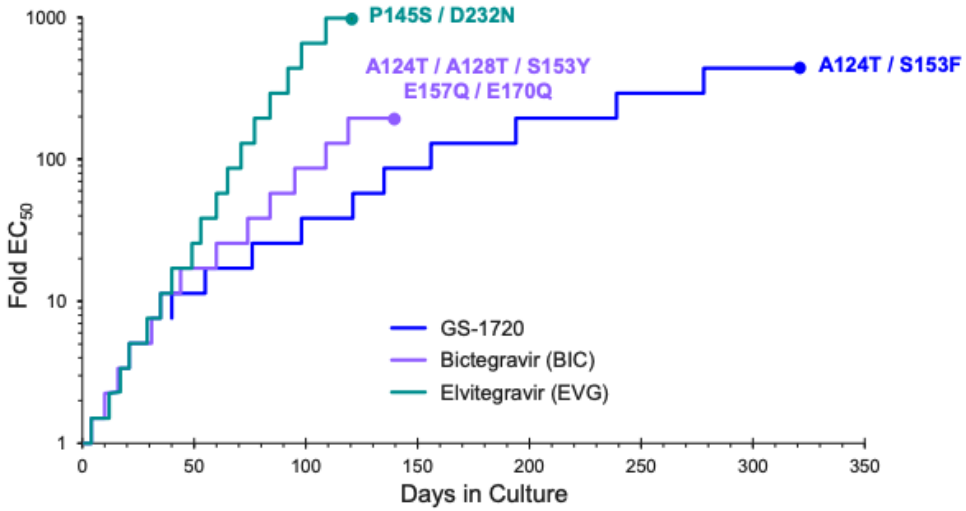
- GS-1720 activity against HIV-1 reporter viruses containing integrase (IN) substitutions associated with INSTI class resistance was assessed at Monogram Biosciences.
- In vitro resistance barrier was studied by serial passage of HIV-1 IIIb- and HXB2-infected MT-2 cells in the presence of increasing concentrations of GS-1720.
- GS-1720 was also evaluated in a 35-day fixed-dose viral breakthrough assay in HIV-1 BaL-infected human PBMCs. Emergent viral variants were characterized genotypically and phenotypically.



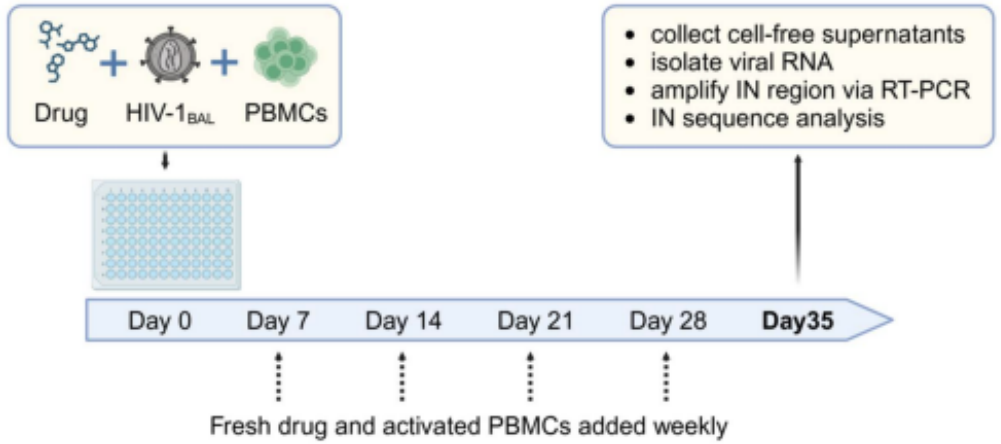
- GS-1720 in vitro resistance profile is comparable to BIC and improved relative to CAB, RAL and EVG
- High-level resistance to GS-1720 requires at least 3 IN mutations (G140A/S + Q148H/K +L74I, T97A or E138A/K)

Hansen. CROI 2025. Abstr 724

Results



GS-1720 Prevents Viral Breakthrough in PBMCs



Drug susceptibility of final selected viral passages in MT-2 cells:

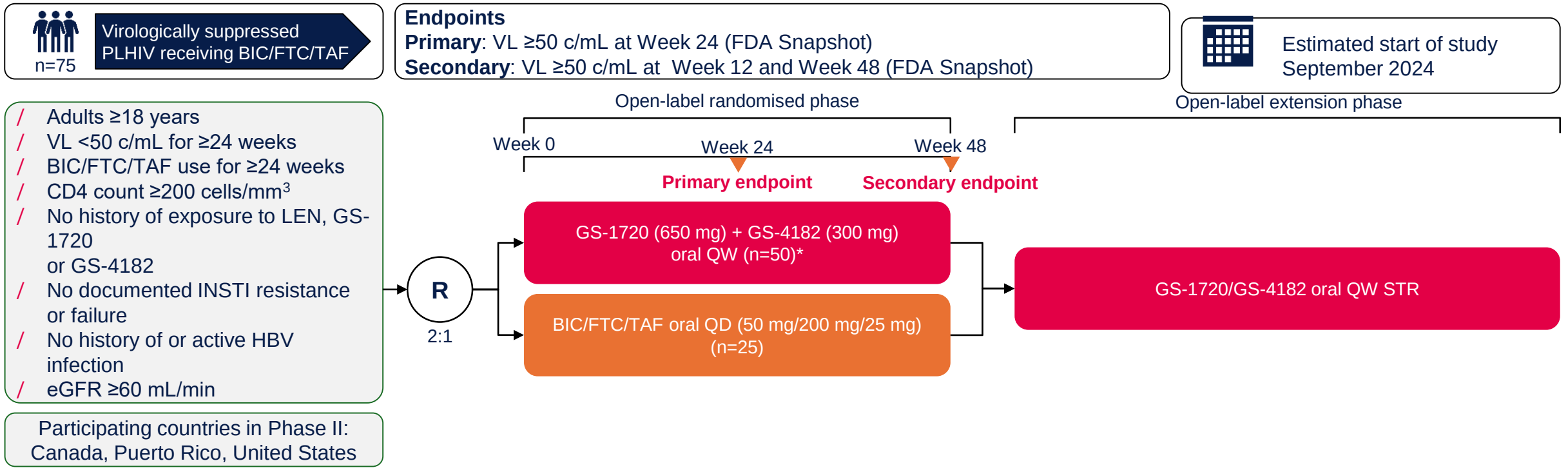
Compound (Class)	EC_{50} Fold-Change (relative to WT)			
	$HIV\text{-}1_{IIIb}$ input virus	Selected $HIV\text{-}1_{IIIb}$ Virus Passage (P)		
		GS-1720, P-16	BIC, P-14	EVG, P-18
GS-1720 (INSTI)	1.0 ± 0.1	9.0 ± 2.5	2.8 ± 0.4	0.6 ± 0.1
Bictegravir (INSTI)	1.0 ± 0.1	6.8 ± 1.8	4.4 ± 0.9	0.5 ± 0.1
Elvitegravir (INSTI)	1.0 ± 0.1	6.0 ± 1.3	1.8 ± 0.3	63 ± 19
Efavirenz (NNRTI, control)	1.0 ± 0.2	2.1 ± 0.3	0.6 ± 0.1	0.9 ± 0.2

INSTIs	Viral Breakthrough in $HIV\text{-}1_{BaL}$-Infected Human PBMCs at Fixed INSTI Concentrations			
	Fixed nM Drug Concentration (IQ)	Fraction of Samples with Breakthrough	Breakthrough Frequency (%)	Integrase Mutations (No.)
GS-1720	6.2 (2.5)	0 / 48	0	N/A
Bictegravir	30 (2.5)	0 / 48	0	N/A
Raltegravir	60 (tissue culture equivalent C_{min})	8 / 44	18	T66A/K (2), E92A (1), T97A (1), Q148R (1), V151I (3), N155H (1)
Elvitegravir	48 (tissue culture equivalent C_{min})	20 / 44	45	T66I/A (8), E92A/G/Q (4), S153A (2), N155H/S (6), R263K (3)

Hansen. CROI 2025. Abstr 724

QW: GS-1720 & GS-4182, WONDERS 1 study

- Phase II/III randomised study
- Oral QD GS-1720 + GS-4182 QW in virologically suppressed people living with HIV
- GS-1720 (a novel and potent INSTI) and GS-4182 (a novel oral prodrug of QW LEN) are being developed as a first-in-class QW oral INSTI + capsid inhibitor combination for HIV treatment



*Participants will receive a 1-day oral loading dose of GS-1720 (1,300 mg) and GS-4182 (600 mg) on Day 1

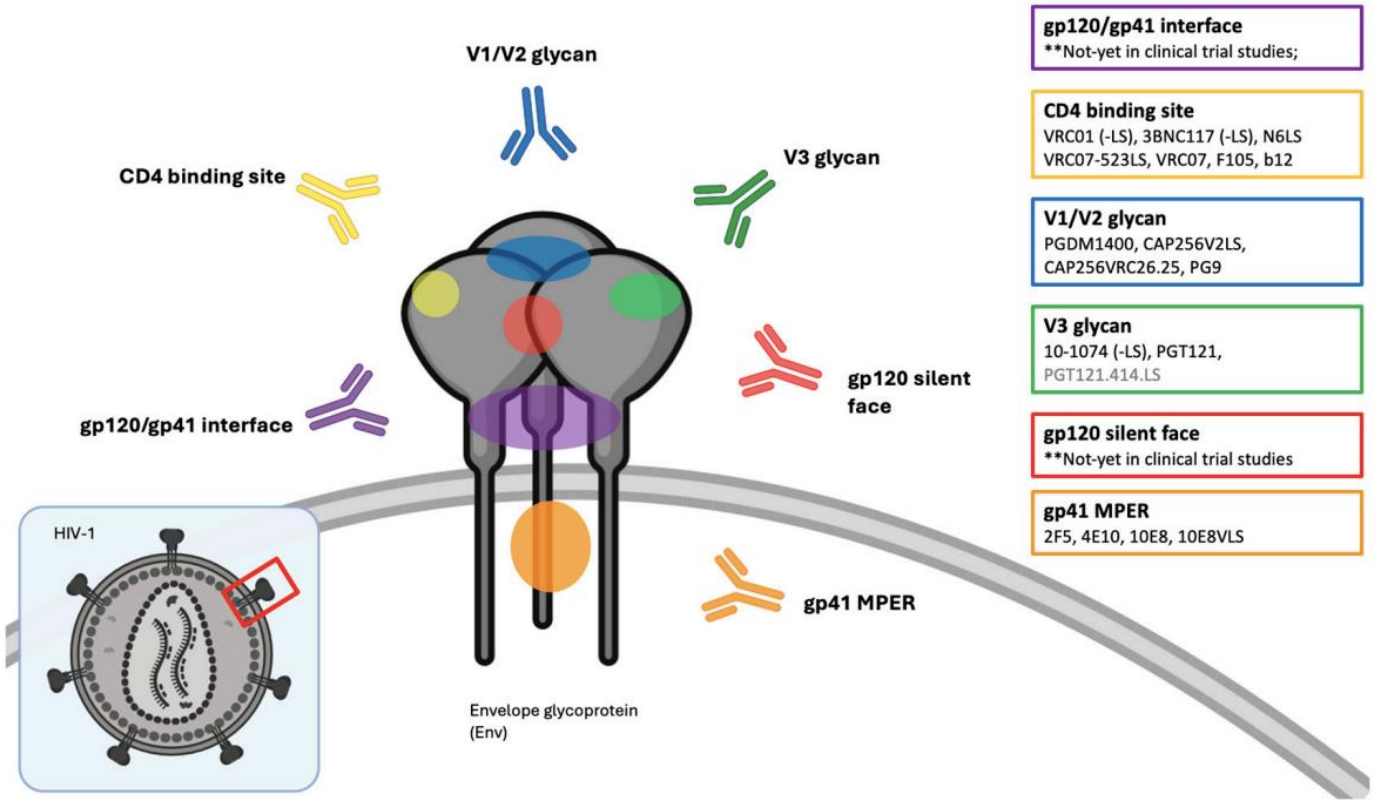
Outline

- What's new on the horizon?
- Oral options
- **Parenteral options**
- A reflection on the future of ART


Apri una parente e chiedi…cosa sono i bnAbs??

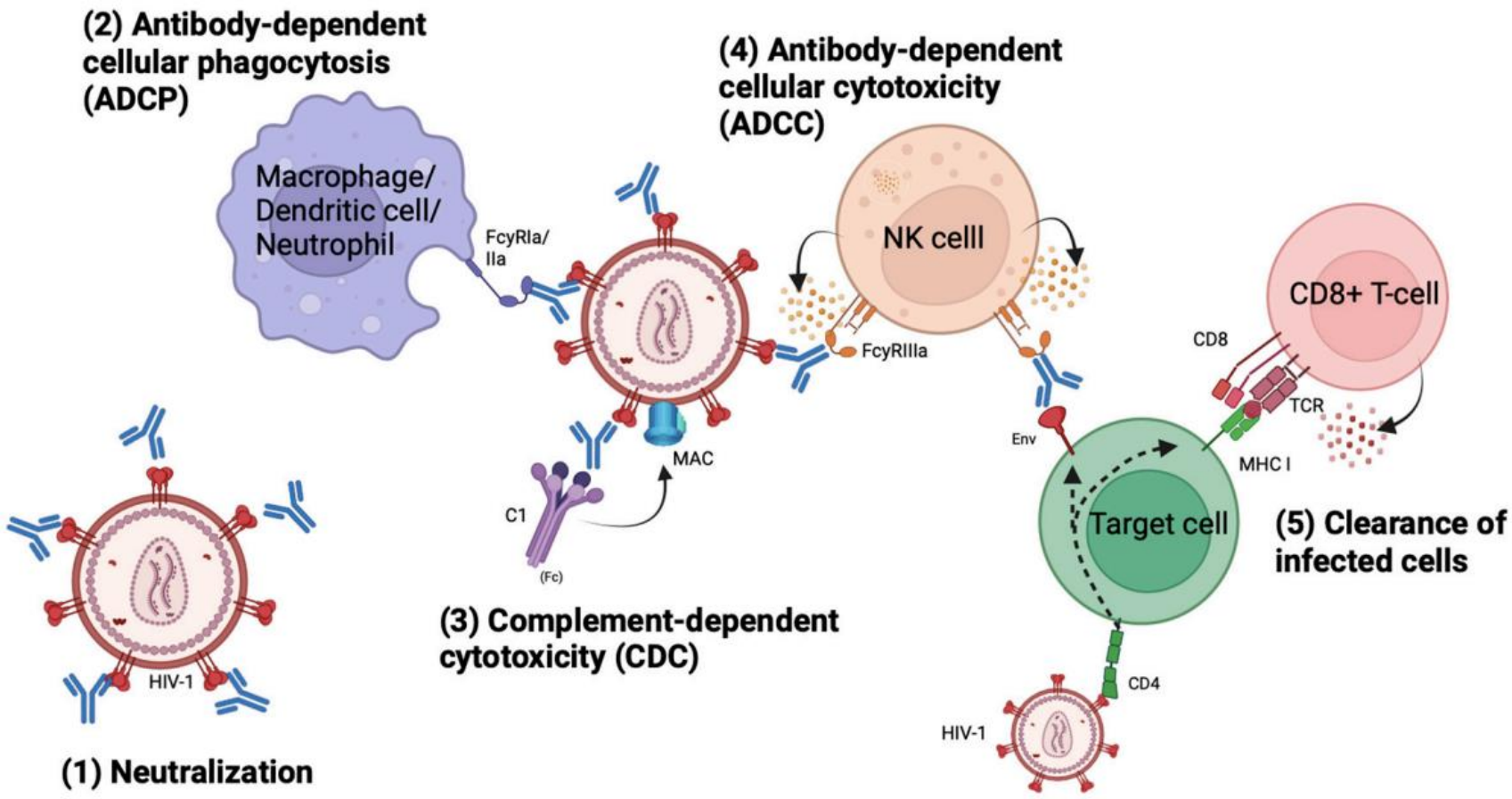
Broadly neutralizing antibodies

- Approximately 10–30% of individuals chronically infected with HIV-1 develop antibodies exhibiting exceptional breadth, capable of neutralizing a wide array of the circulating viral strains;
- These antibodies, termed ‘broadly neutralizing antibodies’ (bNAbs), target conserved regions



Thavarajah JJ. The Use of Broadly Neutralizing Antibodies (bNAbs) in HIV-1 Treatment and Prevention. Viruses. 2024

Mechanisms of action



Thavarajah JJ. The Use of Broadly Neutralizing Antibodies (bNAbs) in HIV-1 Treatment and Prevention. Viruses. 2024

Activity	Pros	Cons
Viral activity	Target conserved regions of HIV-1's envelope glycoprotein, neutralizing diverse strains	Effective only in if sensitive strains: pre-screening needed; Long-term suppression challenging without combination therapy (≥2 bnAbs)
Viral reservoirs	Some combinations have shown reductions in the intact proviral reservoir	Mixed results. BnAbs cannot fully eliminate the latent HIV reservoir
PK	Long half-life (less frequent dosing compared to current ART)	Potentially reduced penetration in tissue reservoirs, e.g. brain (0.1% plasma concentration in CSF)
Resistance	Neutralization sensitivity similar after viral rebound in AHI	Single bNAb use leads to rapid emergence of resistant strains

Q6M: LEN + 2 bNAbs, results of the Phase Ib study

- The HIV-1 capsid inhibitor LEN was evaluated in a twice-yearly combination regimen with the bNAb Teropavimab (TAB, GS-5423) and Zinlirvimab (ZAB, GS-2872) in a randomised Phase Ib study (NCT04811040)[1]
- Participants received LEN + TAB with a low or high dose of ZAB[1]

Virological results at Week 26 (FDA Snapshot)[1]

	LEN + TAB + ZAB 10 mg/kg (n=14)*	LEN + TAB + ZAB 30 mg/kg (n=16)
VL ≥50 c/mL, n	3	0
VL <50 c/mL, n	11	15
Absence of virological data Week 26*	0	1†

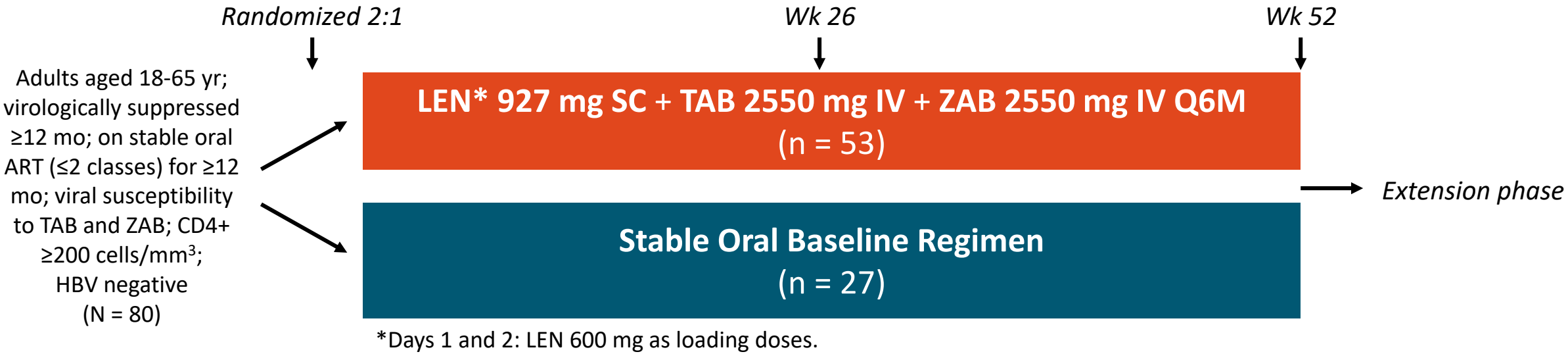
- None of the participants in the high dose ZAB group experienced virological rebound (VL ≥50 c/mL) at 6 months

→ • **All participants who received high-dose LEN, TAB and ZAB maintained viral suppression, with no differences in safety or tolerability between dose groups[1]**

*Reasons other than AE/death or lack of efficacy (e.g. discontinued study drug due to investigator's discretion, participant decision, lost to follow-up, non-compliance with study drug, protocol violation, pregnancy or study terminated by sponsor); †Withdrew from study after Week 12
TAB, teropavimab; **ZAB**, zinlirvimab
1. Cook PP, et al. HIV Glasgow. Abstract O23; **2**. NCT05729568. Available at: https://clinicaltrials.gov/study/NCT05729568. Accessed February 2025

Lenacapavir, Teropavimab, and Zinlirvimab for People Living With Virologically Suppressed HIV

- Multicenter, randomized phase II study; TAB and ZAB are investigational bNAbs



- **Primary endpoint:** HIV-1 RNA ≥50 copies/mL per FDA snapshot at Wk 26
- **Secondary outcomes:** safety; CD4+ cell count change from baseline; LEN, TAB, and ZAB pharmacokinetics; antidrug antibodies at Wk 26

Ogbuagu. CROI 2025. Abstr 151.

Slide credit: clinicaloptions.com

Baseline characteristics

	LEN, TAB, and ZAB n=53	Oral Stable Baseline Regimen n=27
Median (range) age, years	46 (20–65)	57 (28–65)
Female sex at birth, n (%)	8 (15)	4 (15)
Race, n (%)		
Asian	1 (2)	1 (4)
Black	21 (40)	8 (30)
White	28 (53)	16 (59)
Other	3 (6)	2 (7)
Hispanic or Latine ethnicity, n (%)	13 (25)	7 (26)
Median (range) weight, kg	93 (56–156)	87 (58–157)
Median (IQR) BMI, kg/m^2	29.2 (25.5–33.8)	29.2 (25.5–32.0)
Median (IQR) CD4+ T-cell count, cells/µL	710 (552–895)	738 (583–869)
USA region[a], n (%)	48 (91)	19 (70)

Lenacapavir, Teropavimab, and Zinlirvimab: Efficacy, Virologic Response, and Safety Outcomes at Wk 26

Parameter, n (%)	LEN + TAB + ZAB (n = 53)	Baseline ART (n = 27)
HIV-1 RNA ≥50 c/mL	1 (1.9)	0
HIV-1 RNA <50 c/mL	51 (96.2)	26 (96.3)
No virologic data in Wk 26 window*	1 (1.9)†	1 (3.7)‡

*Last available HIV-1 RNA <50 c/mL for both persons with no virologic data in window. †Discontinued early due to investigator discretion. ‡Discontinued early due to metastatic pancreatic carcinoma.

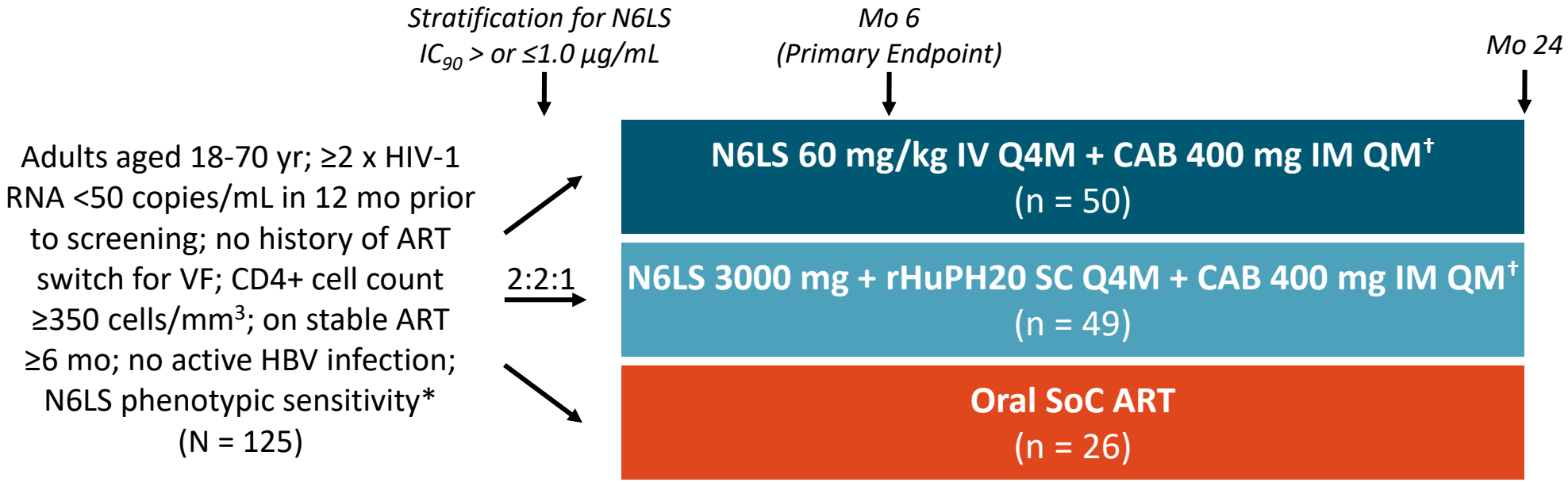
- Treatment-emergent ADAs:
  - Against TAB: n = 6 (11.3%)
  - Against ZAB: n = 9 (17%)
- Assay failure rate: 41/241
  - n = 99 of those assayed had susceptibility to TAB and ZAB

- 1 participant with virologic failure had detectable HIV-1 RNA at Wk 12 (resuppressed with no regimen change)
  - By Wk 12, LEN concentrations lower than 1 SD below mean
  - Wk 24:
    - Resistance to LEN detected (Q67H in capsid)
    - Loss of ZAB susceptibility; TAB susceptibility unchanged from baseline (both concentrations similar to mean through Wk 26)
  - Wk 29: restarted BIC/FTC/TAF
- Most common AEs were ISRs; most were grade 1

Ogbuagu. CROI 2025. Abstr 151.

EMBRACE: CAB IM + N6LS Either IV or SC for People Living With Virologically Suppressed HIV

- Multicenter, randomized, open-label phase IIb trial; N6LS is an investigational bNAb



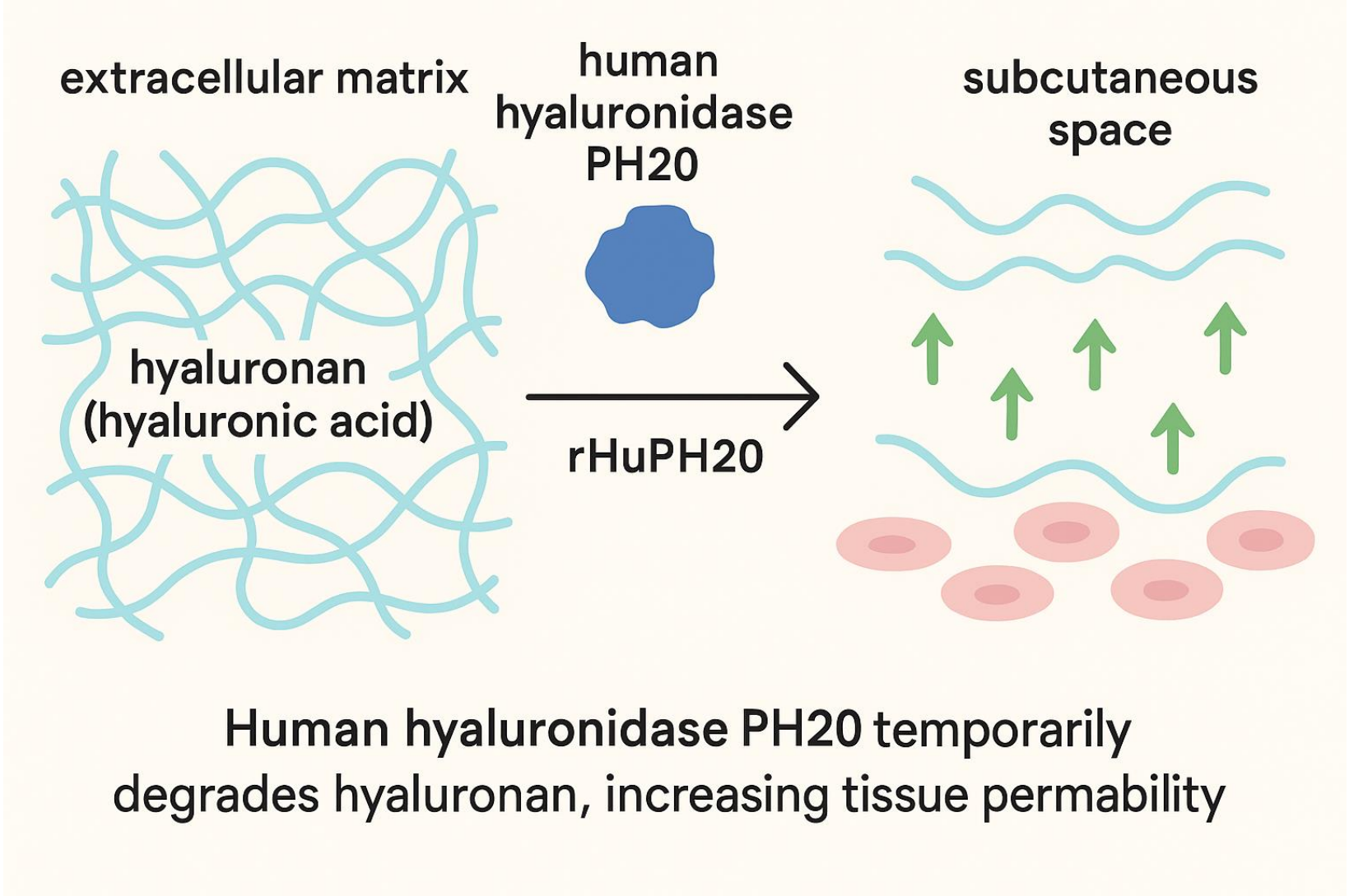
*IC_{90} ≤2.0 µg/mL and MPI >98% by PhenoSense mAb DNA assay. †CAB IM 600 mg loading dose given on Day 1.

- **Primary endpoint:** HIV-1 RNA ≥50 copies/mL at Mo 6 (FDA snapshot)
- **Key secondary endpoints:** CVF (2 consecutive HIV-1 RNA ≥200 copies/mL), CD4+ cell count response, ISR, safety

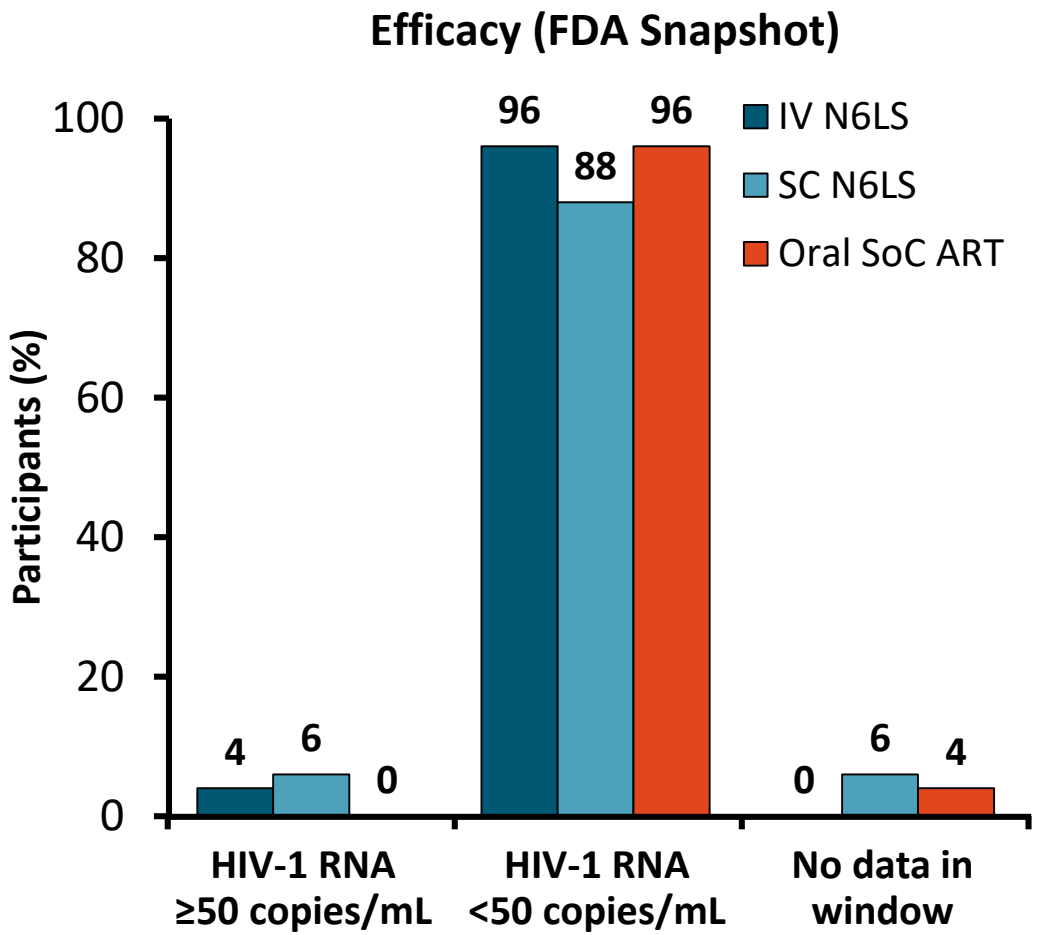
Taiwo. CROI 2025. Abstr 203. NCT05996471.

Slide credit: clinicaloptions.com

Activity of human hyaluronidase



EMBRACE: Efficacy, CVF, and Safety Outcomes at Mo 6

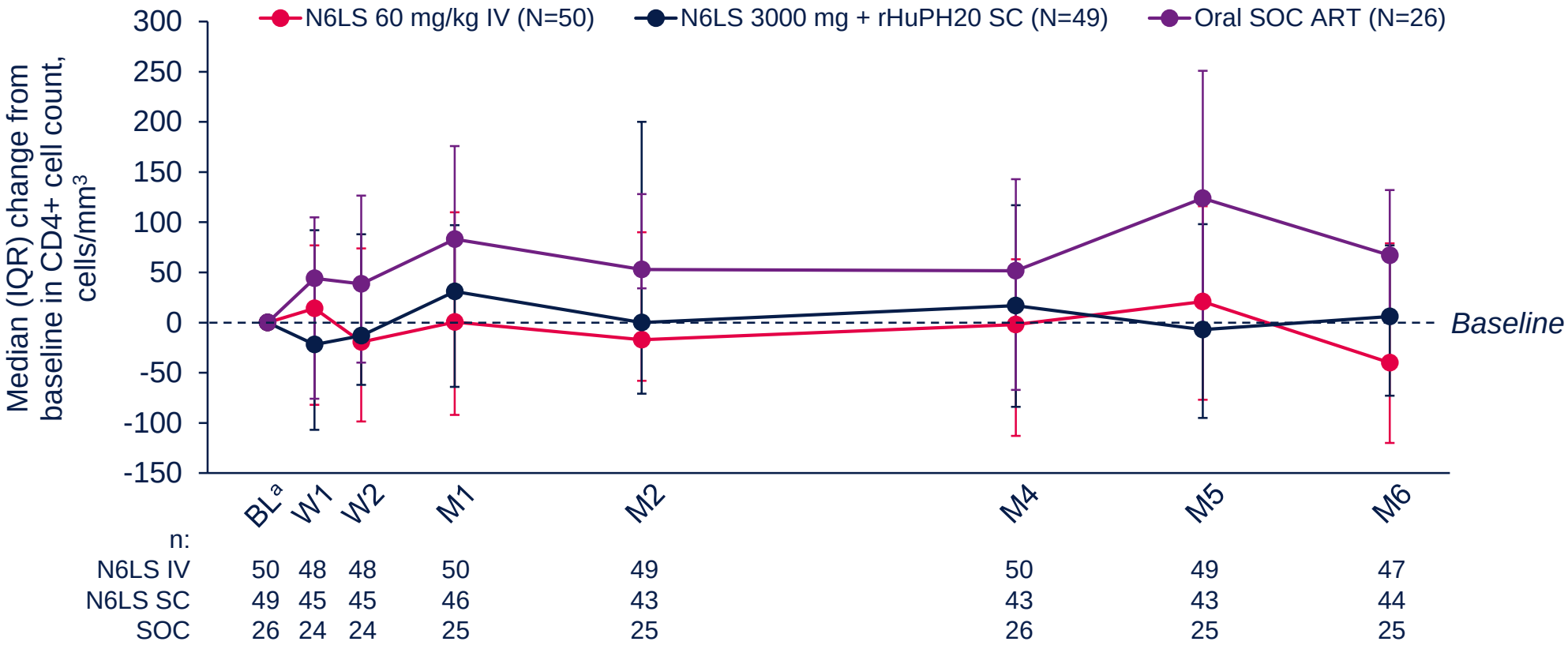


- 4 of 5 participants with HIV-1 RNA ≥50 c/mL met CVF criteria
  - **IV N6LS** arm (n = 2): neither with INSTI RAMs; both with N6LS IC_{90} >2 µg/mL
  - **SC N6LS** arm (n = 2): 1 participant with INSTI RAM; neither with N6LS IC_{90} >2 µg/mL
  - All with CVF resuppressed with SOC ART
- No AEs leading to withdrawal in IV arm; no serious AEs related to CAB or N6LS
  - ISRs less frequent with **IV** vs **SC** N6LS

IV N6LS Q6M + LA CAB selected for continued evaluation in part 2 of EMBRACE

Taiwo. CROI 2025. Abstr 203.

No Trend Was Observed for Median Change From Baseline in CD4+ Cell Count Through Month 6



ART, antiretroviral therapy; BL, baseline; IV, intravenous; N6LS, VH3810109; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SOC, standard of care.

[a]Median (range) CD4+ cell count at baseline: N6LS IV, 602 (309-1210) cells/mm^3; N6LS SC, 759 (351-1635) cells/mm^3; SOC, 644 (307-1174) cells/mm^3.

Taiwo. CROI 2025. Abstr 203.

Safety Summary

Participants, n (%)	N6LS 60 mg/kg IV (N=50)	N6LS 3000 mg + rHuPH20 SC SC (N=49)	Oral SOC ART (N=26)
Any AE[a]	46 (92)	40 (82)	17 (65)
Grade 1-2	41 (82)	23 (47)	15 (58)
Grade 3	5 (10)	15 (31)	1 (4)
Grade 4	0	2 (4)	1 (4)
N6LS/CAB-related AEs	32 (64)	32 (65)	–
Grade 3	0	8 (16)[b]	–
Grade 4	0	0	–
Any serious AE	0	3 (6)	2 (8)
N6LS/CAB-related serious AEs serious AEs	0	0	–
AEs leading to withdrawal	0	3 (6)[c]	0

- N6LS was generally well tolerated when given IV, with no AEs leading to withdrawal and no N6LS- or CAB-related serious AEs reported
- Participants receiving N6LS SC had 3 serious AEs and 3 AEs leading to withdrawal
- CAB LA QM safety and tolerability were consistent with product label

AE, adverse event; ART, antiretroviral therapy; CAB, cabotegravir; IV, intravenous; LA, long-acting; N6LS, VH3810109; QM, every month; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SOC, standard of care.

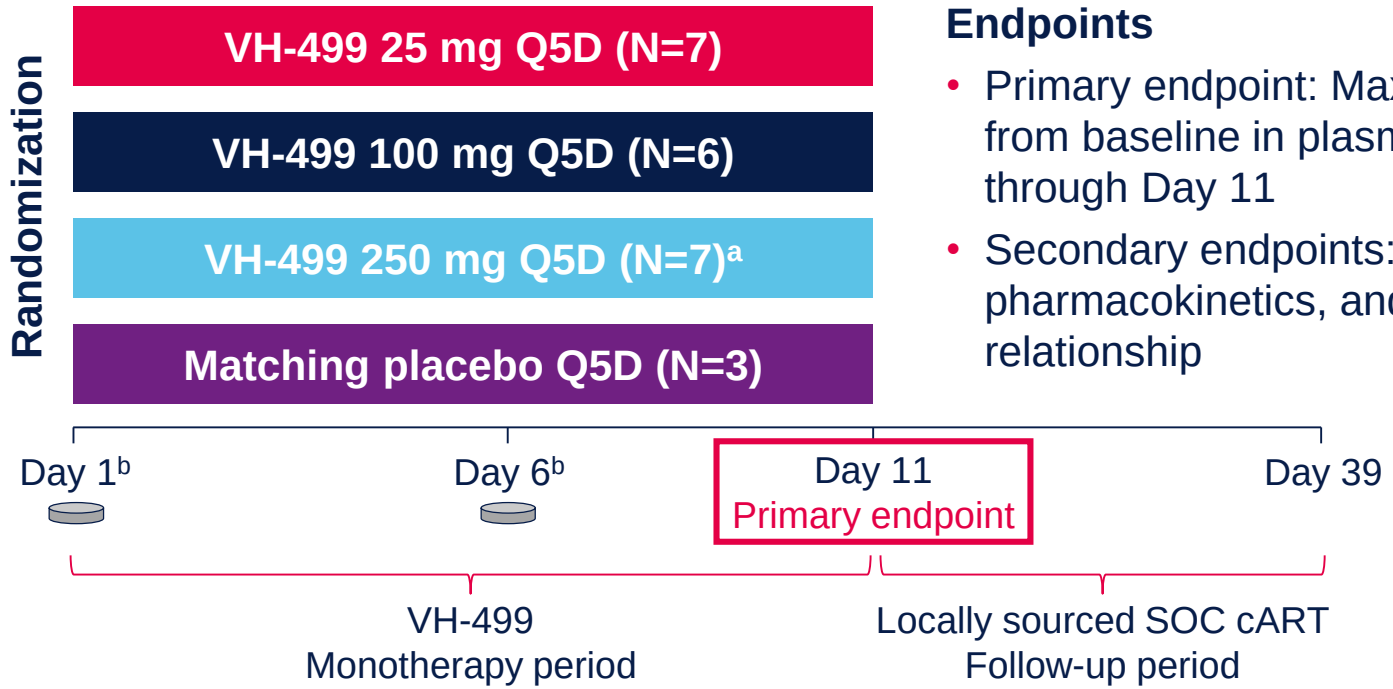
[a]AEs occurring in ≥10% of participants receiving N6LS IV included injection site pain, fatigue, COVID-19, increased lipase, and headache. AEs occurring in ≥10% of participants receiving N6LS SC included infusion site erythema, injection site pain, infusion site pain, infusion site induration, infusion site swelling, and injection site nodule. [b]Included infusion site erythema (n=6), infusion site swelling (n=3), infusion site induration (n=2), and injection site pain (n=1). [c]Included CAB-associated injection site pain (n=1), hepatitis B reactivation (n=1), and anxiety and depression (n=1).

Proof-of-Concept Trial of Oral VH4011499 (VH-499), a New HIV-1 Capsid Inhibitor

Double-blind, randomized, placebo-controlled, adaptive, proof-of-concept, phase 2a study

Inclusion criteria

- Aged 18-65 years
- Naive to ART
- HIV-1 RNA ≥3000 c/mL
- CD4+ cell count ≥200 cells/mm^3
- BMI 18.5-31.0 kg/m^2



Endpoints

- Primary endpoint: Maximum change from baseline in plasma HIV-1 RNA through Day 11
- Secondary endpoints: Safety, tolerability, pharmacokinetics, and exposure-response relationship

ART, antiretroviral therapy; BMI, body mass index; cART, combination ART; Q5D, every 5 days; SOC, standard of care; VH-499, VH4011499.

[a]The decision to proceed with the VH-499 250 mg dose in part 2 was determined by an informal interim analysis conducted after participants completed their Day 11 visit in part 1 (VH-499 25 mg, n=7; VH-499 100 mg, n=6; placebo, n=2).
[b]Participants received oral VH-499 or matching placebo on Day 1 (baseline) and Day 6.

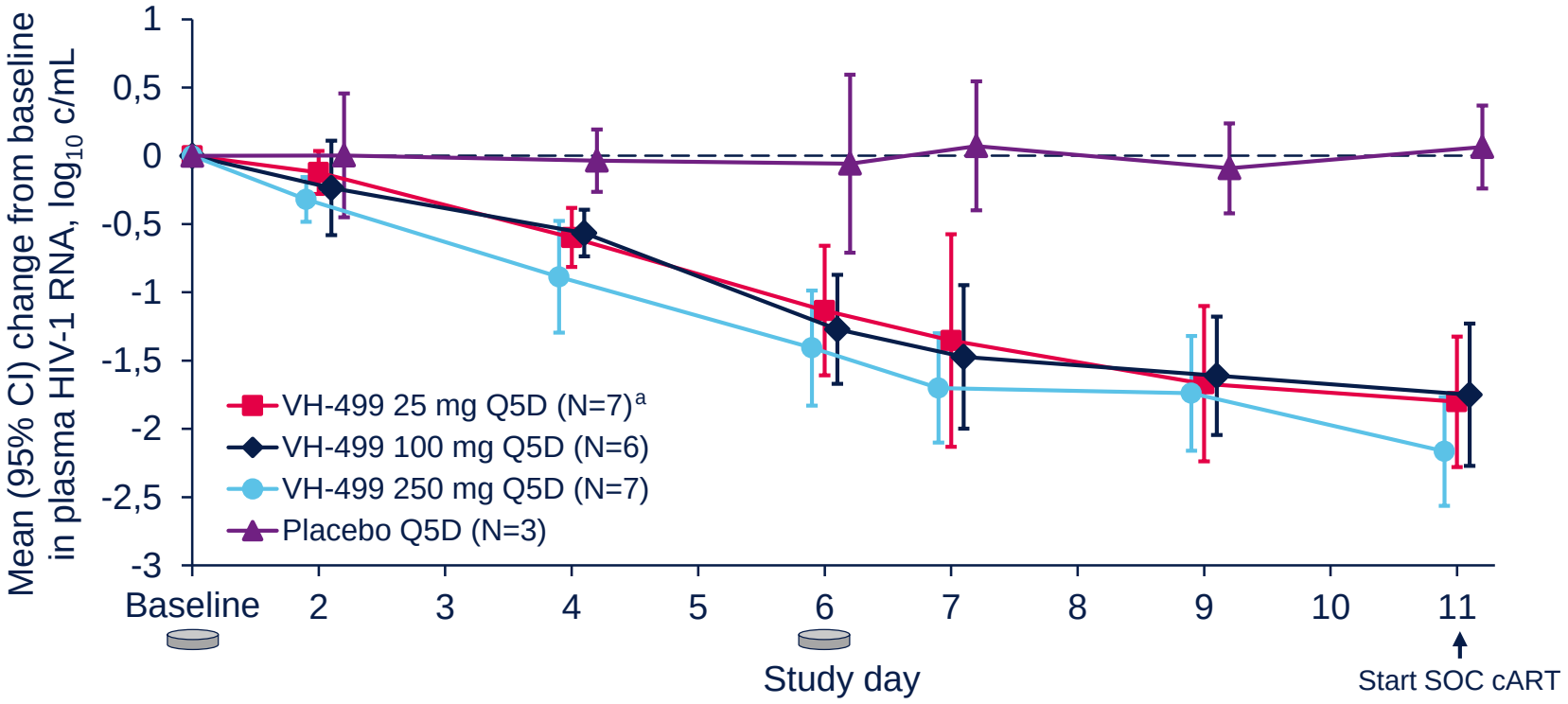
Participant Demographics and Baseline Characteristics

Parameter	VH-499 25 mg Q5D (N=7)	VH-499 100 mg Q5D (N=6)	VH-499 250 mg Q5D (N=7)	Placebo Q5D (N=3)	Total (N=23)
Age, median (range), y	31 (20-46)	48 (41-62)	25 (18-48)	27 (23-28)	31 (18-62)
Male, n (%)[a]	7 (100)	3 (50)	6 (86)	3 (100)	19 (83)
Race, n (%)					
American Indian or Alaska Native	0	0	4 (57)	0	4 (17)
Black or African American	0	3 (50)	0	1 (33)	4 (17)
White	7 (100)	3 (50)	3 (43)	2 (67)	15 (65)
Ethnicity, Hispanic or Latin American, n (%)	5 (71)	1 (17)	7 (100)	2 (67)	15 (65)
Body mass index, median (range), kg/m^2	24.5 (21.4-29.1)	25.0 (21.6-30.0)	24.3 (20.9-30.7)	24.2 (23.5-26.3)	24.3 (20.9-30.7)
Baseline CD4+ cell count, median (IQR), $cells/mm^3$	489 (338, 655)	462 (425, 546)	481 (236, 734)	1027 (468, 1411)	481 (416, 655)
Baseline plasma HIV-1 RNA, median (IQR), log_{10} c/mL	4.85 (4.53, 5.66)	4.21 (3.92, 5.03)	5.18 (4.38, 5.64)	5.11 (3.82, 5.21)	4.85 (3.98, 5.21)

Q5D, every 5 days; VH-499, VH4011499.

[a]Sex assigned at birth.

Antiviral Activity



Plasma HIV-1 RNA change from baseline (FAS)	VH-499 25 mg Q5D (N=7)	VH-499 100 mg Q5D (N=6)	VH-499 250 mg Q5D (N=7)	Placebo Q5D (N=3)
Maximum change, mean (SD), log_{10} c/mL	−1.83 (0.51)	−1.80 (0.45)	−2.17 (0.43)	−0.18 (0.20)

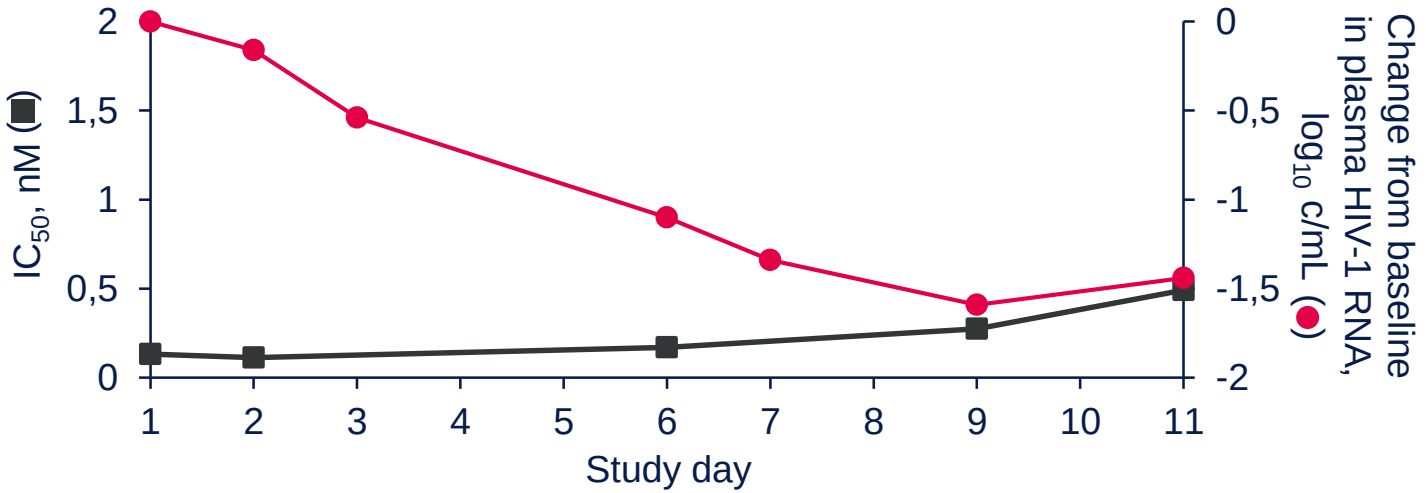
cART, combination ART; FAS, full analysis set; Q5D, every 5 days; SOC, standard of care; VH-499, VH4011499.

[a]n=6 for Days 2, 4, 7, and 9.

Majority (19/20) of Participants Had No Emergent Genotypic Capsid Inhibitor Resistance

- 19/20 participants receiving VH-499 Q5D had no emergent genotypic capsid inhibitor RAMs during monotherapy
- 1 participant receiving VH-499 25 mg Q5D had **an emergent capsid inhibitor RAM (Q67Q/H)** with a 3.9-fold loss of phenotypic sensitivity by Day 11
  - This participant achieved undetectable viral load (<50 c/mL) on SOC ART (DTG/3TC)

Resistance summary and viral load in participant with emergent resistance to VH-499



ART, antiretroviral therapy; DTG/3TC, dolutegravir/lamivudine; IC_{50}, half-maximal inhibitory concentration; NA, not available; Q5D, every 5 days; RAM, resistance-associated mutation; SOC, standard of care; VH-499, VH4011499.

Favorable Safety Profile

Participants reporting AEs during the monotherapy period, n (%)	VH-499 25 mg Q5D (N=7)	VH-499 100 mg Q5D (N=6)	VH-499 250 mg Q5D (N=7)	Total VH-499 Q5D (N=20)	Placebo Q5D (N=3)
Any AE	2 (29)	4 (67)	2 (29)	8 (40)	1 (33)
Grade 1	1 (14)	3 (50)	2 (29)	6 (30)	1 (33)
Grade 2	1 (14)	1 (17)	0	2 (10)	0
Grade 3-5	0	0	0	0	0
AEs reported in >1 participant					
Headache	1 (14)	1 (17)	1 (14)	3 (15)	1 (33)
Vessel puncture site hematoma	0	1 (17)	2 (29)	3 (15)	0
Drug-related AEs	0	3 (50)[a]	0	3 (15)	0

- No trends were observed in types of AEs, and each drug-related AE was only reported once
- No AEs leading to withdrawal, serious AEs, or deaths were reported
- There were no clinically relevant changes in laboratory parameters (eg, lipids, liver biochemistry), electrocardiograms, or vital signs

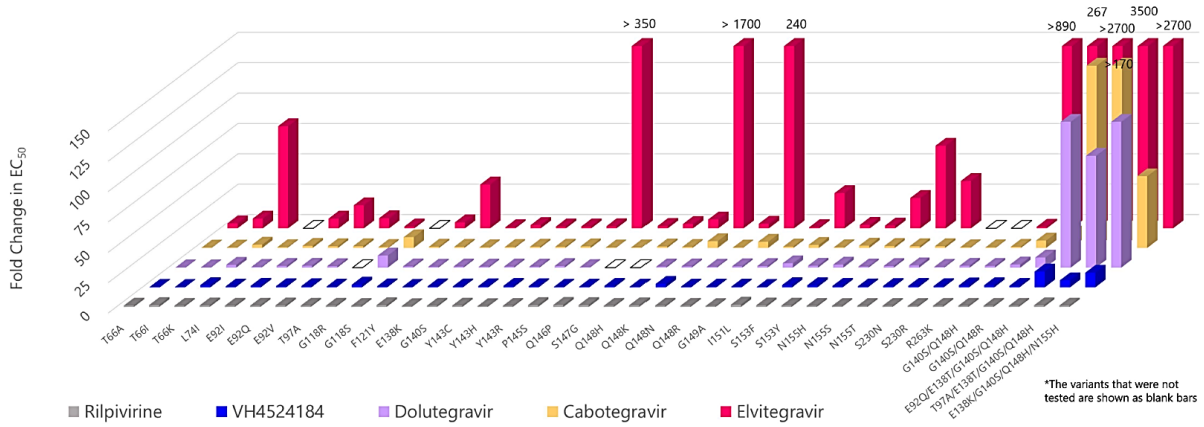
AE, adverse event; Q5D, every 5 days; VH-499, VH4011499.

[a]3 participants reported 8 drug-related AEs.

Q6M: VH-184, new third-generation INI

- *In vitro* characterisation of VH-184: The anti-HIV-1 activity of VH-184 was assessed by assaying it against laboratory strains of HIV NL432
  and clinical isolates using MT4 cells and/or PBMC[1]
- VH-184 exhibits anti-HIV activity comparable to that of DTG and CAB, and a superior resistance profile that retained antiviral activity against second-generation INSTI-resistant isolates[1]
- Phase I study: Double-blind, randomised, placebo-controlled, first-in-human study of VH-184 in adults without HIV-1[2]
- During Phase I, 84 participants were included (VH-184, n=63; placebo, n=21), all of whom completed the study[2]
- 44 AEs were reported in 29 participants and were generally mild, and none were serious[2]

Antiviral activity of VH-184 against a panel of HIV-1 molecular clones exhibiting INSTI-RAMs*[1]



→ **$t_{1/2}$: 22–28 hours; PK parameters increased by 1.5- to 1.8-fold when comparing administration of VH-184**
100 mg under fed vs fasted conditions

→ **Ongoing: Phase IIa oral trial in people living with HIV**
and phase I LA injectable in participants without HIV

VH-184 is a third-generation INI with LA potential and a resistance profile different from second-generation INIs
1

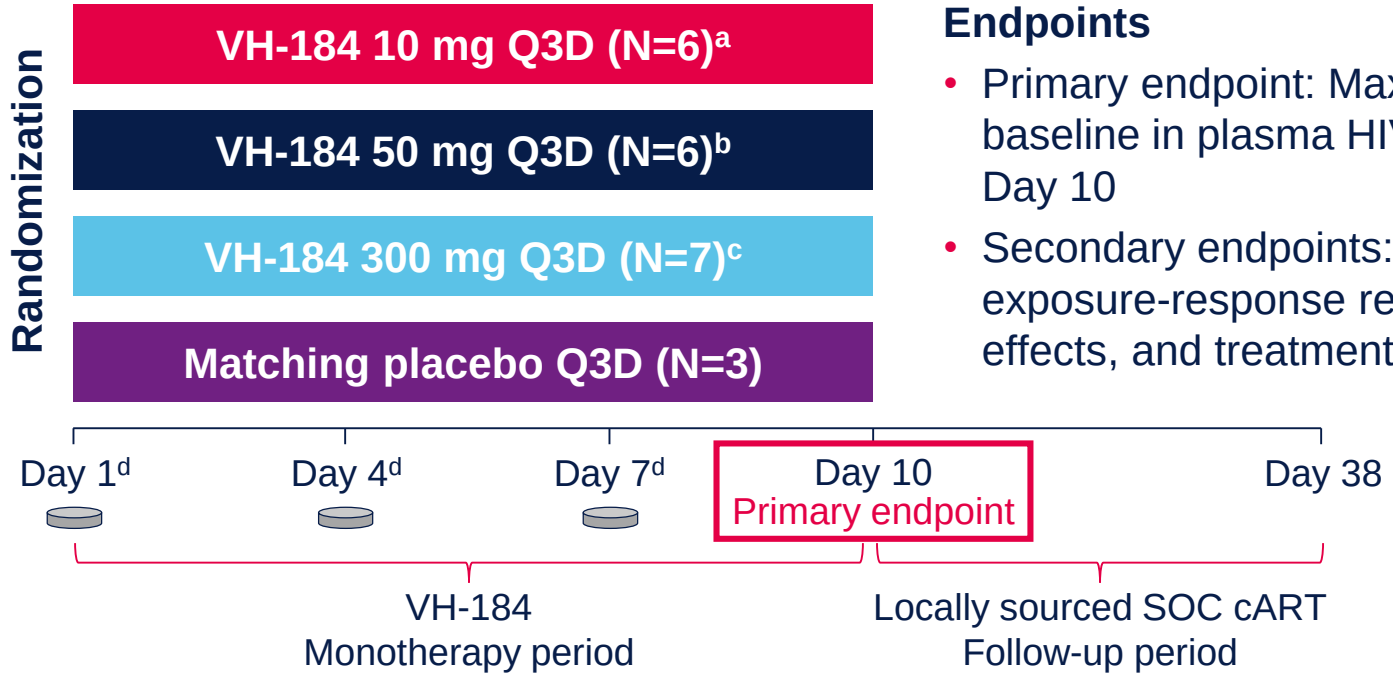
***Variants that have not been tested are indicated by blank bars
PBMC, peripheral blood mononuclear cell
1. Seki T, et al. AIDS 2024. WEPEB114; **2.** Rogg L, et al. AIDS 2024. Oral OAB2603

Phase 2a Study Design

Double-blind, randomized, placebo-controlled, proof-of-concept, phase 2a study

Inclusion criteria

- Aged 18-65 years
- Naive to ART
- HIV-1 RNA ≥3000 c/mL
- CD4+ cell count ≥200 cells/mm^3
- BMI 18.5-31.0 kg/m^2



Endpoints

- Primary endpoint: Maximum change from baseline in plasma HIV-1 RNA through Day 10
- Secondary endpoints: Safety, tolerability, exposure-response relationship, immunologic effects, and treatment-emergent resistance

ART, antiretroviral therapy; BMI, body mass index; cART, combination ART; PA-IC$_{90}$, protein-adjusted 90% inhibitory concentration; Q3D, every 3 days; SOC, standard of care; VH-184, VH4524184.

[a]Target concentration of 1 × PA-IC$_{90}$. [b]Target concentration of 4 × PA-IC$_{90}$. [c]Target concentration of 24 × PA-IC$_{90}$. [d]Participants received oral VH-184 or matching placebo on Days 1 (baseline), 4, and 7.

Participant Demographics and Baseline Characteristics

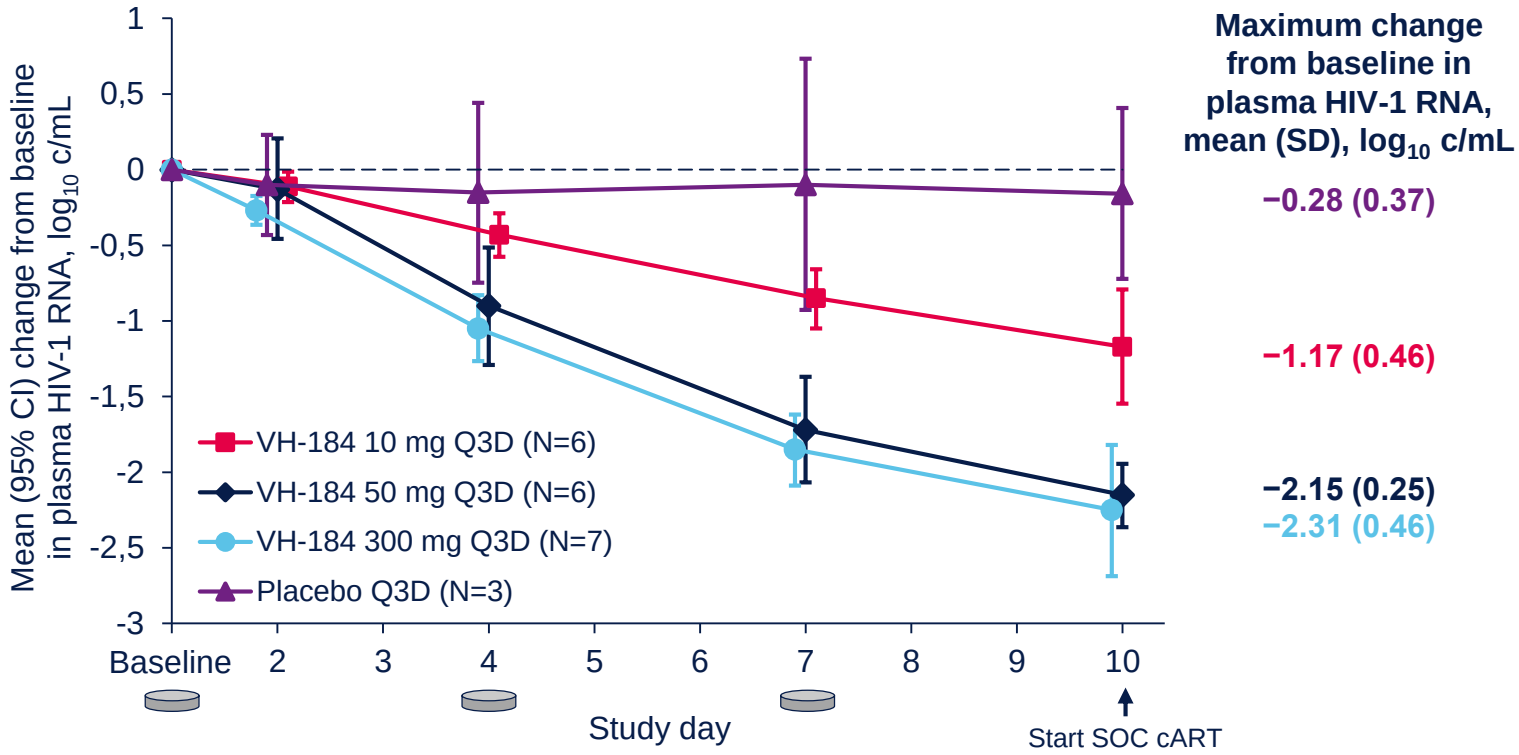
Parameter	VH-184 10 mg Q3D (N=6)	VH-184 50 mg Q3D (N=6)	VH-184 300 mg Q3D (N=7)	Placebo Q3D (N=3)	Total (N=22)
Age, median (range), y	34 (21-51)	33 (19-59)	31 (23-60)	31 (25-32)	32 (19-60)
Male, n (%)[a]	6 (100)	4 (67)	6 (86)	3 (100)	19 (86)
Race, n (%)					
American Indian or Alaska Native	1 (17)	0	2 (29)	0	3 (14)
Asian	0	1 (17)	0	0	1 (5)
Black or African American	1 (17)	0	0	2 (67)	3 (14)
White	4 (67)	5 (83)	5 (71)	1 (33)	15 (68)
Ethnicity, Hispanic or Latin American, n (%)	3 (50)	2 (33)	7 (100)	1 (33)	13 (59)
Body mass index, mean (SD), kg/m^2	23.9 (2.5)	23.0 (2.1)	23.6 (2.7)	24.1 (3.1)	23.6 (2.4)
Baseline CD4+ cell count, mean (SD), $cells/mm^3$	387 (204)	596 (330)	491 (276)	661 (200)	—
Baseline plasma HIV-1 RNA, mean (SD), log_{10} c/mL	5.00 (0.79)	4.74 (0.73)	4.32 (0.67)	4.42 (0.93)	—

Q3D, every 3 days; VH-184, VH4524184.

[a]Sex assigned at birth.

Rapid and Highly Potent Antiviral Activity, with No Resistance

- Antiviral activity[a]
  - All VH-184 doses reduced plasma HIV-1 RNA levels from baseline through Day 10
  - These decreases are similar to those seen with DTG monotherapy (−1.51 to −2.46 log_{10} c/mL)[1]
- Resistance
  - No genotypic or phenotypic resistance to VH-184 was detected at the end of the monotherapy period (Day 10)



cART, combination antiretroviral therapy; DTG, dolutegravir; Q3D, every 3 days; SOC, standard of care; VH-184, VH4524184.

[a]Full analysis set.

1. Min et al. *AIDS*. 2011;25:1737-1745.

VH-184 Was Well Tolerated and Had a Favorable Safety Profile

Participants reporting AEs during the monotherapy period, n (%)	VH-184 10 mg Q3D (N=6)	VH-184 50 mg Q3D (N=6)	VH-184 300 mg Q3D (N=7)	Total VH-184 Q3D (N=19)	Placebo Q3D (N=3)
Any AE	2 (33)	3 (50)	3 (43)	8 (42)	2 (67)
Grade 1	2 (33)	3 (50)	2 (29)	7 (37)	2 (67)
Grade 2	0	0	1 (14)[a]	1 (5)	0
Grade 3-5	0	0	0	0	0
AEs reported in >1 participant					
Vomiting	0	1 (17)	1 (14)	2 (11)	0
Drug-related AEs[b]	1 (17)	2 (33)	2 (29)	5 (26)	0

- There were no observable trends in types of AEs; each drug-related AE was reported in 1 participant
- No serious AEs, AEs leading to withdrawal, or deaths were reported during the study period
- There were no clinically relevant changes in laboratory parameters, electrocardiograms, or vital signs

AE, adverse event; Q3D, every 3 days; VH-184, VH4524184.

[a]Non–drug-related AE of influenza-like illness was reported as grade 2 in the monotherapy period, improved to grade 1 during the follow-up period, and resolved 9 days after initial onset. [b]All drug-related AEs were grade 1 (n=1 event each diarrhea, dizziness, fatigue, increased amylase, increased lipase, nausea, and vomiting).

Pipeline: Phase IIa Proof-of Concept Studies

VH-184: Third-Generation INSTI[1,2]

- In vitro activity demonstrated to DTG-and CAB-resistant viruses
- Maximum change from baseline in HIV-1 RNA through Day 10: >2 $\log_{10}$ c/mL decline with 50-mg and 300-mg doses
- AEs grade 1/2; no serious AEs

Plan to investigate as LA injectable for HIV treatment

VH-499: HIV-1 Capsid Inhibitor[3]

- Maximum change from baseline in HIV-1 RNA through Day 11: 1.8-2.2 $\log_{10}$ c/mL decline (highest seen with 250-mg dose)
- 1 participant receiving VH-499 25 mg had an emergent capsid inhibitor RAM (Q67Q/H)
- AEs grade 1/2; no serious AEs

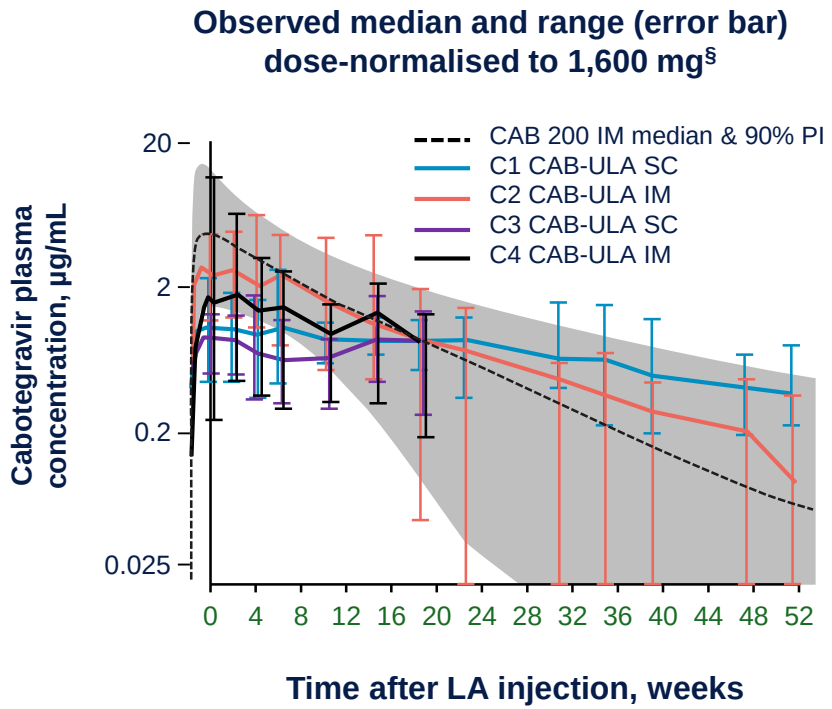
Plan to investigate as LA injectable for HIV treatment

1. Rogg. CROI 2025. Abstr 152. 2. Rogg. AIDS 2024. Abstr OAB2603. 3. Grisel. CROI 2025. Abstr 153.

Q4M: New ultra-long-acting formulation of cabotegravir (CAB-ULA)

- Phase I dose-escalation study evaluating CAB 200 mg/ml SC + recombinant human hyaluronidase PH20 and CAB-ULA* SC or IM, in adults without HIV (aged 18–55 years), BMI 18–32 kg/m^2
- Study of PK, safety, tolerance, after single administration, over 52 weeks

Part A	Dose CAB200 (+ rHuPH20 10,000 IU)	Method of administration	N
A1	800 mg (4 mL)	SC†	10
A2	1 600 mg (8 mL)	SC†	10
A3	3 200 mg (16 mL)	SC†	2
Part B	Not achieved – dosing strategy has not progressed		
Part C	**Dose CAB-ULA**	**Method of administration**	**N**
C1	800 mg (2 mL)	SC†	8
C2	800 mg (2 mL)	IM‡	8
C3	1 200 mg (3 rnL)	SC†	8
C4	1 200 mg (3 ml)	IM‡	8
C5	1 600 mg (3 mL)	IM‡	16



*CAB-ULA is a new formulation with higher CAB concentration than approved CAB200; †Abdominal; ‡Gluteus medius; §Error bars before Week 2 are not displayed for visibility
CAB200, CAB 200 mg/mL; **IM,** intramuscular; **LA,** long acting; **PI,** prediction interval; **rHuPH20,** recombinant human hyaluronidase PH20
Han K, et al. CROI 2024. Abstract 130

Q4M: New ultra-long-acting formulation of cabotegravir (CAB-ULA)

- **CAB 200 SC + rHuPH20:[1]**
  - ISR grade is dose-dependent, increasing grade with increasing CAB dose
  - ISRs occurred in all patients (n=22/22 patients) → **development not continued**
- **CAB-ULA:[2]**
  - SC: ISRs occurred in 100% (16/16) of participants; most common were erythema, nodule and pain
  - IM: ISRs occurred in 69% (22/32) of participants; most common was pain and except for 1, all were mild (Grade 1)
  - Slower absorption and longer $t_{1/2}$ than CAB 200 mg/mL IM
  - CAB-ULA $t_{1/2}$ for SC and IM was predicted to be >6x and > 2x that of CAB200 IM, respectively*

→ • **New CAB-ULA formulation exhibits favourable tolerability and safety profiles with IM doses up to 1,600 mg[1]**

→ • **PK modelling predicts better plasma exposure with CAB-ULA IM at dose interval ≥4 months versus approved CAB200 Q2M IM[1]**

→ • **Ongoing: Further development of CAB-ULA Q4M IM for PrEP and treatment[1]**

→ • **Development in combination with RPV ULA Q4M (data not available) by IM route[2]**

***Current follow-up time is insufficient to calculate final $t_{1/2}$ value for CAB-ULA

Q4M, every 4 months

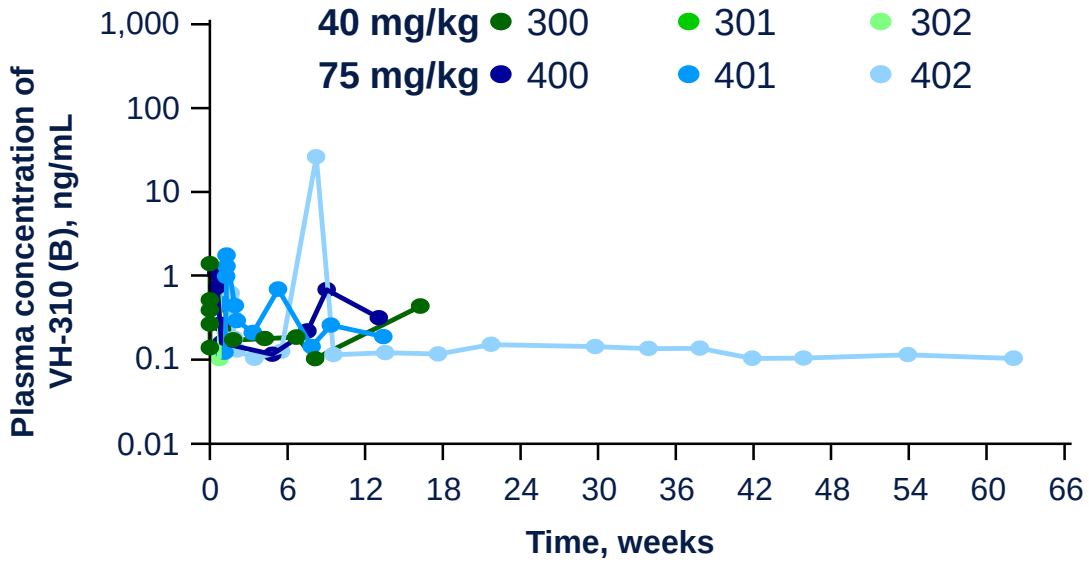
1. Han K, et al. CROI 2024. Abstract 130; **2.** Ghosn J. Personal communication. February 2025

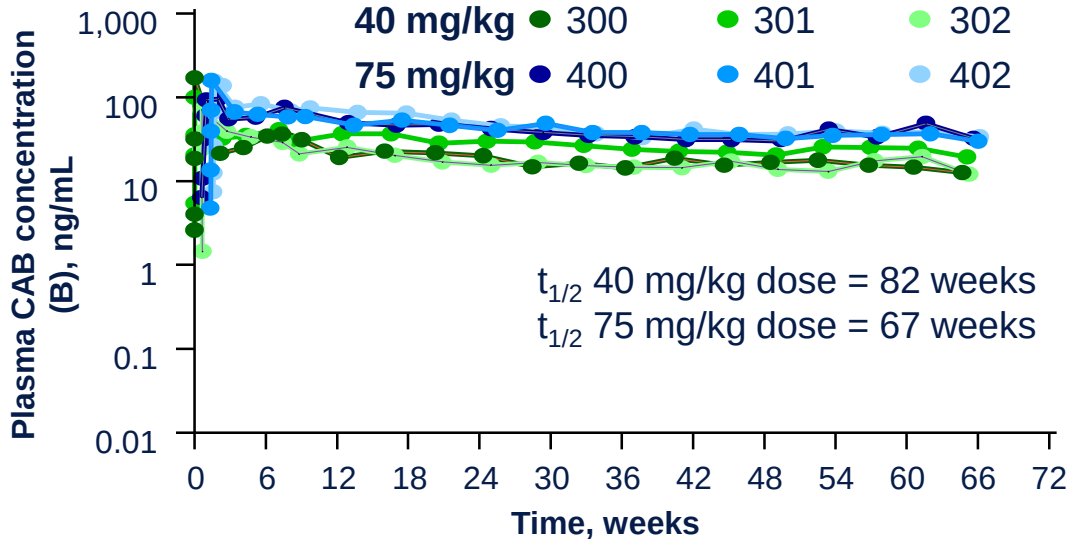
These representations/data refer to unpublished data, which can be made available upon request

Q6M: VH-310, prodrug of CAB, animal data

- Two new formulations (A and B) of VH-310, a prodrug of CAB, were studied pre-clinically in SC administration in rats (n=3 for each formulation; 75 mg/kg) and macaques (n=3 for each formulation; 40 and 75 mg/kg)[1]
- Preclinical data suggests an apparent half-life >28 weeks in humans → formulations allowing SC injection every 6 months[1]
- VH-310 was well tolerated in rats and macaques after SC injection[1]

Plasma concentration versus time curves in each macaque after injection of a single subcutaneous dose of VH-310 at 40 or 75 mg/kg for formulation B of VH-310 and formulation B of CAB[1]





→ **Upcoming: Potential use as injectable ARV ≥6 months[2]**

1. Baker M, et al. AIDS 2024. Poster WEPEA028
2. HIV Glasgow 2024. The long-acting HIV treatment era is just beginning. Available at: https://hivglasgow.org/the-long-acting-hiv-treatment-era-is-just-beginning/. Accessed February 2025

Outline

- What's new on the horizon?
- Oral options
- Parenteral options
- **A reflection on the future of ART**

Clinical Infectious Diseases
REVIEW ARTICLE

Challenges for Novel Antiretroviral Development in an Era of Widespread tenofovir-disoproxil/lamivudine (or emtricitabine)/dolutegravir availability (TLD) Availability

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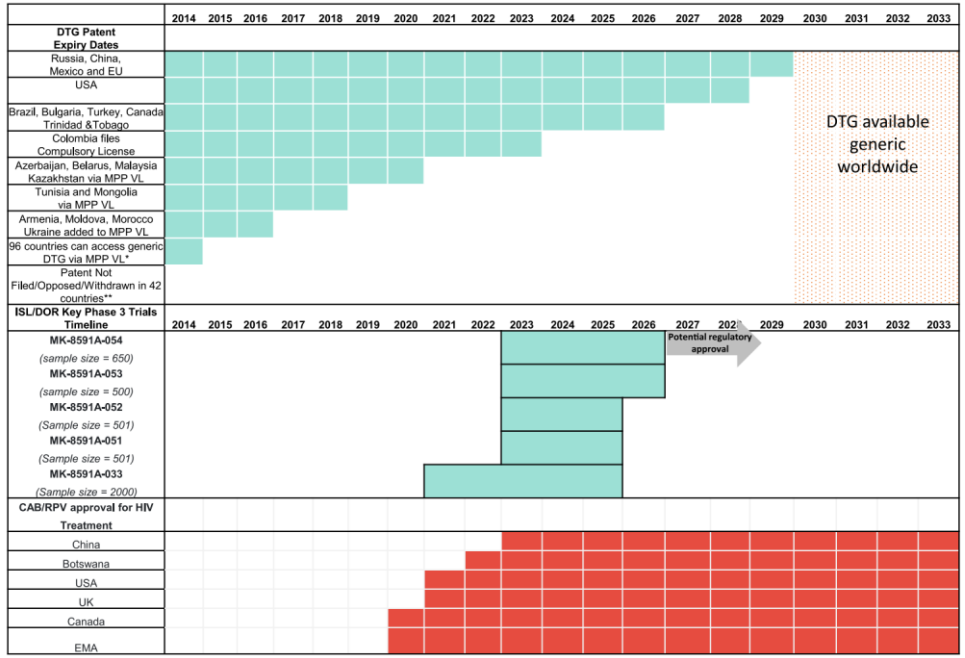
Eighth benchmark for which novel ART should aim:

- superior efficacy;
- high genetic barrier to resistance;
- safety in hepatitis B coinfection;
- favourable drug interaction profiles;
- HIV2 efficacy;
- safety in pregnancy,
- long-acting formulation availability and
- affordable pricing

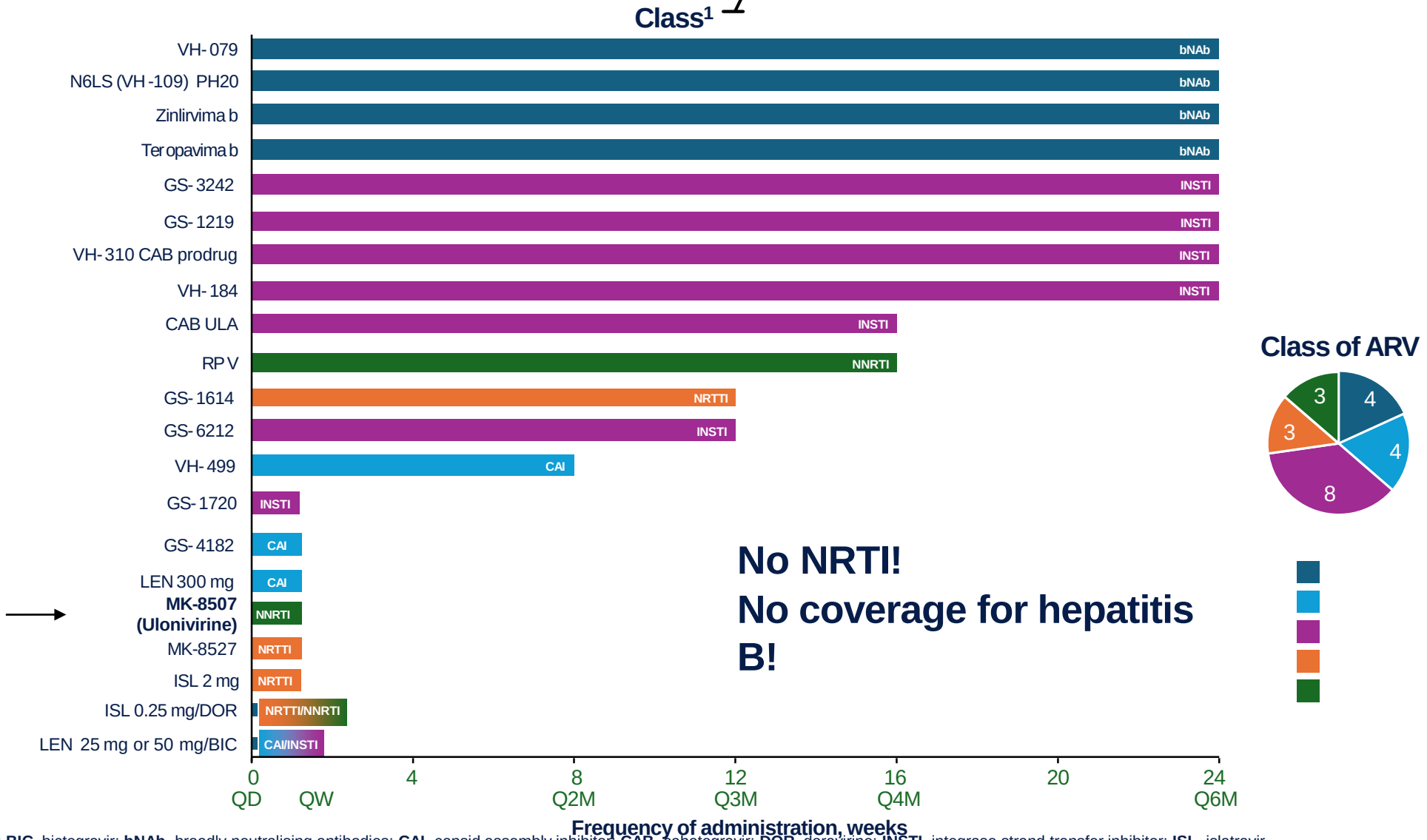


Comparison

	Benchmark	TDF/3TC/DTG	DOR/ISL	CAB/RPV
1	Efficacy in treatment-naive individuals	Unsurpassed	Likely noninferior to DTG + 2NRTI	Noninferior to DTG + 2NRTI
2	High genetic barrier to resistance	Yes	No	No
3	Safe in hepatitis B coinfection (hepatitis B surface antigen or hepatitis B virus DNA positive)	Yes	No	No
4	Effective against human immunodeficiency virus type 2	Yes	No	No
5	Safely coadministered with anti-tuberculosis medication	Yes	No	No
6	Acceptable safety in pregnancy	Yes	Insufficient data	Insufficient data
7	Course price per person per year	<45 (generic)	DOR $22 673–$5966 (no data for ISL)	$20 643–$11 771
8	Availability in long-acting formulations	Under investigation	Studies held: ISL with lenacapavir under investigation	Available in injectable monthly or 2-monthly formulation

Abbreviations: 3TC, lamivudine; CAB, cabotegravir; DOR, doravirine; DTG, dolutegravir; ISL, islatravir; NRTI, nucleoside reverse-transcriptase inhibitor; RPV, rilpivirine; TDF, tenofovir-disoproxil.

The pipeline by 'planned' administration and by class



ARV, antiretroviral; **BIC,** bictegravir; **bNAb,** broadly neutralising antibodies; **CAI,** capsid assembly inhibitor; **CAB,** cabotegravir; **DOR,** doravirine; **INSTI,** integrase strand transfer inhibitor; **ISL,** islatravir **LEN,** lenacapavir; **NNRTI,** non-nucleoside reverse transcriptase inhibitor; **NRTTI,** nucleoside reverse transcriptase translocation inhibitor; **RPV,** rilpivirine; **QD,** once daily; **QW,** once weekly; **QXM,** every X months **ULA,** ultra-long acting. **1.** Arribas J, et al. HIV Glasgow 2024. New treatments and future combinations; **2.** Merck. Merck Provides Update on Phase 2 Clinical Trial of Once-Weekly Investigational Combination of MK-8507 and Islatravir for the Treatment of People Living with HIV-1. Available at: https://www.merck.com/news/merck-provides-update-on-phase-2-clinical-trial-of-once-weekly-investigational-combination-of-mk-8507-and-islatravir-for-the-treatment-of-people-living-with-hiv-1/. Accessed February 2025

Conclusions

- Next generation antiretroviral regimens are of paramount importance:
  - In ameliorating quality of life in PLWH;
  - To offer newer options in those who are failing or not tolerating their regimen.

- Objective criteria to guide antiretroviral treatment decisions other than virological suppression are lacking, but fundamental for a personalized medicine

- From a strictly virological point of view, current treatment are unsurpassed in terms of potency. Is it time for a paradigm shift?


THANKS
FOR YOUR
ATTENTION