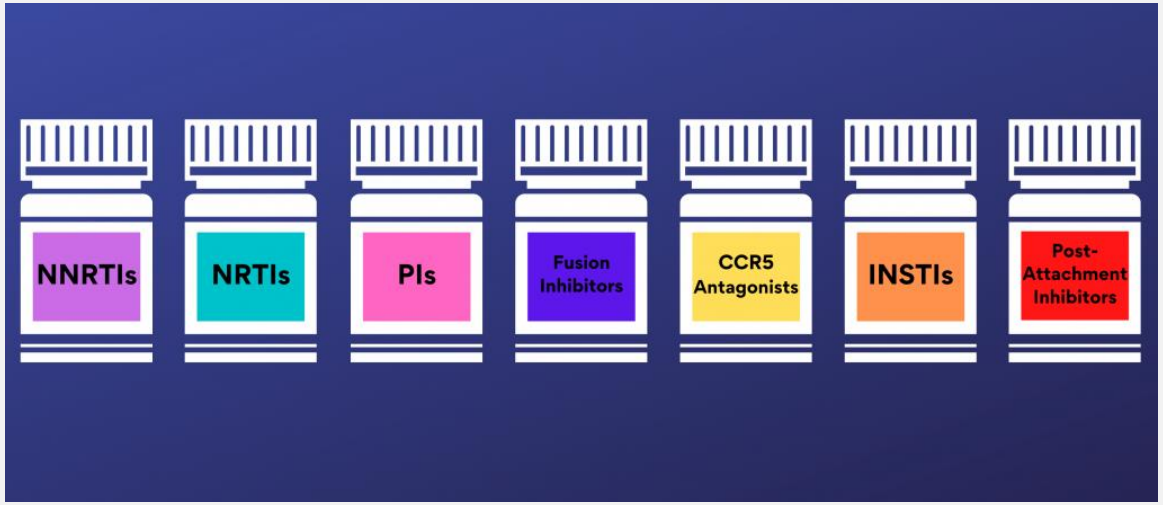

QUALE TERAPIA ANTI-HIV USEREMO DOPO-DOMANI?

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Disclosure of potential conflicts of interest

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

HIV Medication Chart

Combination Antiretrovirals

Single-Tablet Regimens

Atripla† (EFV/TDF/FTC)

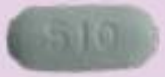
Biktarvy (BIC/TAF/FTC)

Complera (RPV/TDF/FTC)

Delstrigo (DOR/TDF/3TC)

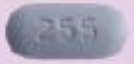
Dovato (DTG/3TC)

Genvoya (EVG/COBI/TAF/FTC)



Juluca (DTG/RPV)

Odefsey (RPV/TAF/FTC)



Stribild (EVG/COBI/TDF/FTC)

Symtuza (DRV/COBI/TAF/FTC)

Triumeq (DTG/ABC/3TC)

Long-Acting Injectable Regimens

Cabenuva (CAB/RPV)

Regimens Used in Combination with Other HIV Medications

Combivir† (ZDV/3TC)

Descovy (TAF/FTC)

Epzicom† (ABC/3TC)

Truvada† (TDF/FTC)

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)

Emtriva*† (emtricitabine, FTC)

Epivir*† (lamivudine, 3TC)

Viread*† (tenofovir DF, TDF)

Ziagen*† (abacavir, ABC)

Vemlidy (tenofovir alafenamide, TAF)
FDA approved for HBV only

Protease Inhibitors (PI)

Evotaz (ATV/COBI)

Kaletra* (lopinavir/ritonavir, LPV/RTV)

Prezcobix (DRV/COBI)

Prezista* (darunavir, DRV)

Reyataz*† (atazanavir, ATV)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

Edurant (rilpivirine, RPV)

Intelence† (etravirine, ETR)

Pifeltro (doravirine, DOR)

Sustiva† (efavirenz, EFV)

Viramune*† (nevirapine, NVP)

Entry Inhibitors

Rukobia (fostemsavir, FTR)
gp120 Attachment Inhibitor

Selzentry* (maraviroc, MVC)
CCR5 Antagonist

Trogarzo (ibalizumab, IBA)
Post-Attachment Inhibitor

Boosting Agents

Norvir†* (ritonavir, RTV)

Tybost (cobicistat, COBI)

Integrase Inhibitors (INSTI)

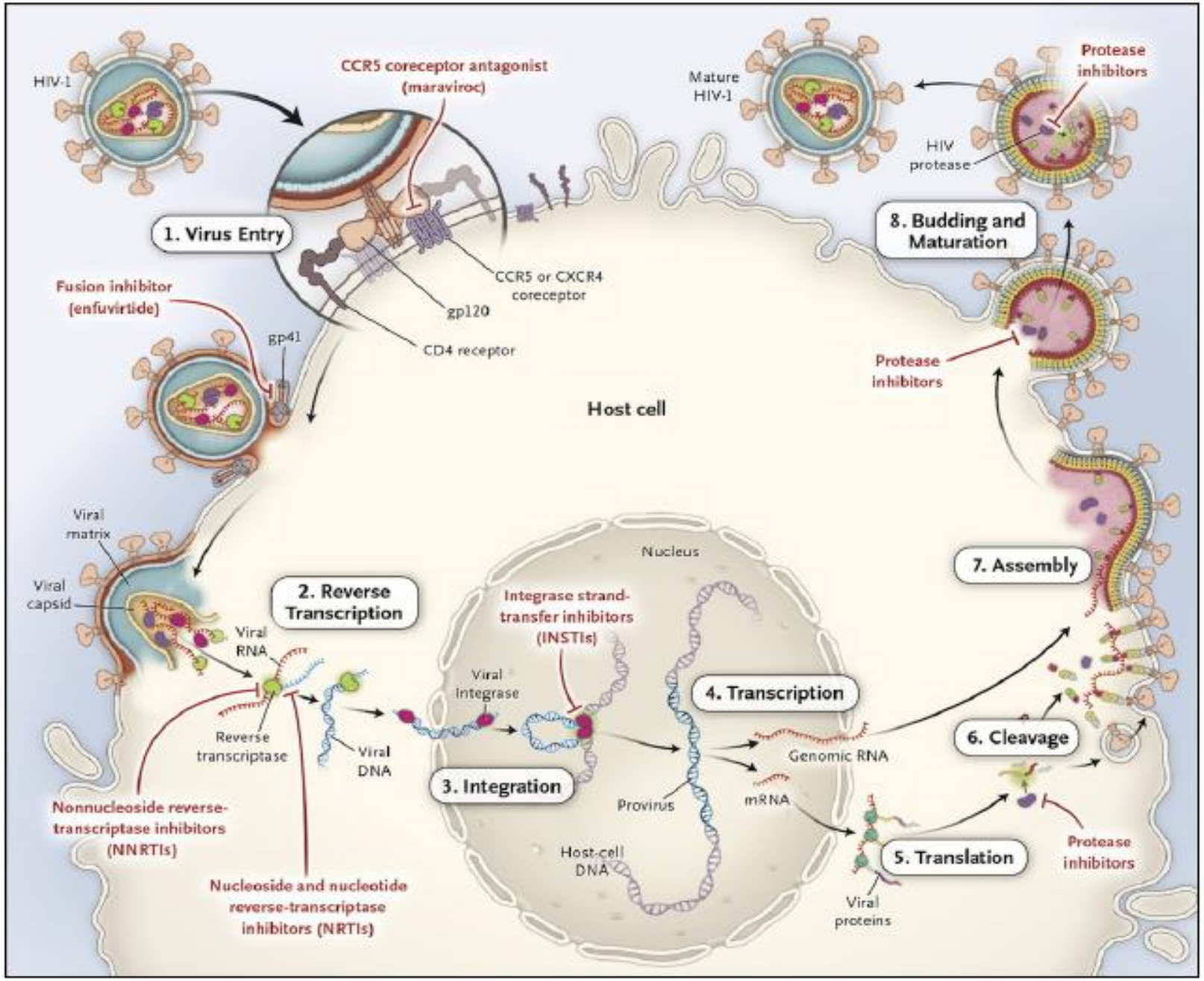
Isentress*▲ (raltegravir, RAL)

Isentress HD (raltegravir, RAL)

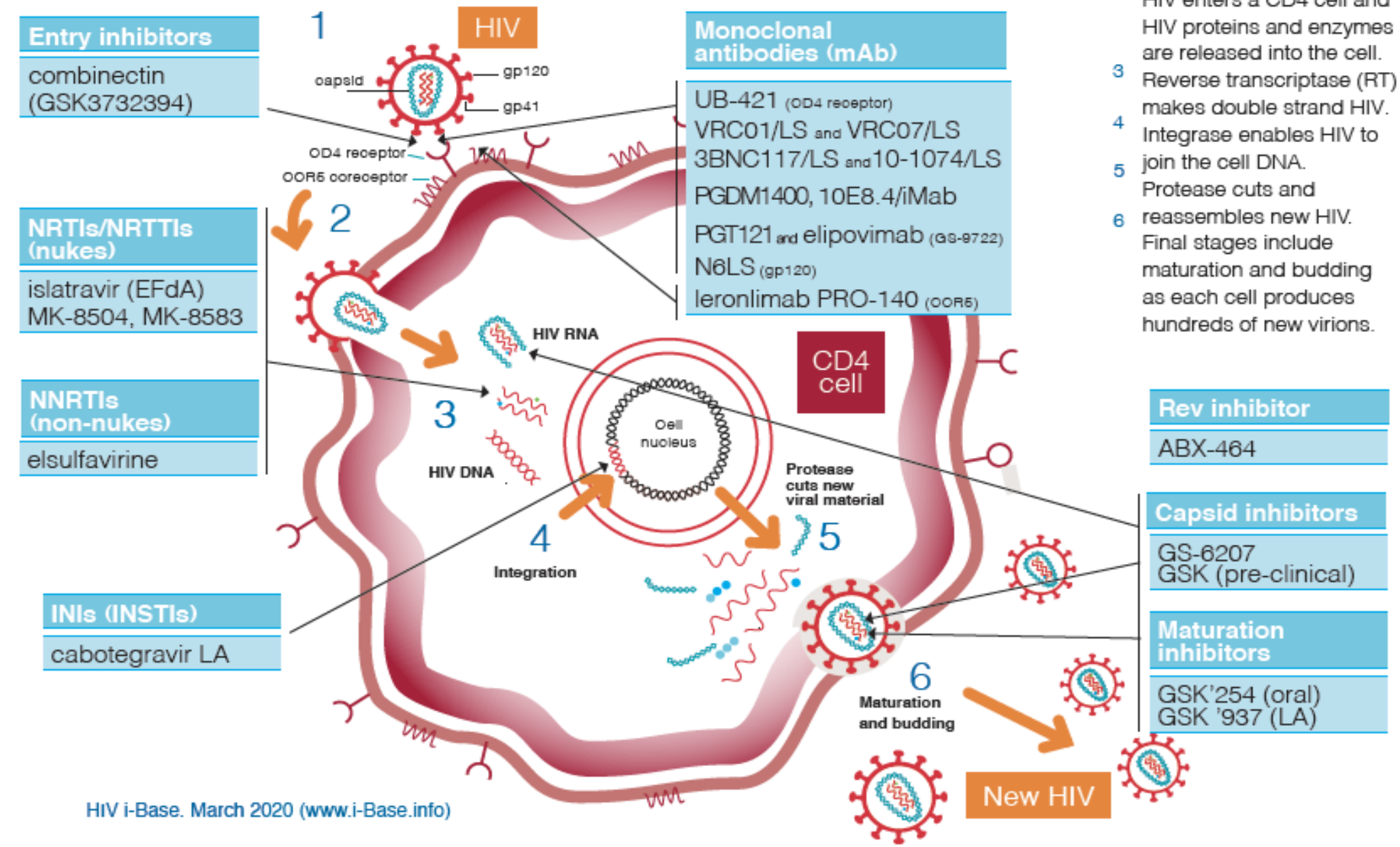
Tivicay* (dolutegravir, DTG)

Vocabria (cabotegravir, CAB)

THE HIV LIFE CYCLE AND ANTIRETROVIRAL DRUG TARGETS



HIV pipeline 2020: targets in the HIV lifecycle



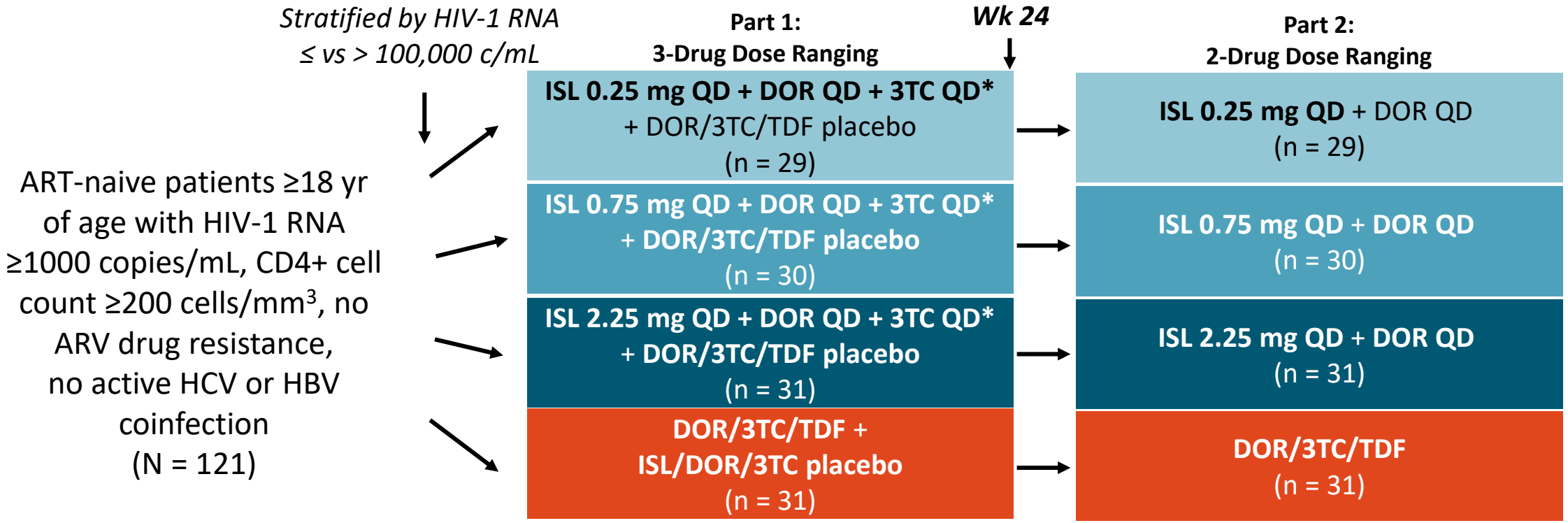
Targets in the HIV lifecycle

1. HIV attaches to a CD4 cell.
2. HIV enters a CD4 cell and HIV proteins and enzymes are released into the cell.
3. Reverse transcriptase (RT) makes double strand HIV.
4. Integrase enables HIV to join the cell DNA.
5. Protease cuts and
6. reassembles new HIV. Final stages include maturation and budding as each cell produces hundreds of new virions.

HIV i-Base. March 2020 (www.i-Base.info)

P011: Islatravir + Doravirine vs DOR/3TC/TDF in Treatment-Naive Adults

- **Islatravir: investigational nucleoside reverse transcriptase translocation inhibitor (NRTTI)**
- International, randomized, double-blind phase IIb trial

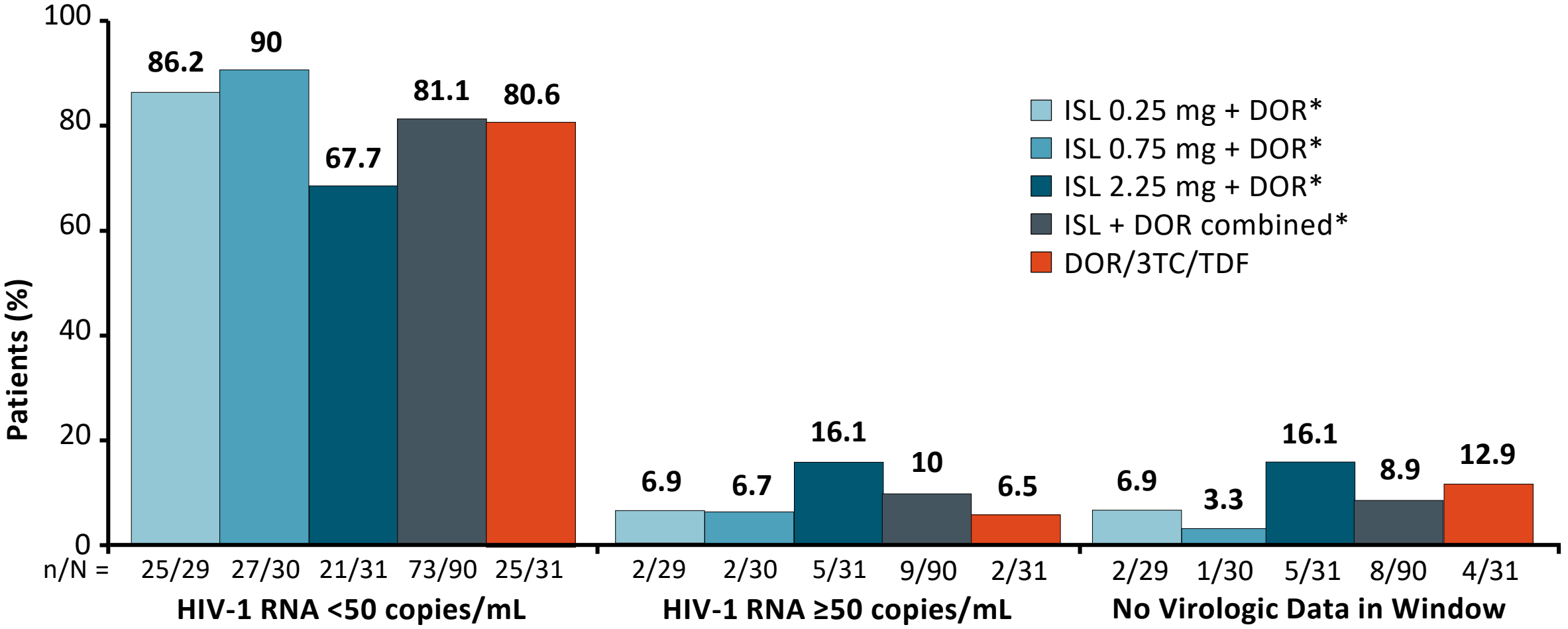


*Patients discontinued 3TC after 24 wk if HIV-1 RNA <50 copies/mL.

- Primary efficacy endpoints: HIV-1 RNA < 50 c/mL at Wk 24 and 48 (FDA Snapshot)

DeJesus. AIDS 2020. Abstr OAB0305.

P011: Virologic Outcomes With Islatravir + Doravirine Through Wk 96 (FDA Snapshot)



*Participants initially received ISL + DOR + 3TC and switched to ISL + DOR during the Wk 24-96 period of the study.

Molina. HIV Glasgow 2020. Abstr O415.

ISL Phase 2 and 3 Study Overviews

Study #	Phase	Population	Regimen Frequency	N	Sampling	Comparator *ISL Doses*	Labs
P016	2	HIV Prevention (Low Risk)	QM	~100/arm	36 weeks	Placebo ISL: *60 and 120 mg*	Lymphocytes
P011	2	Treatment Naive	QD	~30/arm	144 weeks	DOR/3TC/TDF DOR+ISL *0.25, 0.75, 2.25 mg*	Lymphocytes CD4+
P017	3	Virologically Suppressed	QD	~330/arm	48 weeks	Baseline ART DOR/ISL *0.75 mg*	Lymphocytes CD4+
P018	3	Virologically Suppressed	QD	~325/arm	48 weeks	BIC/FTC/TAF DOR/ISL *0.75 mg*	Lymphocytes CD4+

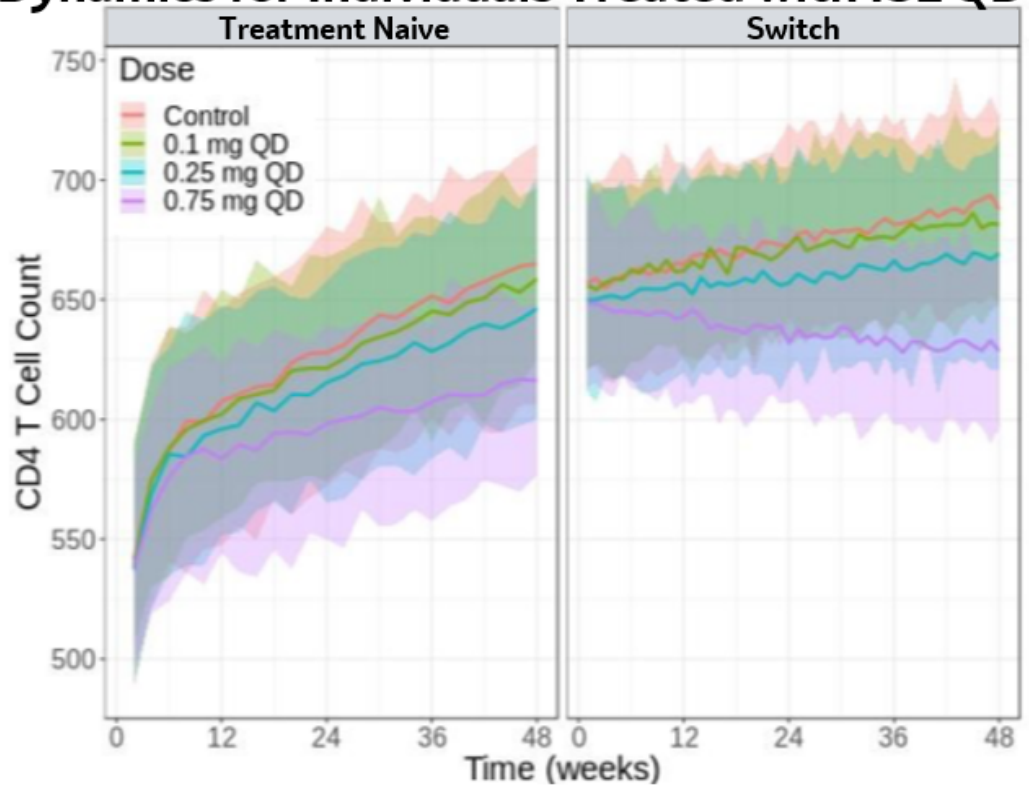
ISLATAVIR

- Exposure-related decreases in total lymphocytes and CD4+ T-cell counts were observed across ISL development programs
- ISL-TP preferentially accumulates in lymphocytes and high levels of ISL-TP leads to apoptosis
- ISL related reductions in lymphocyte and CD4+ T-cell counts are not related to mitochondrial toxicity
- Identify once daily (QD) doses of ISL that would be efficacious and not have effects on lymphocytes and CD4+ T cells
  - Developed lymphocyte and CD4+ T cells models relating intracellular ISL-TP concentrations with cell changes over time

Press release sept 2022. New Phase 3 studies will evaluate a once-daily oral combination of doravirine 100 mg and a lower dose of islatravir (DOR/ISL).

Predicted CD4+ T cell Increases for ISL 0.25 mg QD are Similar to Standard ART

Clinical Trial Simulation of Predicted CD4+ T cell counts Dynamics for Individuals Treated with ISL QD



Week 48 Predicted CD4+ T Cell: Count & Ratio of ISL vs Control

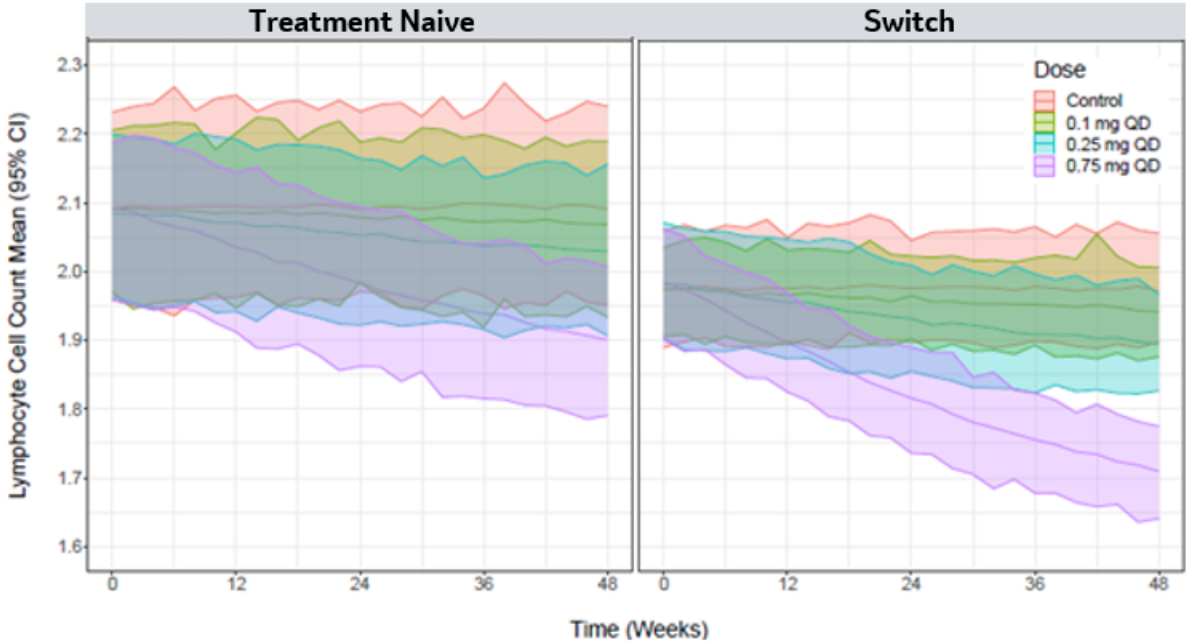
Mean (95% PI)

ISL QD Dose (mg)	Predicted CD4+ T Cell Count	Predicted Change from BL ISL : Control Ratio
Standard ART	719 (664, 766)	-
0.1	713 (671, 752)	0.992 (0.931, 1.07)
0.25	**700 (649, 753)**	**0.984 (0.914, 1.05)**
0.75	668 (630, 711)	0.934 (0.876, 0.994)

BL: baseline, CI: confidence interval, PI: predicted intervals

Predicted Lymphocytes Increases for ISL 0.25 mg QD are Similar to Standard ART

Clinical Trial Simulation of Predicted Lymphocyte Cell Count Dynamics for Individuals Treated with ISL QD



Week 48 Predicted Lymphocytes: Count & Ratio of ISL vs Control

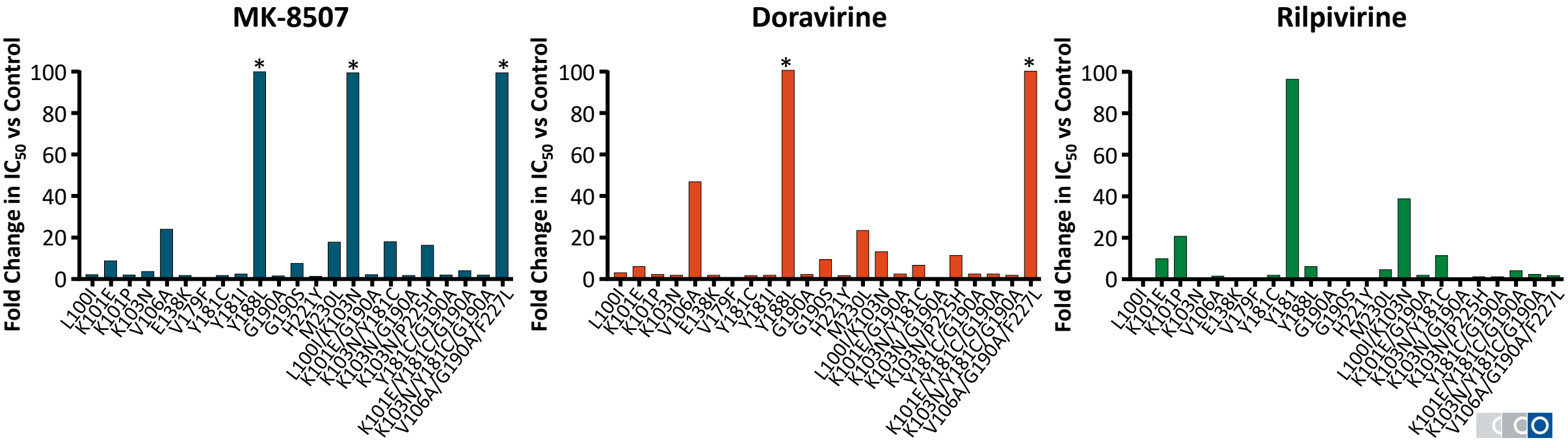
Mean (95% PI)

ISL QD Dose (mg)	Predicted Lymphocyte Cell Count	Predicted Change from BL ISL : Control Ratio
Standard ART	1.97 (1.90, 2.06)	-
0.1	1.94 (1.88, 2.01)	0.993 (0.942, 1.05)
0.25	**1.89 (1.83, 1.97)**	**0.975 (0.927, 1.03)**
0.75	1.71 (1.64, 1.77)	0.910 (0.870, 0.963)

BL: baseline, CI: confidence interval

MK-8507: Investigational Next-Generation NNRTI

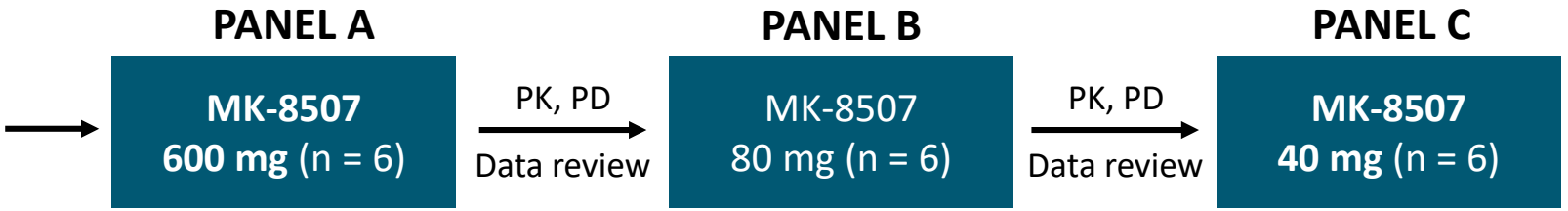
- MK-8507 active across HIV-1 subtypes and against common NNRTI RASs (K103N, Y181C, G190A)
- IC_{50} for WT HIV-1: 51.3 nM; similar activity (<1.5-fold change in IC_{50}) across HIV-1 subtypes
- Resistance profile similar to DOR, distinct from RPV
  - V106A primary mutation with subtype B, V106M primary mutation with subtypes A and C



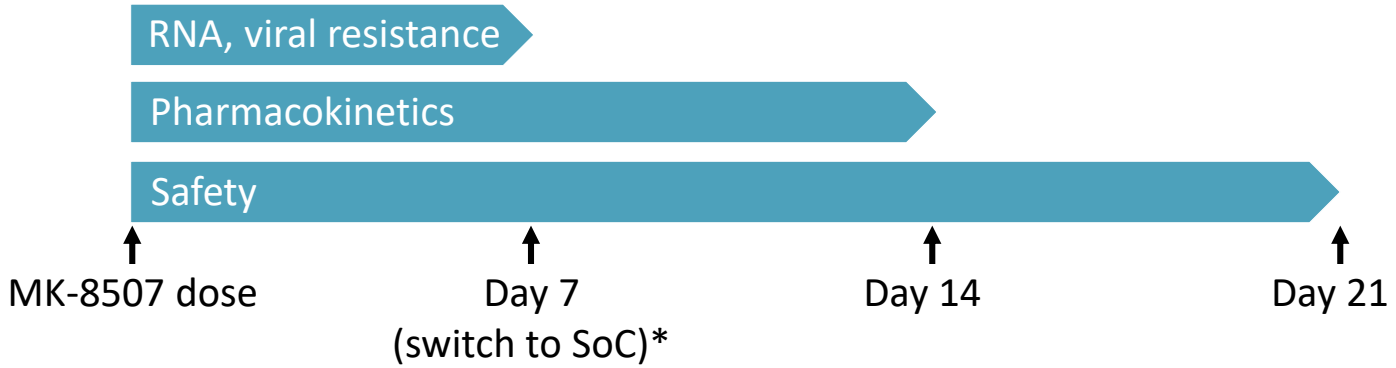
Diamond. CROI 2021. Abstr 129.

Single Oral Dose of Novel NNRTI MK-8507 in Treatment-Naive Patients With HIV

ARV-naive patients with HIV-1 RNA ≥ 10,000 copies/mL, CD4+ cell count > 200 cells/mm^3, no NNRTI resistance, no active HCV/HBV infection (N = 18)



Time Course of Analysis in Each Panel:



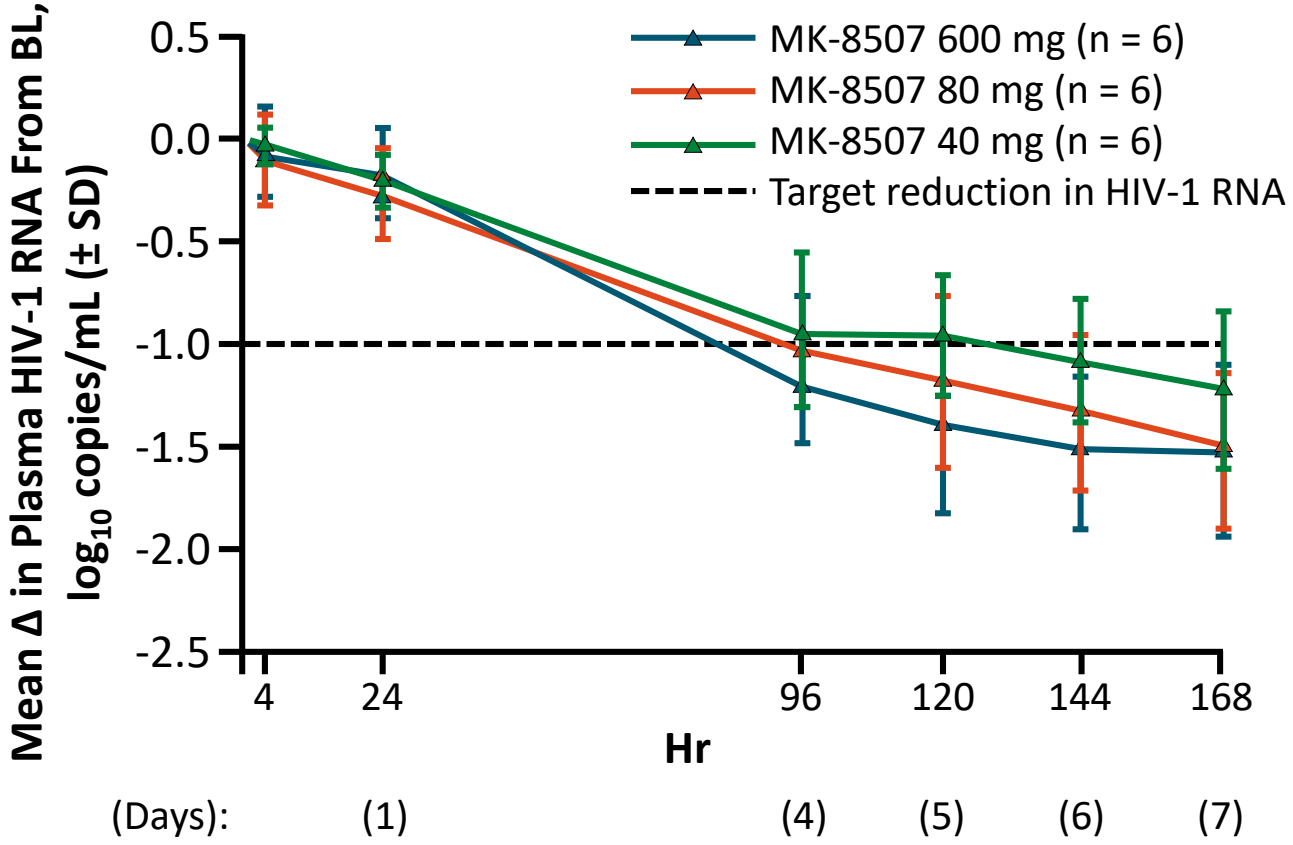
*n = 3 in Panel A switched to SoC immediately after Day 14 analyses; n = 1 in Panel C declined SOC.

- Target: ≥ 1 $\log_{10}$ copies/mL HIV-1 RNA decrease from BL vs historical placebo data

Ankrom. HIV Glasgow 2020. Abstr O416.

Single-Dose MK-8507: Antiviral Efficacy

- All doses achieved target HIV-1 RNA reduction by Day 7



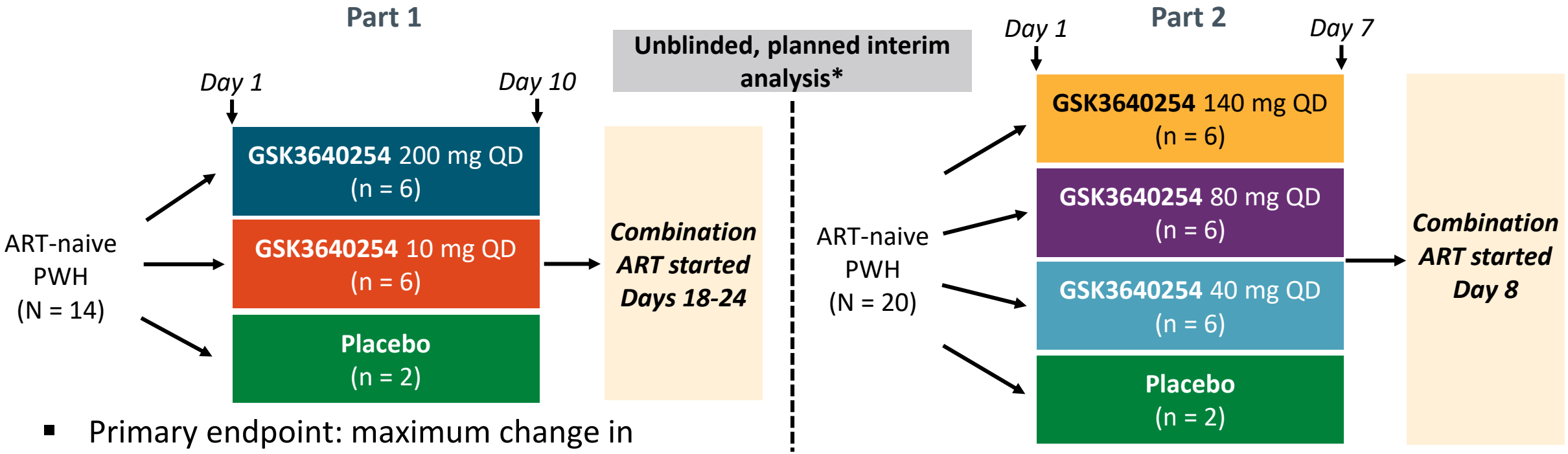
HIV-1 RNA Change From BL at Day 7, log_{10} c/mL (95% CI)	
MK-8507 600 mg (n = 6)	-1.53 (-1.84 to -1.23)
MK-8507 80 mg (n = 6)	-1.50 (-1.80 to -1.19)
MK-8507 40 mg (n = 6)	-1.22 (-1.52 to -0.91)

Pharmacokinetic analysis supports once weekly dosing

Ankrom. HIV Glasgow 2020. Abstr O416.

Phase IIa Study of GSK3640254 in Treatment-Naive PWH

- **GSK3640254: investigational HIV-1 maturation inhibitor**
- Multicenter, randomized, double-blind (sponsor-unblinded), placebo-controlled trial

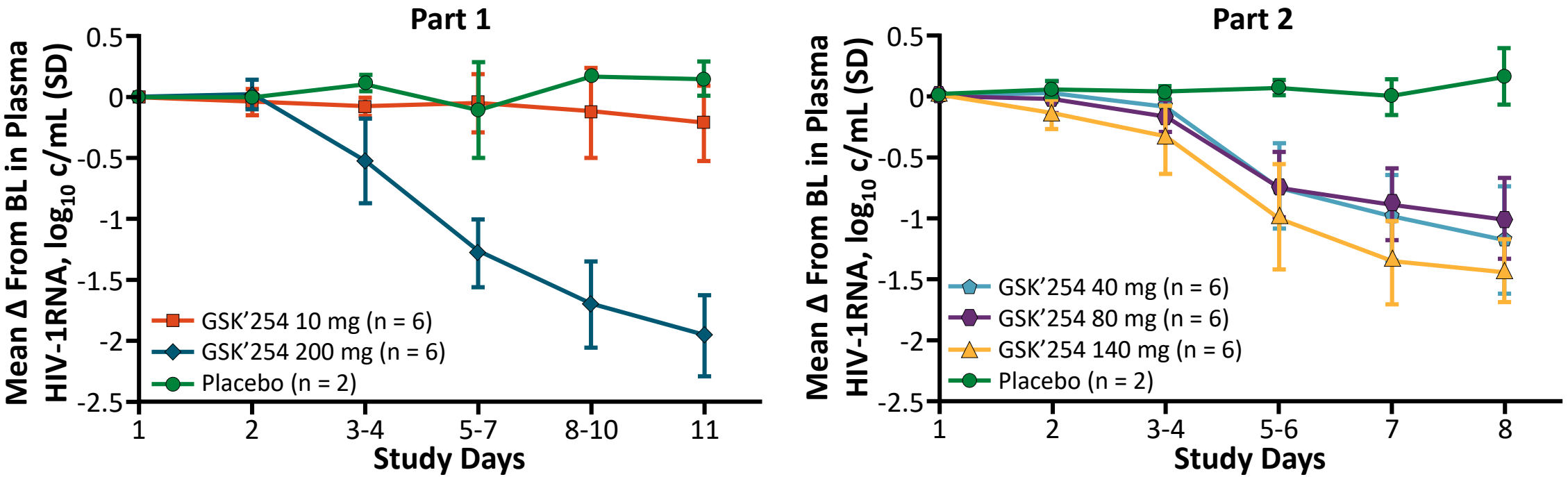


- Primary endpoint: maximum change in HIV-1 RNA vs Day 1 during parts 1 and 2
- Secondary endpoints: resistance, PK, safety

*Detection of resistance mutations at interim analysis resulted in protocol amendment, reducing duration of monotherapy from 10 days to 7 days in Part 2.

Spinner. CROI 2021. Abstr 126.

Phase IIa Study of GSK3640254: Antiviral Activity, Pharmacokinetics, and Resistance



- Mean GSK3640254 concentrations remained above clinical efficacy target at all doses
- *Gag* resistance mutation A364A/V detected in 4 of 6 patients receiving GSK'254 200 mg QD at Day 11 in Part 1 (no resistance with 10 mg dose); full conversion and phenotypic resistance in 1 of 4
- No resistance detected at any dose in Part 2 (140 mg, 80 mg, or 40 mg)

Spinner. CROI 2021. Abstr 126.

Capsid is Critical at Multiple Stages of HIV Replication Cycle

- The HIV capsid is transported intact along microtubules to the site of nuclear import
- The capsid passes through the nuclear pore intact
- Reverse transcription is completed within an intact capsid in the nucleus
- Capsid disassembles prior and near the site of integration

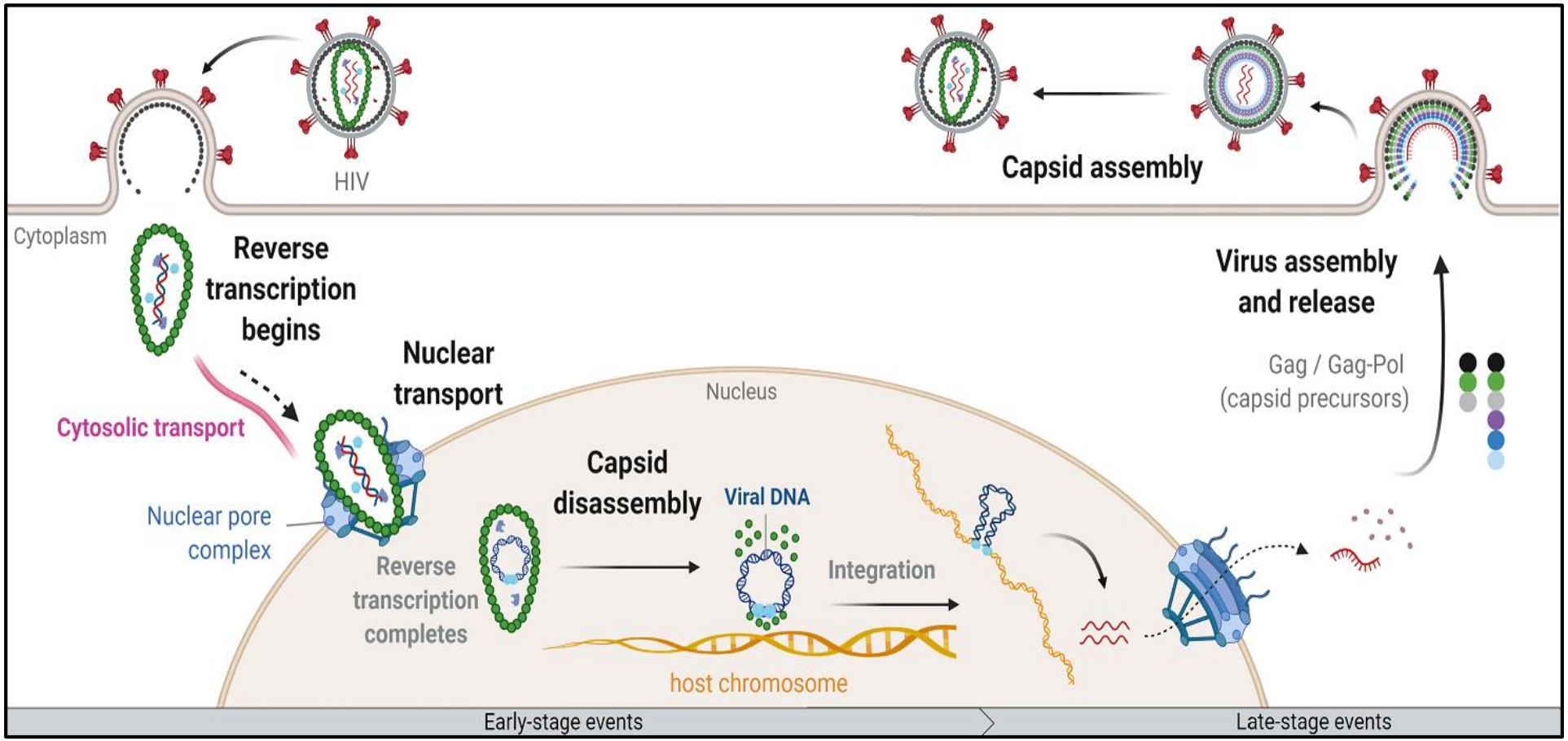


Figure generated based on the following references: Link J, et al. Nature 2020;584:614-618; Bester SM, et al. Science 2020;370:360-364; Cihlar T. vCROI 2021. Oral #22; Muller B. vCROI 2021. Oral #19; Pathak VK. vCROI 2021. Oral #20; Ganser-Pornillos B. vCROI 2021. Oral #21

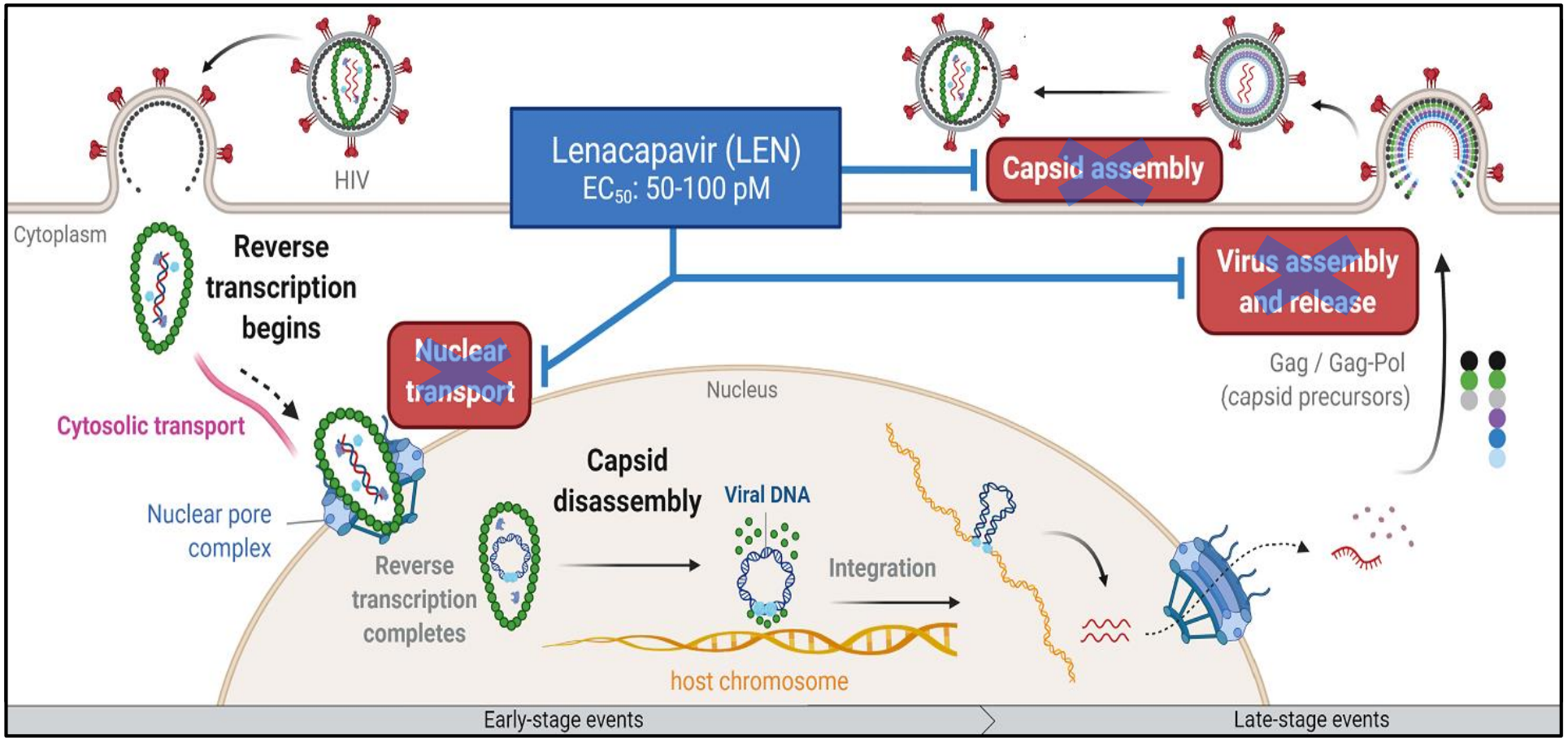
‡

LEN Targets Multiple Stages of the HIV Replication Cycle

https://bit.ly/LEN_MOA

LEN binding directly between capsid protein subunits and inhibits 3 essential steps of the viral lifecycle:

1. Capsid-mediated nuclear uptake of HIV proviral DNA
2. Virus assembly and release
3. Capsid core formation



LEN modulates the stability and/or transport of capsid complexes, leading to inhibition of multiple processes in the HIV lifecycle

Figure generated based on the following references: Link J, et al. Nature 2020;584:614-618; Bester SM, et al. Science 2020;370:360-364; Cihlar T. vCROI 2021. Oral #22; Muller B. vCROI 2021. Oral #19; Pathak VK. vCROI 2021. Oral #20; Ganser-Pornillos B. vCROI 2021. Oral #21

‡

Activity and Resistance Characterization of LEN

Background[1]

- LEN mutations were not found in analysis of 1500 HIV clinical isolates[2]
  - Lack of pre-existing genotypic resistance to LEN
- *In vitro* resistance selections identified 7 mutations arising at 6 amino acids in capsid[3]
  - L56I, M66I, Q67H, K70N, K74S/D, T107N
  - All mutations map to LEN binding site
- Resistance was associated with low replication capacity for most mutants

Resistance Selected by LEN[1]

	PhenoSense Gag-Pro (single cycle)*	
HIV-1 Capsid Sequence	**LEN Fold-Resistance†**	**Replication capacity, % WT‡**
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

WT, wild-type; ND, not determined
* Results were consistent across single- and multi-cycle assay formats, and across primary cells and cell lines
† Ratio of Mutant/WT EC_{50}, determined with SC reporter HIV-1 in PhenoSense Gag-Pro assay
‡ Percentage of reference strain, determined with SC reporter HIV-1 in PhenoSense Gag-Pro assay

Both single and double LEN-selected mutations confer reduced LEN susceptibility and decreased viral fitness

1. VanderVeen L, et al. vCROI 2021. Oral #128
2. Marcelin AG, J Antimicrob Chemother 2020;75:1588-1590
3. Link J, et al. Nature 2020;584:614-618

Study Design

N = 72

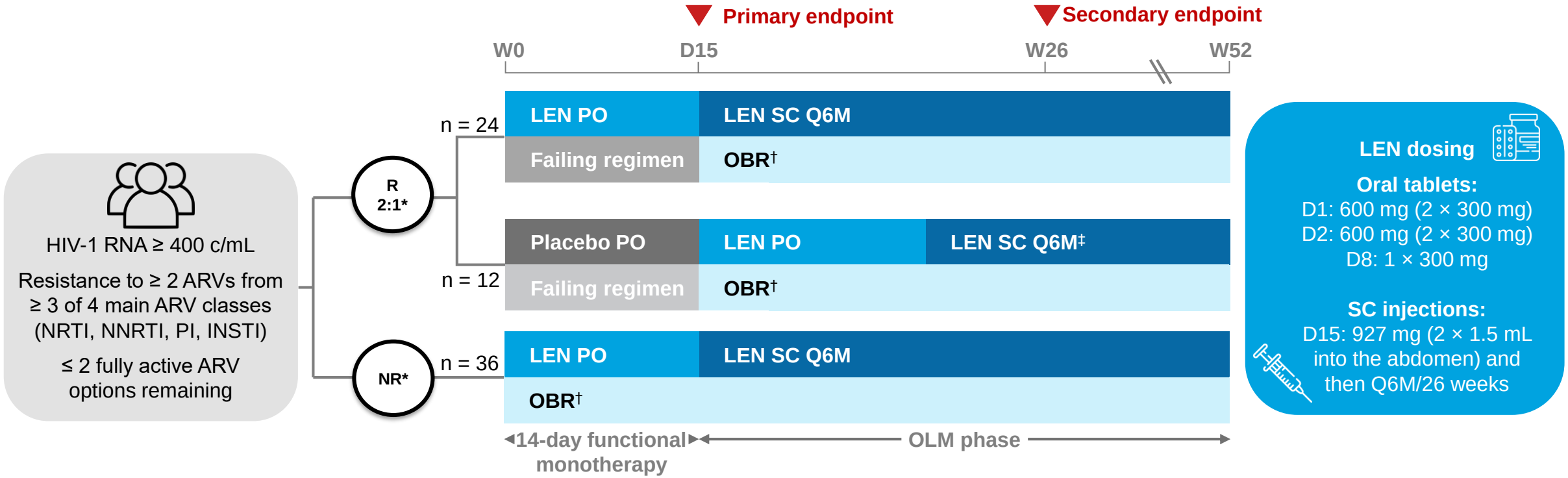
HTE PLWH with MDR, aged ≥ 12 years and weighing ≥ 35 kg

Outcomes (randomized cohort)

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

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

2019 – present (ongoing)



*Participants with < 0.5 $\log_{10}$ c/mL decline in HIV-1 RNA during screening entered the randomized cohort; participants with ≥ 0.5 $\log_{10}$ c/mL decline in HIV-1 RNA during screening entered the nonrandomized cohort; †Investigational agents (e.g., fostemsavir) permitted, atazanavir, atazanavir/cobicistat, atazanavir/ritonavir, efavirenz, etravirine, nevirapine, tipranavir not permitted

BL, baseline; D, day; HTE, heavily treatment-experienced; MDR, multidrug resistance; NR, nonrandomized; OBR, optimized background regimen; OLM, open-label maintenance; PO, by mouth; Q6M, every 6 months; R, randomized; SC, subcutaneous(ly); W, week

Ogbuagu O, et al. CROI 2022, Poster 491

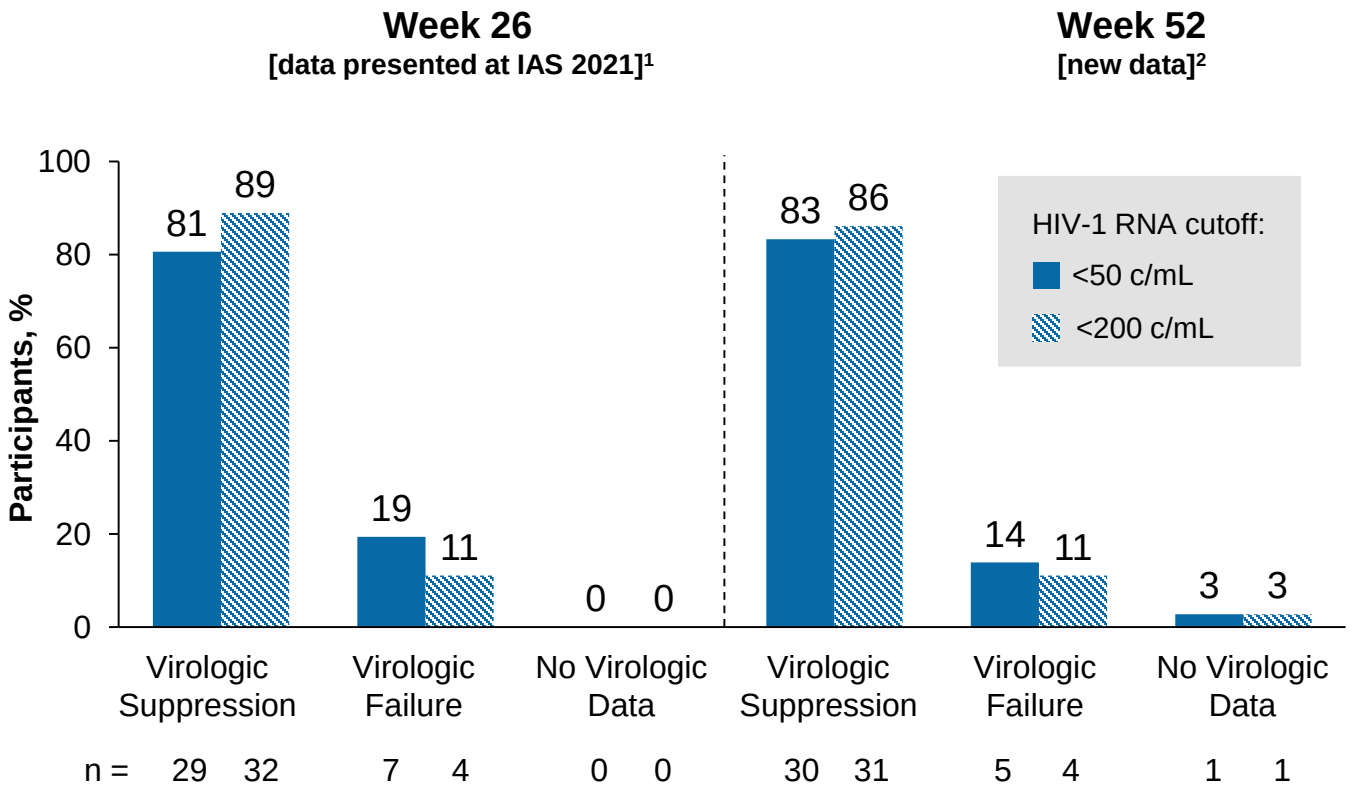
Baseline Characteristics

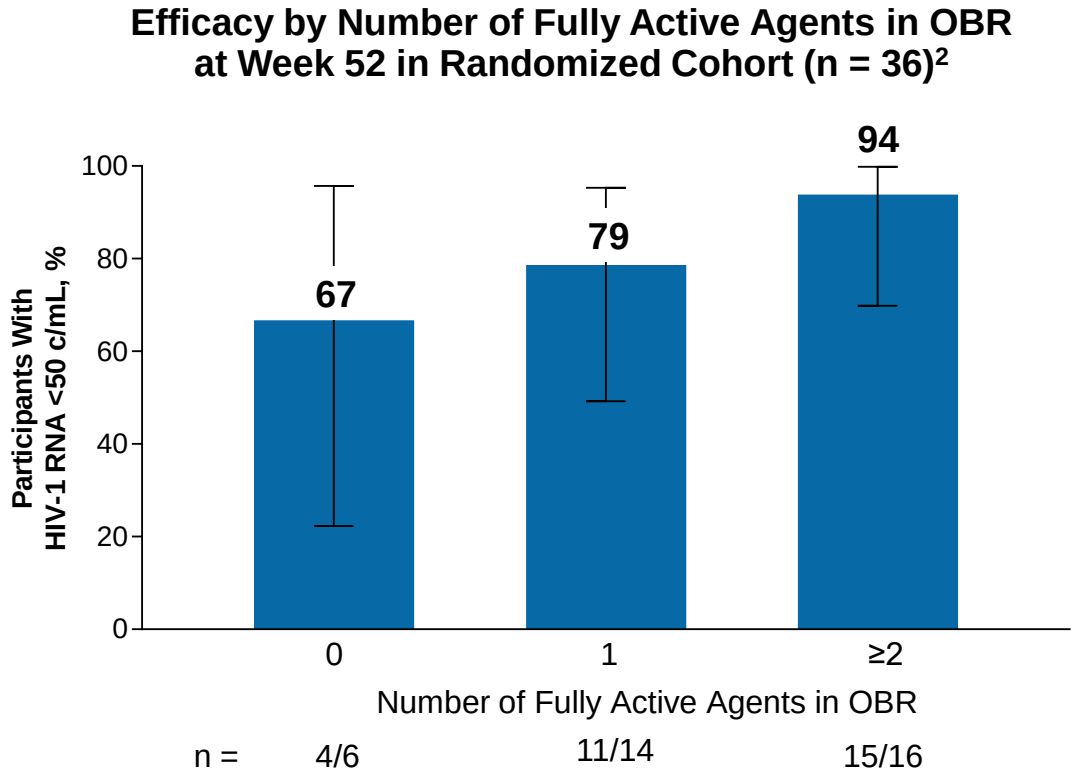
	Randomized		Nonrandomized	Total (N = 72)
	LEN (n = 24)	Placebo (n = 12)	LEN (n = 36)	
Age, median (range), years	55 (24–71)	54 (27–59)	49 (23–78)	52 (23–78)
Sex, % female at birth	29	25	22	25
Race, % Black	42	55	31	38
Ethnicity, % Hispanic/Latinx	25	36	14	21
HIV-1 RNA, median (range), log_{10} c/mL	4.2 (2.3–5.4)	4.9 (4.3–5.3)	4.5 (1.3–5.7)	4.5 (1.3–5.7)
> 75,000 c/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
No. of prior ARV agents, median (range)	9 (2–24)	9 (3–22)	13 (3–25)	11 (2–25)
No. of fully active agents in OBR, %				
0	17	17	17	17
1	29	58	36	38
≥ 2	54	25	47	46
Known resistance to ≥ 2 drugs in class, %				
NRTI	96	100	100	99
NNRTI	92	100	100	97
INSTI	83	58	64	69
PI	83	67	83	81

HTE, heavily treatment-experienced; OBR, optimized background regimen

Ogbuagu O, et al. CROI 2022, Poster 491

Efficacy at Week 52 (FDA Snapshot): Randomized Cohort (n = 36)





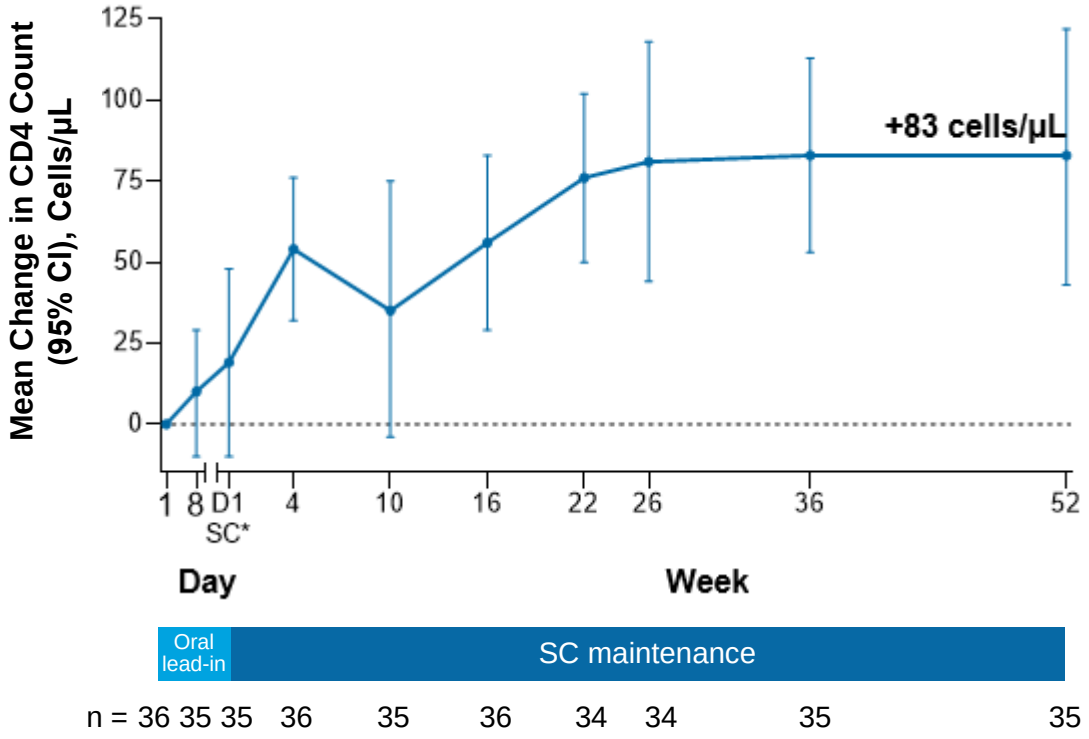
LEN in combination with OBR achieved and maintained high rates of virologic suppression at Week 52 in HTE PLWH

HTE, heavily treatment-experienced; OBR, optimized background regimen

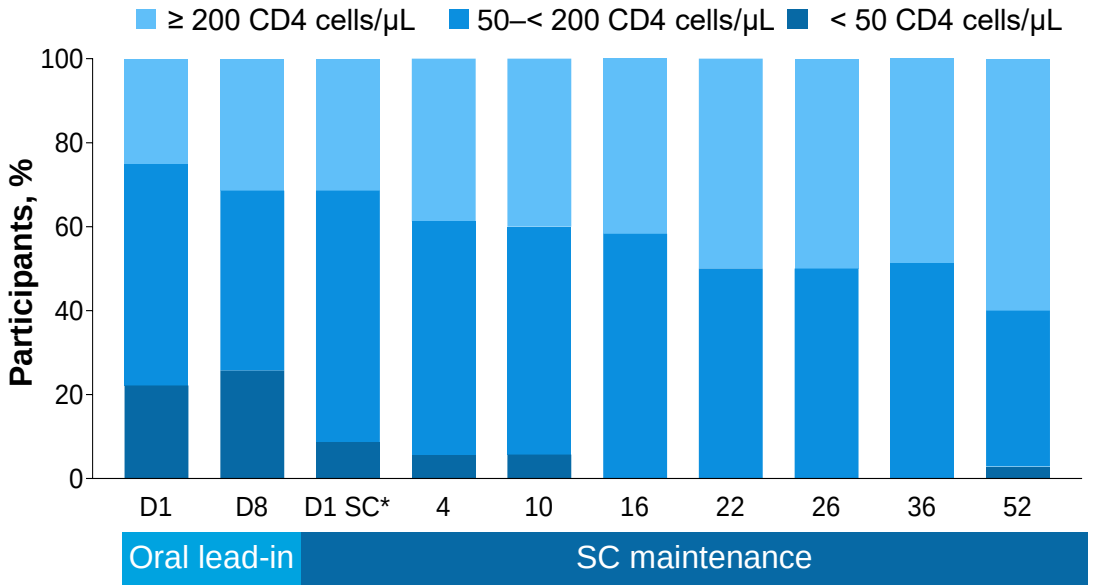
1. Molina JM, et al. vIAS 2021, OALX01LB02; 2. Ogbuagu O, et al. CROI 2022, Poster 491

Changes in CD4: Randomized Cohort (n = 36)

Mean Change in CD4 Count



Changes In CD4 by Category



CD4 cells/µL	Baseline (n = 36)	Week 52 (n = 36)
< 50, %	22	3
≥ 200, %	25	60

LEN in combination with OBR led to clinically meaningful improvement in CD4 cell count in HTE PLWH

*First day LEN SC was administered. D, day; HTE, heavily treatment-experienced; OBR, optimized background regimen

Ogbuagu O, et al. CROI 2022, Poster 491

Post-baseline Resistance Analysis at Week 52

Resistance Category, n (%)	Randomized Cohort n=36	Nonrandomized Cohort n=36	All N=72
Resistance analysis population	11 (31)	10 (28)	21 (29)
With data	11 (31)	9 (25)	20 (28)
Resuppressed <50 copies/mL	4 (11)	4 (11)	8 (11)
With CA-R emerging	4 (11)	4 (11)	8 (11)
M66I, n	4	2	6
Q67H/K/N, n	1	2	3
K70H/N/R/S, n	1	3	4
N74D, n	3	0	3
A105S/T, n	3	1	4
*T107A/C/N, n**	1	3	4
No CA-R emergence	7 (19)	5 (14)	12 (17)

*1 participant had emergent T107A mutation in CA with no loss in LEN susceptibility before achieving HIV-1 RNA suppression; participant was not categorized as having CA-R emergence.

CA-R, capsid resistance; OBR, optimized background regimen

- 21/72 participants met criteria and were analyzed for resistance
- 8/72 participants had emergent LEN resistance at Week 52, with no change since Week 26
  - 4 participants had OBR adherence issues based on drug plasma concentration
  - 4 participants had no fully active ARVs in OBR
- Absence of post-baseline emergence of LEN RAMs was observed in 12 of 72 participants with viremia
- Minimal emergence of resistance to OBR drugs was observed, with resuppression without OBR change

All 8 cases of emergent LEN resistance occurred in the setting of functional monotherapy.
More than half of participants who met criteria for resistance testing did not develop LEN resistance.

Margot N, et al. AIDS 2022. Poster EPB240.

Incidence of ISRs Related to SC LEN*

Incidence of ISRs Related To SC LEN[1,2]

ISR type, %	After first SC dose at Week 1 (n = 72)	After second SC dose at Week 26 (n = 70)	Median duration, days
Swelling	26	13	12
Erythema	24	11	6
Pain	22	21	3
Nodule	22	11	180
Induration	11	10	118

Non-ISR AEs

- No SAEs related to study drug
- No discontinuations due to non-ISR Aes

ISRs

- All nodules were Grade 1, except in 1 participant
  - (n = 1) Grade 2 nodules after the 2nd and 3rd injections (both resolved after 3 days)
- Most ISRs were Grade 1 or 2 in severity (no Grade 4)
  - Grade 3 ISRs in 2 participants:
    - (n = 1) swelling and erythema, resolved in 4 and 8 days, respectively
    - (n = 1) pain, resolved in 1 day
- 1 participant discontinued due to ISR
  - Due to nodule (Grade 1) at Week 52

LEN was generally well tolerated with a single discontinuation (n = 1/72) due to ISR in HTE PLWH

*Only includes AEs related to LEN and excludes AEs unrelated to LEN. HTE, heavily treatment-experienced; ISR, injection-site reaction

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

Recently Approved ARVs for HTE PLWH

	Fostemsavir[1,2]	Ibalizumab[3,4]
FDA Approval	July 2020	March 2018
EMA Approval	February 2021	September 2019
Indication	US: For the treatment of HIV-1 infection in HTE adults with MDR HIV-1 infection falling their current antiretroviral regimen due to resistance, intolerance, or safety considerations EU: For the treatment of adults with MDR HIV-1 infection, for whom it is otherwise not possible to construct a suppressive antiviral regimen	US: For the treatment of HIV-1 infection in HTE adults with MDR HIV infection failing their current antiretroviral regimen EU: For the treatment of adults infected with MDR HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen
MOA	Binds directly to the gp120 subunit within the HIV-1 envelope glycoprotein gp160 and selectively inhibits the interaction between the virus and cellular CD4 receptors, thereby preventing attachment	Blocks HIV-1 from infecting CD4+ T cells by binding to domain 2 of CD4 and interfering with post-attachment steps required for the entry of HIV particles into host cells and preventing the viral transmission that occurs via cell-cell fusion
Dosing	One 600mg tablet taken orally twice daily with or without food	Loading dose of 2,000 mg (10 vials) IV given over 30 mins followed by a maintenance dose of 800 mg (4 vials) IV every 2 weeks given over 15 mins if no infusion associated adverse reaction to loading dose

- Other ARVs used for treatment of HTE PLWH include: dolutegravir BID, boosted darunavir BID, etravirine, enfuvirtide, maraviroc

HTE: heavily treatment-experienced

1.VIIV Healthcare, Inc. Rukobia US Prescribing Information. July 2020
2.VIIV Healthcare, Inc. Rukobia. SmPC. Feb 2021
3.Thera technologies. Trogarzo US Prescribing Information. April 2020.
4.Thera technologies. Trogarzo SmPC. March 2018

Lenacapavir May Address Unmet Needs Remaining for HTE PLWH

- Viral suppression
  - Potent antiviral activity and novel mechanism of action
  - Lack of cross-resistance to existing ARVs
  - Synergistic with other ARV
  - Manageable DDI profile
- Adherence challenges
  - New route of administration with a long-acting 6 month subcutaneous injection
  - Decreased frequency of administration without increasing pill burden
- Quality of life
  - May achieve undetectable or decreased VL
  - May improve immune function by increasing CD4 counts
  - May decrease disease burden and subsequent sequela
  - May improve convenience and ease of administration

HTE: heavily treatment-experienced

1 EACS Guidelines version 10.1. October 2020. Accessed Feb 2021. 2. Saag MS, et al. JAMA . October 2020. Accessed Feb 2021
3. DHHS. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, 2019. Accessed Feb 2021 4. Link JO et al. Nature. 2020. 584,614-618.

Study Design

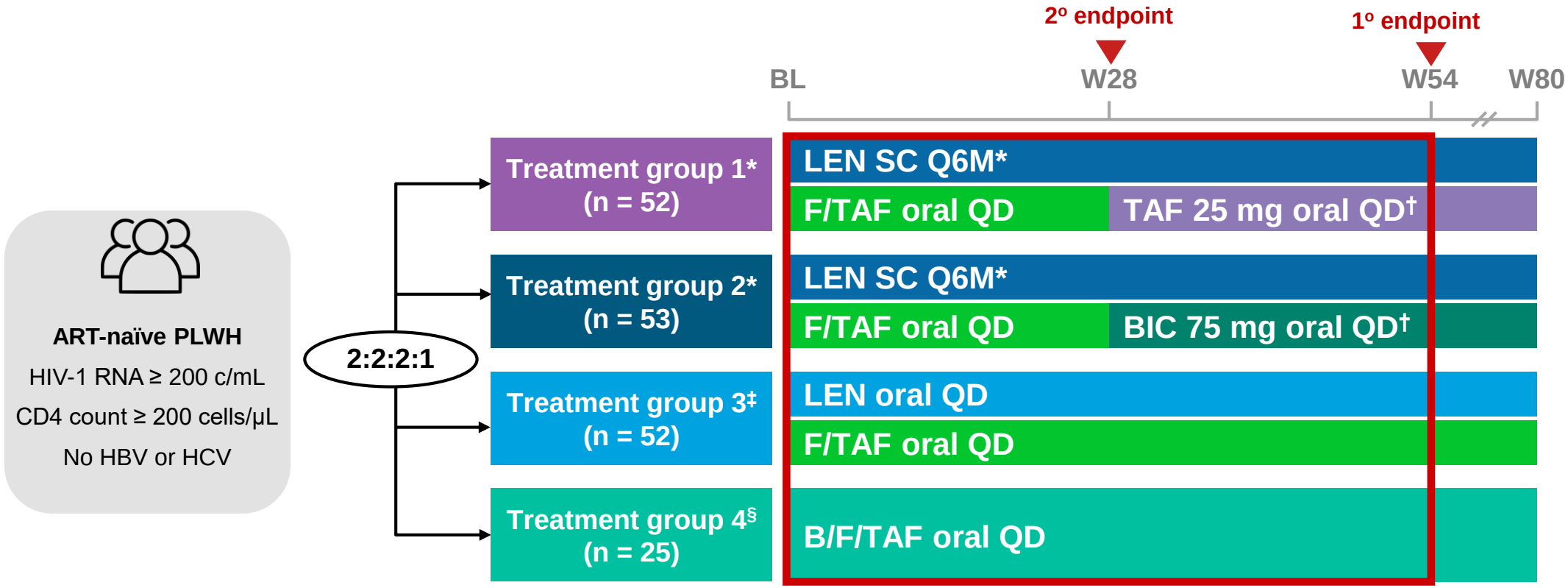
N = 182

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

Outcomes[2]

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

2019 – present (ongoing)



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

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

Baseline Characteristics

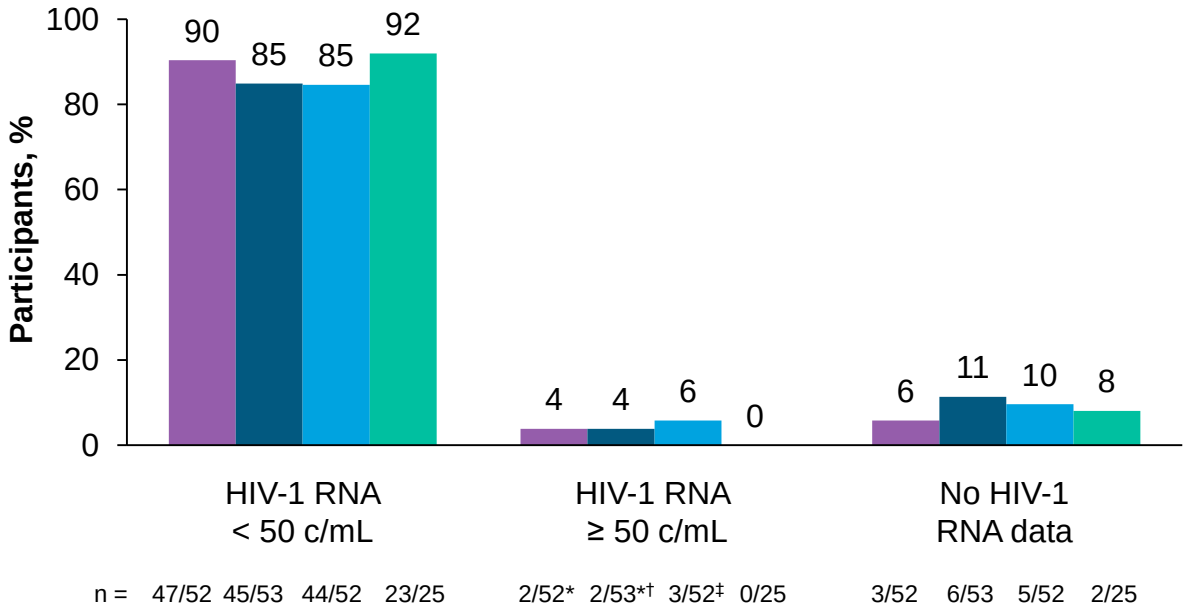
	LEN total			B/F/TAF	
	TG 1 (n = 52)	TG 2 (n = 53)	TG 3 (n = 52)	TG 4 (n = 25)	Overall (N = 182)
Age, median (range), years	31 (19, 61)	28 (19, 56)	28 (19, 72)	29 (21, 61)	29 (19, 72)
Sex, % female at birth	10	2	12	0	7
Race, % Black	46	45	60	64	52
Ethnicity, % Hispanic/Latinx	48	40	46	48	45
HIV-1 RNA, median $\log_{10}$ c/mL	4.27	4.32	4.53	4.37	4.37
Q1, Q3	3.77, 4.63	3.96, 4.74	3.82, 4.83	4.09, 4.77	3.86, 4.74
> 100,000 c/mL, %	10	17	17	16	15
CD4 count, median cells/μL	404	450	409	482	437
Q1, Q3	320, 599	332, 599	301, 600	393, 527	332, 599
< 200 cells/μL, %	0	2	6	0	2

Q, quartile; QD, once daily; TG, treatment group

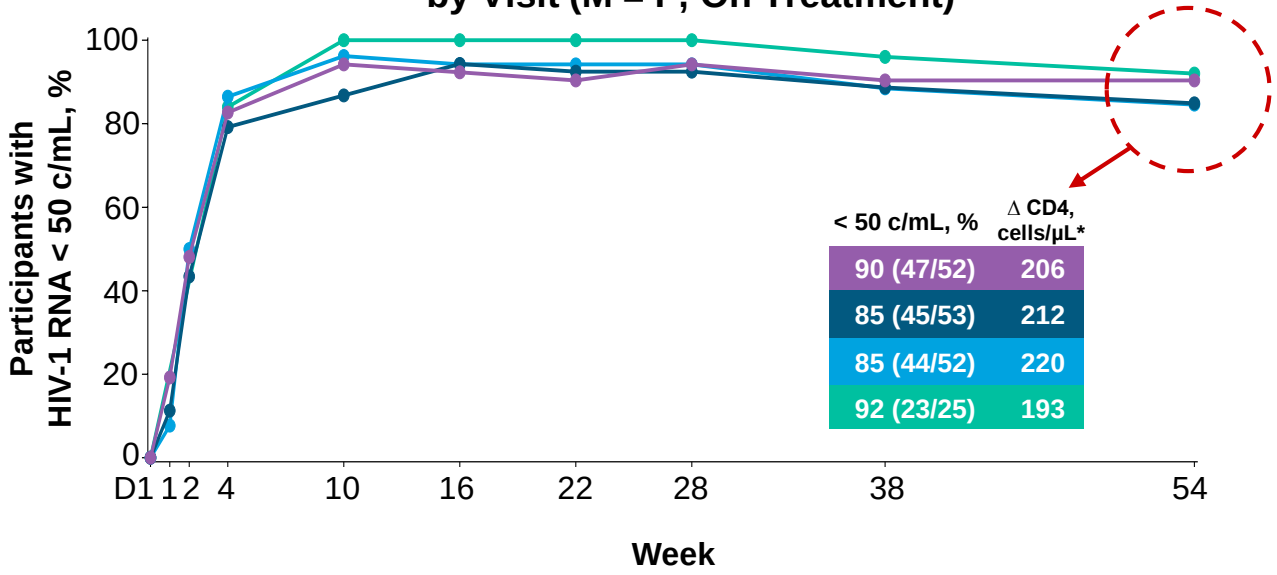
Gupta SK, et al. CROI 2022, Oral 138

Efficacy at Week 54

Efficacy at Week 54 (FDA Snapshot)



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



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

In treatment-naïve PLWH, LEN (SC and oral) in combination with oral F/TAF, and later TAF or BIC rapidly achieved and maintained high rates of virologic suppression at 1 year

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

Gupta SK, et al. CROI 2022, Oral 138

Resistance Analysis Week 54

Number of Participants Meeting the Resistance Testing Criteria[1–3]

Participants, n	TG 1 (n = 52)	TG 2 (n = 53)	TG 3 (n = 52)	TG 4 (n = 25)
Participants meeting the resistance testing criteria*	1	1	3	1
Emergent LEN resistance	0	1	1	0

- **Emergent LEN resistance in 2/157 (1.5%) participants**
  - One participant in TG 2 developed capsid resistance at Week 10 (Q67H + K70R; LEN fold change = 20), preceded by M184M/I in RT[1,2]
    - Pattern of mutation emergence suggests incomplete adherence to F/TAF
  - One participant in TG 3 developed capsid resistance at Week 54 (Q67H; LEN fold change = 7)[3]
    - Nonadherence to F/TAF, as assessed by pill count and drug levels
  - Both participants later resuppressed on a regimen of INSTI + 2 NRTI

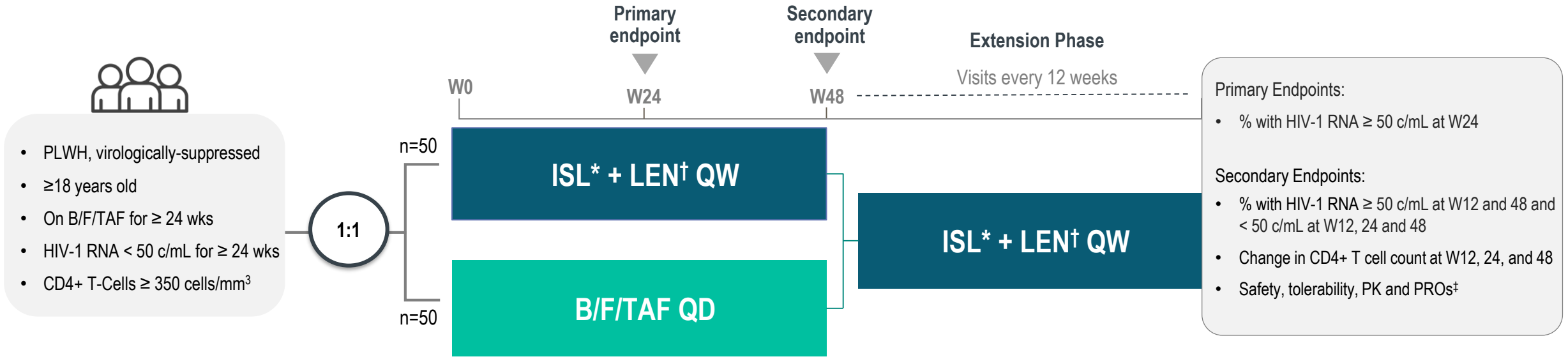
There were 2 cases of treatment-emergent capsid resistance (1.5%), which occurred in participants with likely or confirmed nonadherence to oral ART

*Genotypic and phenotypic resistance testing performed on any participants with confirmed HIV-1 RNA ≥ 50 c/mL and <1 $\log_{10}$ HIV-1 RNA reduction from Day 1 at the Week 10 visit, at any visit after achieving HIV-1 RNA < 50 c/mL and a rebound to ≥ 50 c/mL, and at any visit with > 1 $\log_{10}$ increase from the nadir
M = F, missing equals failure; QD, once daily; TG, treatment group

1. Gupta SK, et al. IAS 2021, Abstract OALB0302; 2. VanderVeen L, et al. ID Week 2021, Oral 73; 3. Gupta SK, et al. CROI 2022, Oral 138

ISL + LEN Long-Acting Oral Weekly in PLWH who are Virologically-Suppressed

Phase 2, randomized, open-label, active-controlled, multicenter study to evaluate safety, efficacy, and PK of ISL + LEN in PLWH who are virologically suppressed (N=100)#



*ISL dosing: Day 1: 2 mg [2 × 1 mg capsule]; Day 8 and every week thereafter: 2mg [2 x 1 mg capsule]
†LEN dosing: Day 1: 600 mg [2 × 300 mg tablets]; Day 2: 600 mg [2 × 300 mg tablets]; Day 8 and every week thereafter: 300 mg [1 x 300 mg tablet]
Study design, inclusion criteria, and endpoints depicted for Cohort 2
‡ PROs are exploratory endpoints

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; ISL, islatravir; LAO, long-acting oral; LEN, lenacapavir; Ph2, Phase 2; PK, pharmacokinetics; PLWH, people living with HIV; PROs, patient reported outcomes; QD, daily; QW, every week; VS, virologically suppressed; W, week; wks, weeks

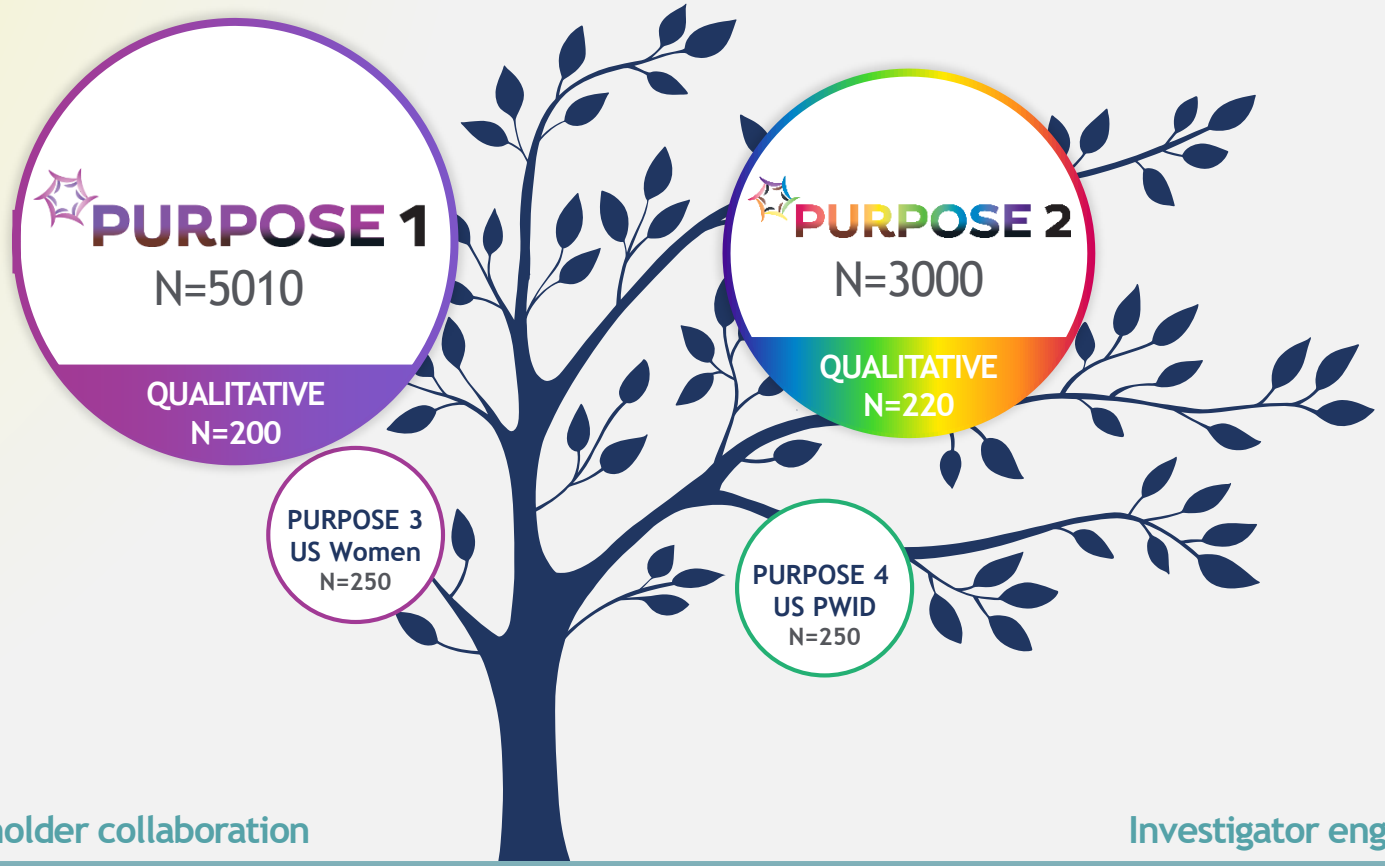
Study design Footnotes

Clinicaltrials.gov URL: https://clinicaltrials.gov/ct2/show/NCT05052996?term=lenacapavir&draw=1&rank=5. Accessed January 03, 2023
Data on file

MSD

Collaboration
Transparency

Prevention with PURPOSE



Community & stakeholder collaboration

Investigator engagement

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

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

HIV Broadly Neutralizing Antibodies (bNAbs)

Features

- Human monoclonal antibodies able to neutralize wide range of HIV-1 isolates
- Target HIV-1 envelope
- Enhance various effector functions
- Can be genetically engineered to combine multiple specificities or extend half-life

Potential Clinical Uses

- HIV treatment intensification by concomitant use of ART + bNAbs
- Maintenance therapy in virologically suppressed individuals
- HIV immunotherapy: possible treatment alternative (eg, MDR or ART intolerance)
- Prevention: pre- and postexposure prophylaxis; PMTCT (for late presenters)

Potential Advantages

- Infrequent dosing
- No cross-resistance with ARVs
- Established paradigms for therapeutic use in other disease areas
- Potential for overcoming adherence challenges and for less stigma
- Potential to enhance HIV-specific immunity

BNABS FOR HIV PREVENTION, TREATMENT OR CURE RESEARCH

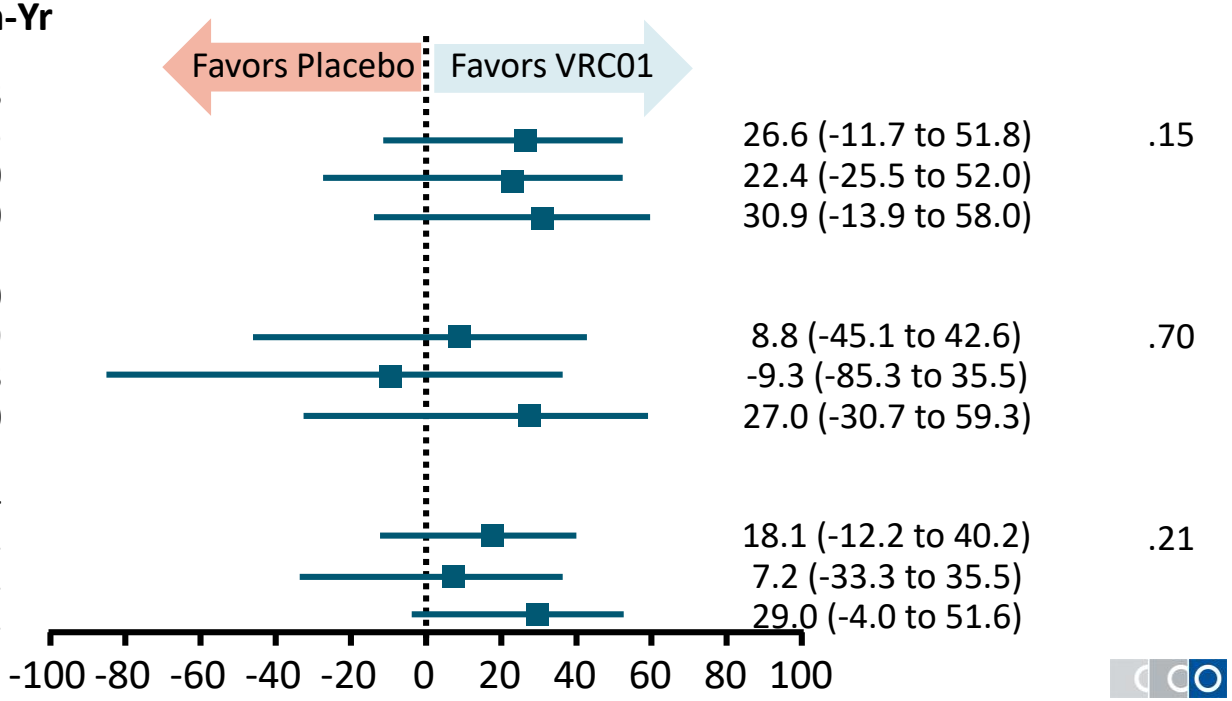
Compound / Company	Target	Notes	Status
ibalizumab	gp120	Already approved in the US and EU for treatment of MDR HIV.	Approved.
leronlimab (PRO 140) CytoDyn	CCR5	Once-weekly sub-cutaneous injection being studied in addition to ART for multi-drug resistance and as monotherapy maintenance therapy (without ART). Phase 3.	Phase 3.
UB-421 United BioPharma	CD4 binding	Infusion dosed either weekly or every two weeks as alternative to ART during treatment interruption. Phase 3.	Phase 3.
VRC01 and VRC01LS US NIH	CD4 binding	Intravenous infusion being studied in cure research and as PrEP (2 large phase 3 studies are ongoing). Sub-cutaneous dosing of infants to prevent transmission at birth or from breastfeeding. VRC01LS is a longer acting formulation. Results as PrEP expected late 2020.	Phase 3.
VRC07, VR07-523LS	CD4 binding	Engineered from VRC01. Being studied with cabotegravir-LA in ACTG trial.	Phase 2.
PGT-121 and GS-9722 (elipovimab). Gilead.	C3/V3	PGT121 is an IgG1 mAb that targets the V3 Env epitope. GS-9722 (elipovimab) is engineered from PGT-121.	Phase 1.
3BNC117 and 10-1074; Rockefeller University and Gilead	CD4 binding and C3/V3	Both bNAbs are available as LS long-acting formulations. Gilead Sciences signed for exclusive global development rights.	Phase 2.
N6 US NIH and ViiV	gp120	Developed by US NIH and now licenced to ViiV.	Phase 1.
Other mAbs: 10E8, trispecific bNAbs, PGDM1400	MPER, V2 and others	Mulitple compounds in preclinical and phase 1 studies.	Phase 1.

http://www.i-Base.info/hiv-pipeline-report-2020

Antibody-Mediated Prevention (AMP) Trials of VRC01

- HVTN 703/HPTN 081: sub-Saharan Africa (N = 1900 women)
- HVTN 704/HPTN 085: Americas, Europe (N = 2700 MSM + TG women)
- 3 arms: VRC01 10 mg/kg, VRC01 30 mg/kg, placebo (10 infusions, each given every 8 wk)

Trial and Treatment Group	No. of HIV Infections	No. of Person-Yr	Rate per Person-Yr	Prevention Efficacy (95% CI)	*P* Value
HVTN 704/HPTN 085					
Placebo	38	1275	2.98		
VRC01 pooled	60	2555	2.35	26.6 (-11.7 to 51.8)	.15
VRC01, low dose	32	1281	2.50	22.4 (-25.5 to 52.0)	
VRC01, high dose	28	1274	2.20	30.9 (-13.9 to 58.0)	
HVTN 703/HPTN 081					
Placebo	29	935	3.10		
VRC01 pooled	47	1889	2.49	8.8 (-45.1 to 42.6)	.70
VRC01, low dose	28	941	2.98	-9.3 (-85.3 to 35.5)	
VRC01, high dose	19	948	2.00	27.0 (-30.7 to 59.3)	
Pooled trials					
Placebo	67	2207	3.04		
VRC01 pooled	107	4436	2.41	18.1 (-12.2 to 40.2)	.21
VRC01, low dose	60	2217	2.71	7.2 (-33.3 to 35.5)	
VRC01, high dose	47	2219	2.12	29.0 (-4.0 to 51.6)	



Corey. NEJM. 2021;384:1003.

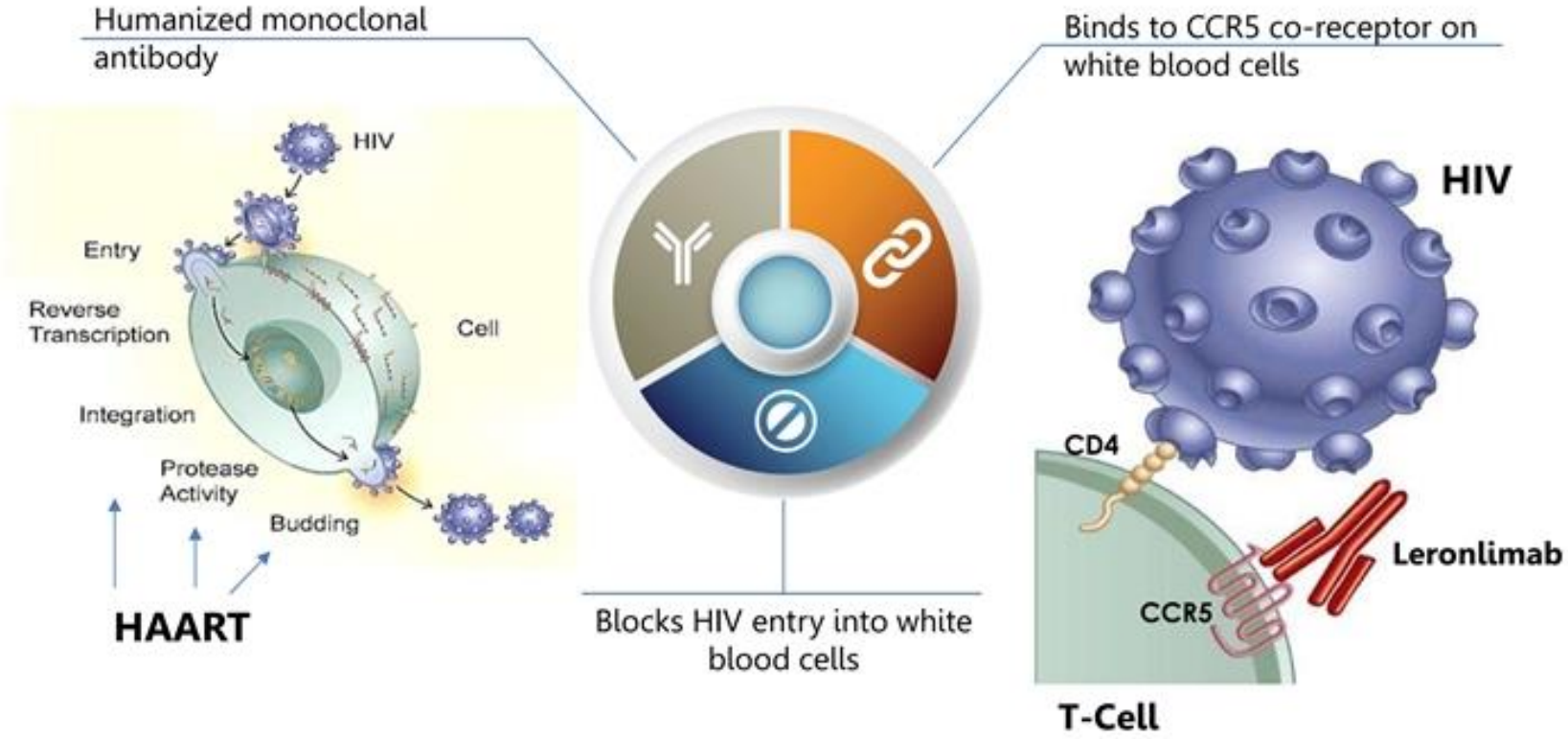
A potential therapy in the treatment of

- COVID-19,
- triple negative breast cancer,
- HIV infection.

Leronlimab (PRO 140) – A Humanized Monoclonal Antibody

CytoDyn

Blocking **HIV** entry receptor (CCR5)
Blocking CCR5/CCL5 interaction with leronlimab for use in **CANCER**



VH3810109 (N6LS) Reduces Viremia Across a Range of Doses in ART-Naive Adults Living With HIV: Proof of Concept Achieved in the Phase IIa BANNER (207959, NCT04871113) Study

Peter Leone,[1] Alejandro Ferro,[2] Charlotte-Paige Rolle,[3] Sergio Lupo,[4] Joseph McGowan,[5] Marina Klein,[6] Pedro Cahn,[7] Paul Benson,[8] Marisa Sanchez,[9] Christopher Bettacchi,[10] Stefan Schneider,[11] Paul Wannamaker,[1] Beta Win,[12] Judah Abberbock,[13] Mark Baker,[12] Viviana Wilches,[13] Darren Bentley,[14] Margaret Gartland,[1] Max Lataillade,[15] Jan Losos[1]

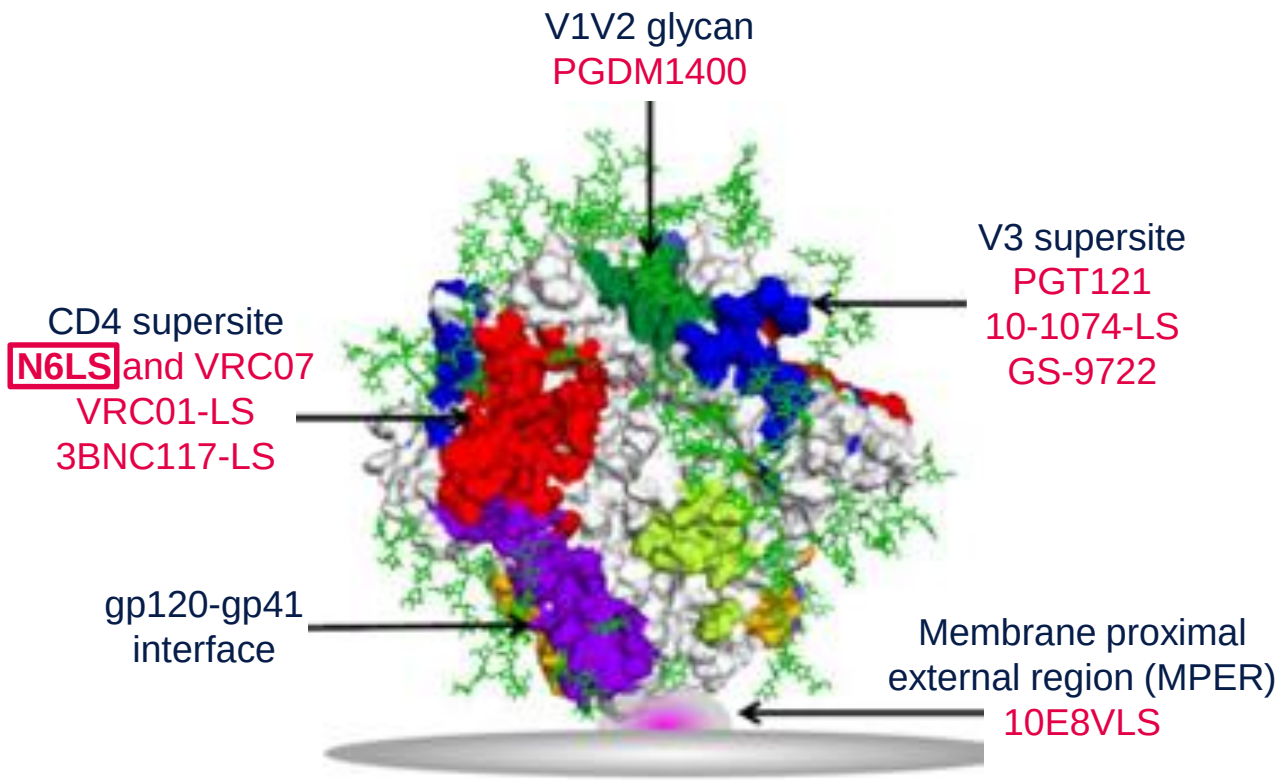
[1]ViiV Healthcare, Durham, NC, USA; [2]Centro de Investigaciones Medicas, Mar del Plata, Argentina; [3]Orlando Immunology Center, Orlando, FL, USA; [4]CAICI, Rosario, Argentina; [5]Northwell Health, New York, NY, USA; [6]McGill University Health Centre, Montreal, Quebec, Canada; [7]Fundacion Huesped, Buenos Aires, Argentina; [8]Be Well Medical Center, Berkley, MI, USA; [9]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [10]North Texas Infectious Disease Consultants, Dallas, TX, USA; [11]Long Beach Education and Research Consultants, Long Beach, CA, USA; [12]GSK, Brentford, UK; [13]GSK, Upper Providence, PA, USA; [14]Certara UK Ltd, Sheffield, UK; [15]ViiV Healthcare, Branford, CT, USA

HIV Drug Therapy Glasgow; October 23-26, 2022; Virtual and Glasgow, Scotland

Introduction

- Broadly neutralizing antibodies (bNAbs) are under development for both the treatment and prevention of HIV-1
- VH3810109 (N6LS) is a novel bNAb with broad and potent neutralization activity in vitro targeting the CD4 binding site of the HIV-1 envelope protein
- Here we report first-time antiviral activity during monotherapy and cumulative ongoing safety of VH3810109 in treatment-naive people with HIV-1

bNAbs target 5 conserved regions on the envelope[1-8]



LS-containing bNAbs have been engineered to have long half-lives[9]

1. Bar et al. *N Engl J Med.* 2016;375:2037-2050. **2.** Kwon et al. *Retrovirology.* 2012;9(suppl 2):O34. **3.** Scheid et al. *Science.* 2011;333:1633-1637. **4.** Mouquet et al. *Proc Natl Acad Sci U S A.* 2012;109:E3268-E3277. **5.** Walker et al. *Nature.* 2011;477:466-470. **6.** Caskey. *Curr Opin HIV AIDS*. 2020;15:49-55. **7.** Doria-Rose et al. *J Virol.* 2015;90:76-91. **8.** Kwon et al. *J Virol.* 2016;90:5899-5914. **9.** Huang et al. *Immunity.* 2016;45:1108-1121.

BANNER Study Design: Randomized, Open-label, 2-Part, Multicenter, Single-Dose, Adaptive Study in ART-Naive Adults

Inclusion criteria
- Age 18-65 years
- HIV-1 RNA ≥5000 c/mL
- CD4+ cell count ≥250 cells/mm^3
- ART naive

Randomized 1:1

Single VH3810109 infusion

Part 1
- VH3810109 40 mg/kg IV (n=8)
- VH3810109 280 mg (~4 mg/kg[a]) IV (n=6)

Planned interim analysis[b]
- To determine whether to proceed to part 2 and to determine dose selection in part 2

Monotherapy endpoint criteria (Days 11-84)
- Virologic non-response (viral nadir decline <0.5 $\log_{10}$ c/mL at Day 11)
- Virologic rebound (VL rebound of ≥1.0 $\log_{10}$ c/mL increase from nadir or to <0.5 $\log_{10}$ c/mL from baseline)
- Missing/Delayed data from previous visits
- Reached Day 84

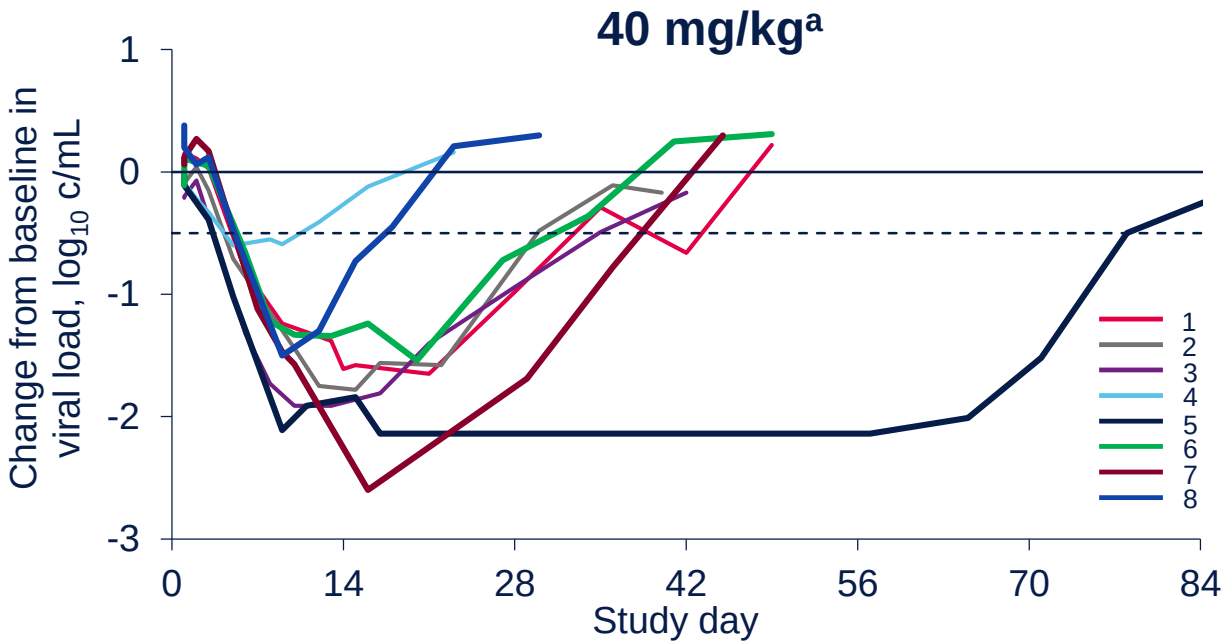
Participants receive INI-based SOC

- Primary endpoints were plasma HIV-1 RNA maximum change from baseline during monotherapy and safety parameters
- Secondary endpoints included VH3810109 PK parameters and incidence and titer of anti-VH3810109 antibodies
  - Antibody susceptibility was determined retrospectively using the PhenoSense monoclonal antibody assay

[a]For a 70-kg individual. [b]A planned interim analysis was performed to evaluate virologic response, safety, and PK from the monotherapy and ongoing SOC periods in part 1. [c]An SOC integrase inhibitor–based regimen (DTG/3TC) was provided at the end of the monotherapy periods in parts 1 and 2.

Leone et al. HIV Drug Therapy Glasgow 2022; Virtual and Glasgow, Scotland. Slides O34.

VH3810109 Led to Virologic Response in 13/14 Participants



Viral dynamic measures	VH3810109 40 mg/kg IV (n=8)
Median (range) viral nadir from baseline, log_{10} c/mL	−1.72 (−0.60, −2.60)
Median (range) time to viral nadir, days	16 (5-21)
Maximum viral nadir from baseline, log_{10} c/mL	−2.60
Median (range) time to viral rebound among responders, days	35 (12-78) [n=8]

Solid line represents no change from baseline and dashed line represents virologic non-response (viral nadir decline <0.5 log_{10} c/mL at Day 11).
[a]Each line represents an individual participant. [b]For a 70-kg individual. [c]Participant 14 is the only female participant in the study.

UPDATE ON CURE RESEARCH

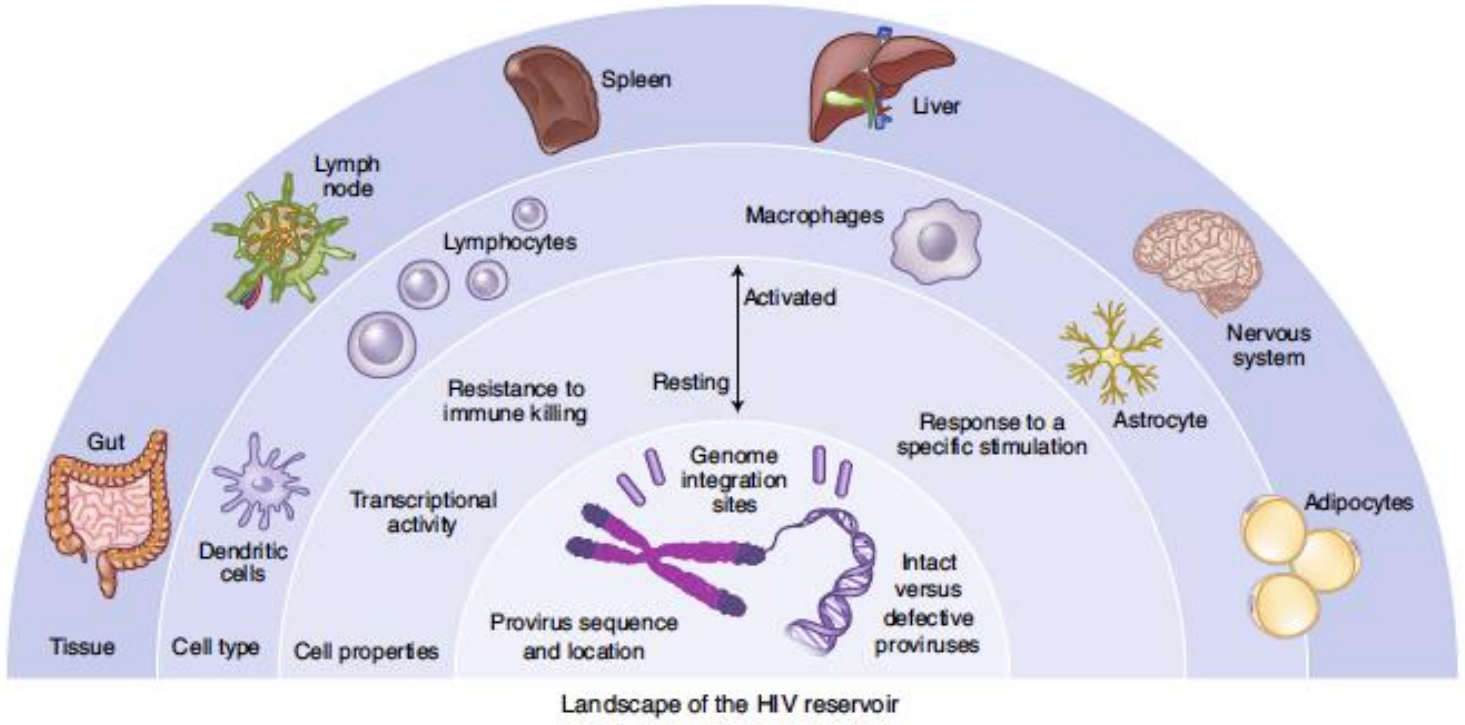
Research priorities for an HIV cure: International AIDS Society Global Scientific Strategy 2021

Steven G. Deeks[1]✉, Nancie Archin[2], Paula Cannon[3], Simon Collins[4], R. Brad Jones[5], Marein A. W. P. de Jong[6], Olivier Lambotte[7], Rosanne Lamplough[8], Thumbi Ndung'u[9,10,11], Jeremy Sugarman[12], Caroline T. Tiemessen[13], Linos Vandekerckhove[14], Sharon R. Lewin[15,16,1] and The International AIDS Society (IAS) Global Scientific Strategy working group*

nature medicine
REVIEW ARTICLE
https://doi.org/10.1038/s41591-021-01590-5

Key research goals to be addressed in the next 5 years

Understanding HIV reservoirs
HIV reservoir measurement
Mechanisms of virus control
Targeting the provirus
Targeting the immune system
Cell and gene therapy
Pediatric remission and cure
Social, behavioral, and ethical aspects of cure



Multidimensional nature of the HIV reservoir. The HIV reservoir can be defined across a number of dimensions, including: (1) anatomical and microanatomical locations, (2) cell type (for example, CD4+ T cell or macrophage), (3) cell functional profile (activated or resting; resistance to killing), (4) pool of proviruses with a particular functional profile (for example, interferon-alpha resistant) or (5) triggering event (for example, response to stimulation with a particular antigen), and (6) integration-site features of the rebounding virus

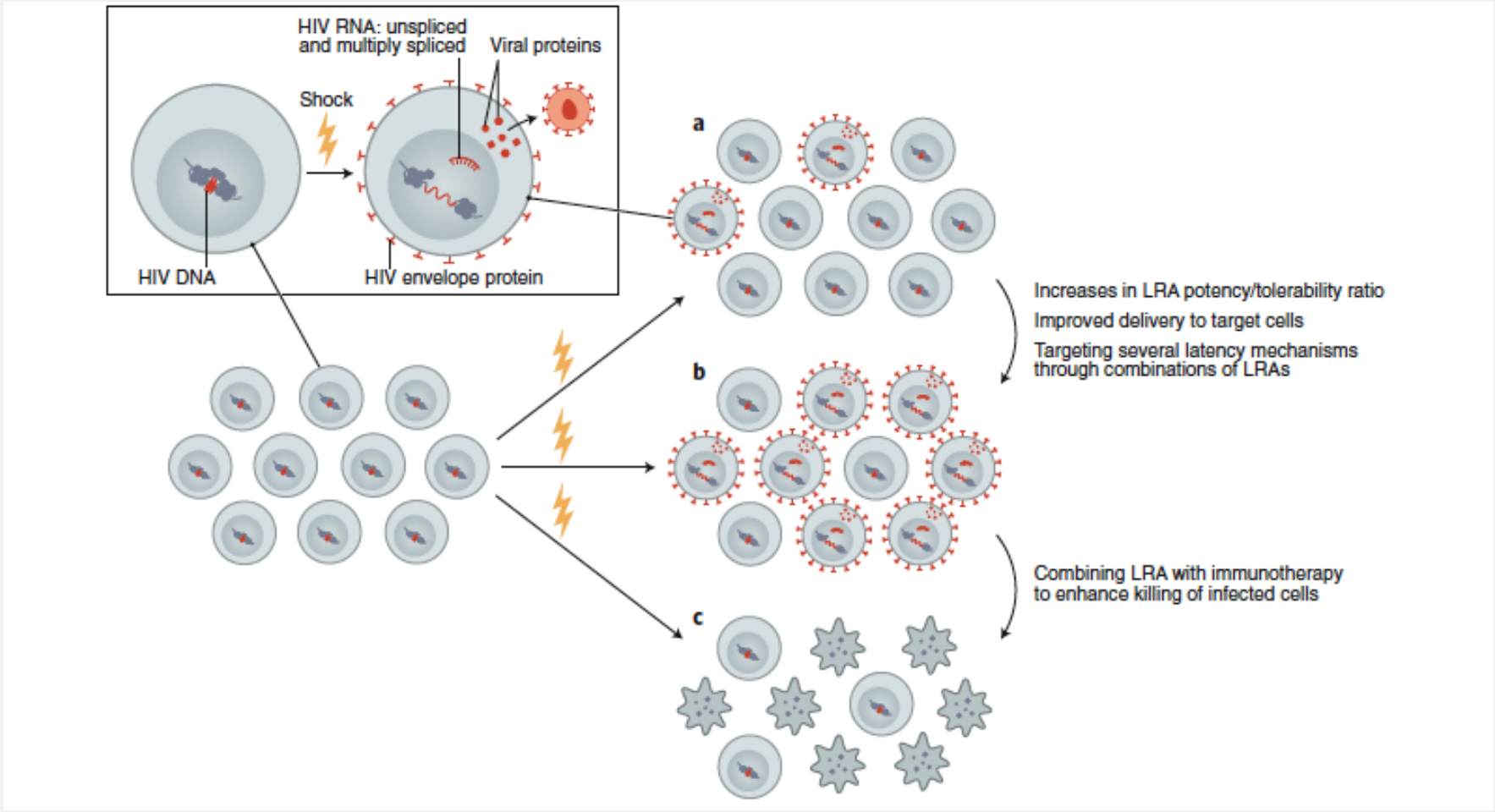
Research priorities for an HIV cure: International AIDS Society Global Scientific Strategy 2021

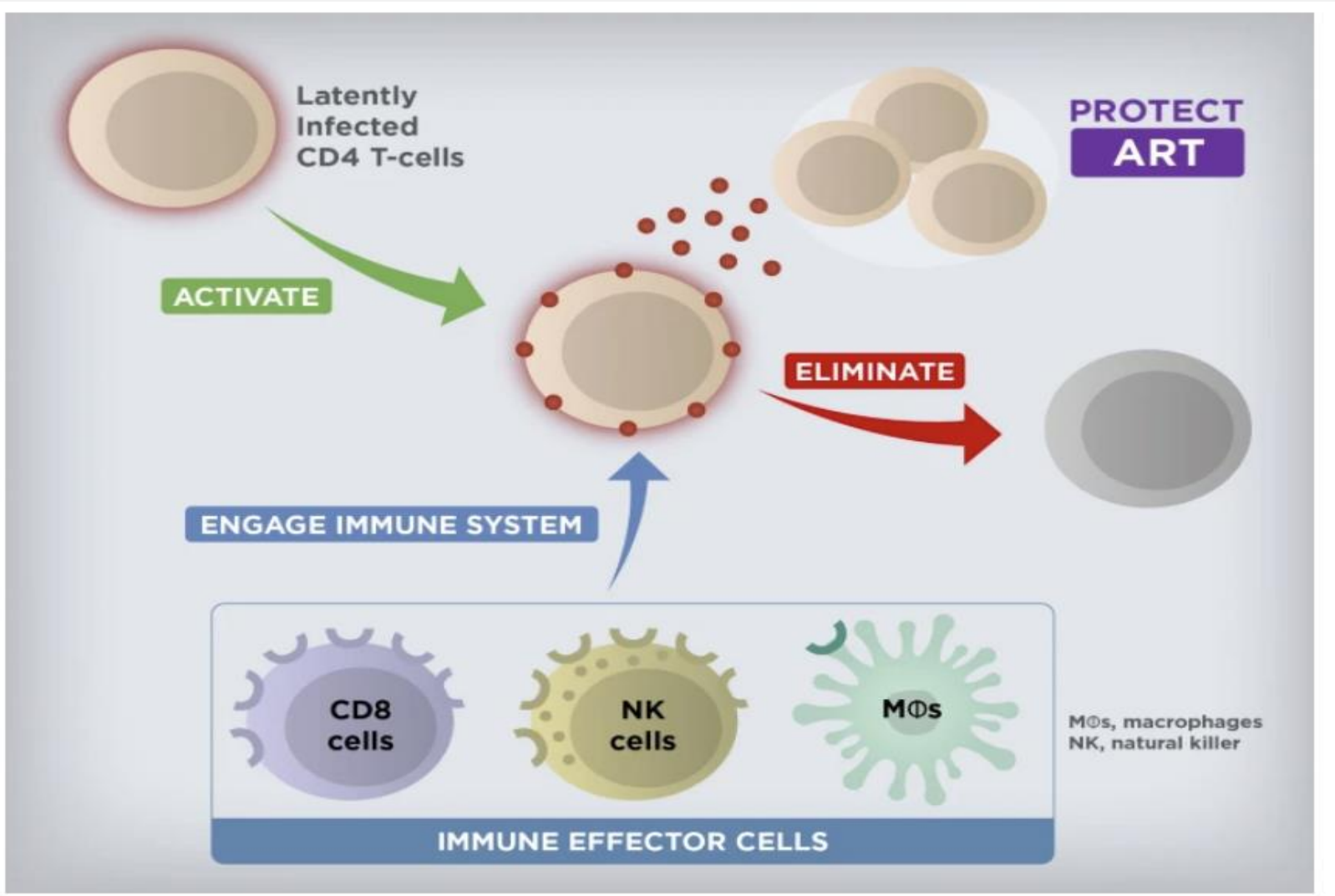
Steven G. Deeks[1]✉, Nancie Archin[2], Paula Cannon[3], Simon Collins[4], R. Brad Jones[5], Marein A. W. P. de Jong[6], Olivier Lambotte[7], Rosanne Lamplough[8], Thumbi Ndung'u[9,10,11], Jeremy Sugarman[12], Caroline T. Tiemessen[13], Linos Vandekerckhove[14], Sharon R. Lewin[15,16,1]
and The International AIDS Society (IAS) Global Scientific Strategy working group*

nature medicine
REVIEW ARTICLE
https://doi.org/10.1038/s41591-021-01590-5

Optimizing latency reversal.

a, Currently available LRAs reverse latency in only a subset of infected cells, and, when used alone, do not sufficiently eliminate these.
b, Enhancing the efficacy of an LRA can be achieved with increased potency, targeted delivery or through using combinations of LRAs.
c, Ultimately, depletion of the reservoir will require combining an LRA with other interventions, such as immunotherapy or a proapoptotic drug.





Cure Strategies to Eliminate HIV Reservoirs. *Current research is exploring the potential of combination investigational therapies to induce expression of latent HIV and in parallel stimulate and engage host immune functions to specifically target and eliminate the infected cells from the activated reservoir*

Select HIV Cure Studies Reported in 2021

Intervention	Results
NCT03374202[1]: Phase I **AAV8-VRC07 (VRC07 bNAb delivered by AAV vector)** Dose escalation in 8 adults with HIV on suppressive ART	▪ 5/8 participants followed >1 yr ▪ No serious AEs attributed to intervention ▪ Ab production: early peak followed by decrease then slow secondary increase after 16 wk; VRC07 concentration increased or remained stable for ≥1 yr in 4/5 ▪ Among 3 without secondary VRC07 increase, anti-VRC07 antibodies were detected ▪ Purified VRC07 from participants was biologically active in pseudovirus neutralization assays
NCT03803605[2]: Phase I **VRC07-523LS + vorinostat** 8 adults with HIV on suppressive ART	▪ 2 cycles (separated by ≥1 mo) of VRC07-523LS 40 mg/kg IV followed by oral VOR 400 mg every 72 hr x 10 ▪ Persistent low-level viremia in 1 participant ▪ Trends toward decreases in some parameters of HIV persistence, but no definitive HIV reservoir reduction (ie, ≥50% decrease in Quantitative Viral Outgrowth Assay)
NCT03707977[3]: Phase I/II **Dual bNAb therapy:** VRC01LS + 10-1074 Children with HIV on suppressive ART	▪ 6 early ART-treated children treated with IV infusions of 10-1074 (30 mg/kg) + VRC01LS (30 mg/kg first dose, 15 mg/kg maintenance dose) Q4W for 32 wk ▪ No infusion reactions, no expedited AEs, no grade 3/4 events related to dual bNAb ▪ Monthly dosing achieved target steady state concentrations
NCT03091374[4]: Phase II **Somatotropin (rhGH)** 12 adults with HIV on suppressive ART	▪ rhGH 3 mg/day for 24 wk, followed by 1.5 mg/day for 24 wk ▪ 9/12 discontinued before 48 wk ▪ 0.8 mean fold decrease in frequency of CD4+ T-cells harboring total HIV DNA (P = .01); 0.41 mean fold decrease in frequency of CD4+ T cells harboring replication competent HIV (P = .08)

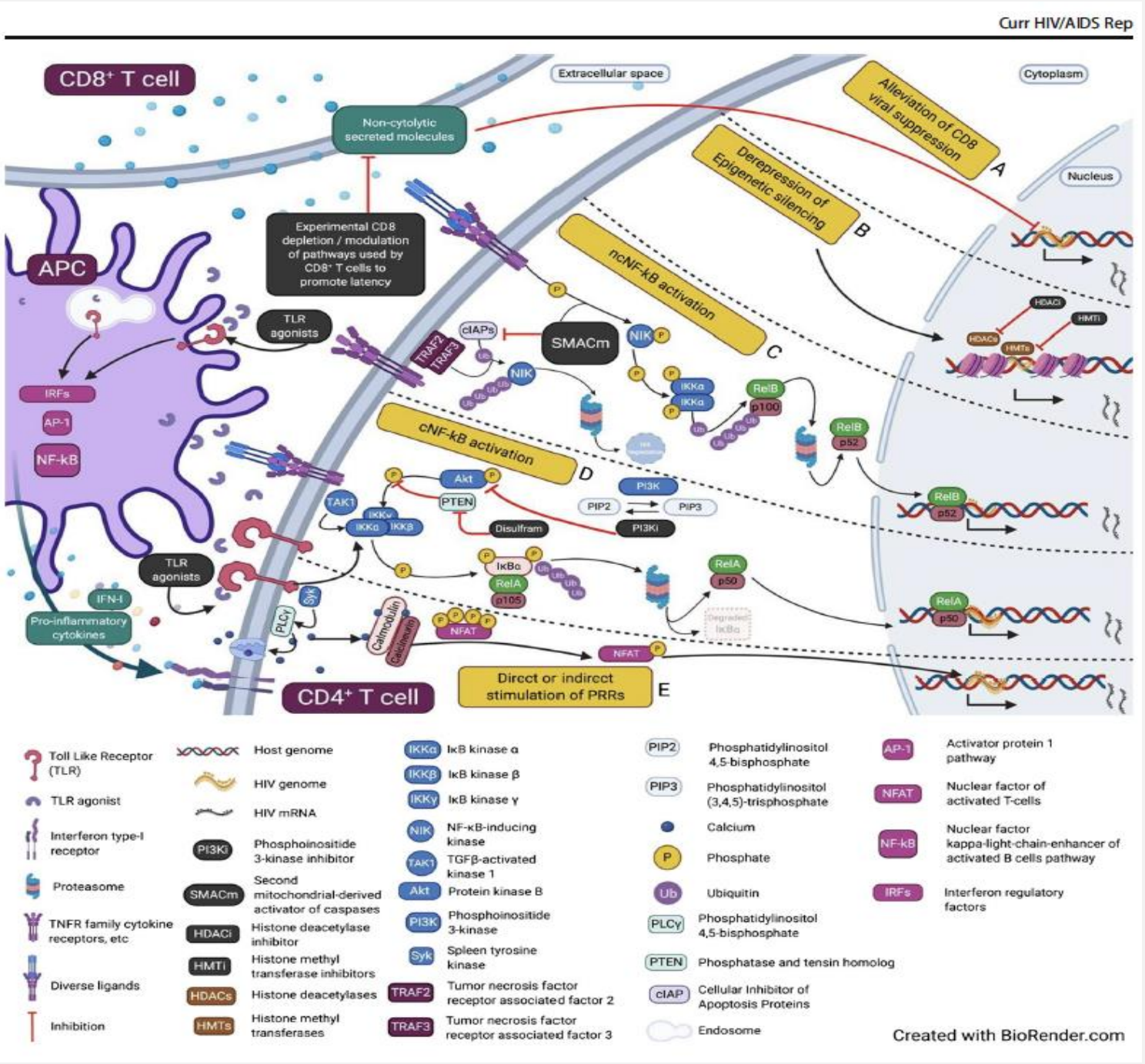
1. Casazza CROI 2021. Abstr 160. 2. Margolis. IAS 2021. Abstr OALA01LB03. 3. Capparelli. CROI 2021. Abstr 609. 4. Turcotte. CROI 2021. Abstr 298.

Latency Reversal 2.0: Giving the Immune System a Seat at the Table

Vidisha Singh[1] · Amir Dashti[1] · Maud Mavigner[1,2] · Ann Chahroudi[1,2,3]

Recent advances in latency reversal strategies that target specific signaling pathways within CD4+ T cells or other immune cells to induce expression of latent HIV (immune-based latency reversal, or LRA 2.0).

Current HIV/AIDS Reports
https://doi.org/10.1007/s11904-020-00540-z



Key Take-home Points on HIV Cure Research

- Progress towards a cure or long-term ART-free remission remains slow
- The field is moving towards combination approaches
- Better latency reversal agents are needed
- The safety of various immunomodulators remains a concern

LIKELY POSITIONING FOR NEW DRUGS

Indication	Name
treatment-naive	islatravir, doravirine/islatravir
switch options on ART	islatravir, doravirine/islatravir, cabotegravir LA/ rilpivirine LA, bNAbs,
multidrug resistance (MDR)	islatravir, bNAbs, new classes: capsid and maturation inhibitors.
PrEP	cabotegravir-LA; islatravir; VRC01, all other mAbs.
maintenance without ART	bNAbs - in combinations as switch after viral load suppressed on ART.

http://www.i-Base.info/hiv-pipeline-report-2020

COMPOUNDS WITH LONG-ACTING FORMULATIONS

Compound	Company
cabotegravir	ViiV Healthcare
islatravir	Merck/MSD
MK-8504 / MK-8583	Merck/MSD
bNAbs: including 3BNC117 and 10-1074; PGDM1400 and PGT121, 10E8.	Various including NIH/NIAID, Rockefeller University, ViiV Healthcare, Gilead Sciences.
GS-6207 (capsid)	Gilead Sciences
GSK '937 (maturation)	ViiV Heathcare
combinectin	ViiV Heathcare
elsulfavirine	Viriom

http://www.i-Base.info/hiv-pipeline-report-2020

Aspirational Vision*

Lenacapavir Vision: The foundation for new long-acting therapy options for HIV treatment and prevention

Person-centric options addressing the needs and preferences of PLWH and PWBP which may contribute to ending the HIV epidemic

Options-driven, iterative development approach, addressing clinical and public health needs

Timing	Near-term (1-2 years)	Mid-term (3-5 years)	Long-term (5+years)
HIV Treatment	**Significant Unmet Need** Initial launch for HTE PLWH (LEN SC + OBR) **Q6M LAI** Robust early-phase program to select partner(s) for complete LA treatment	**Options-driven Paradigm** Launch LEN-containing LAI (Q1-3M) and LAO (QW) complete regimens **Q1-3M LAI** **QW LAO**	**Ultimate Transformative Therapy** Launch best in class LEN-containing LAI therapies to optimize frequency, formulation and dosing (aspirationally, a Q6M complete regimen) **Q6M LAI**
HIV Prevention	Initiate pivotal Ph3 program of Q6M LEN SC and begin establishing the benefits of long-acting PrEP	**Diverse Options for People Who May Benefit from PrEP** • Launch Q6M LEN for PrEP • PrEP long-acting options, an important strategy in ending the epidemic, will allow for **more flexibility for PWBP to take control of their health** **Q6M LAI**	

62 * Aspirational life cycle vision that will be informed by ongoing clinical trials

HTE, heavily treatment-experienced; PLWH, people living with HIV; PWBP, people who may benefit from pre-exposure prophylaxis; SC, subcutaneous; OBR, optimized background regimen; LAI, long –acting injectable; LAO, long-acting oral; QW, every week; Q1-3m, every 1-3 months; Q6M, every 6 months

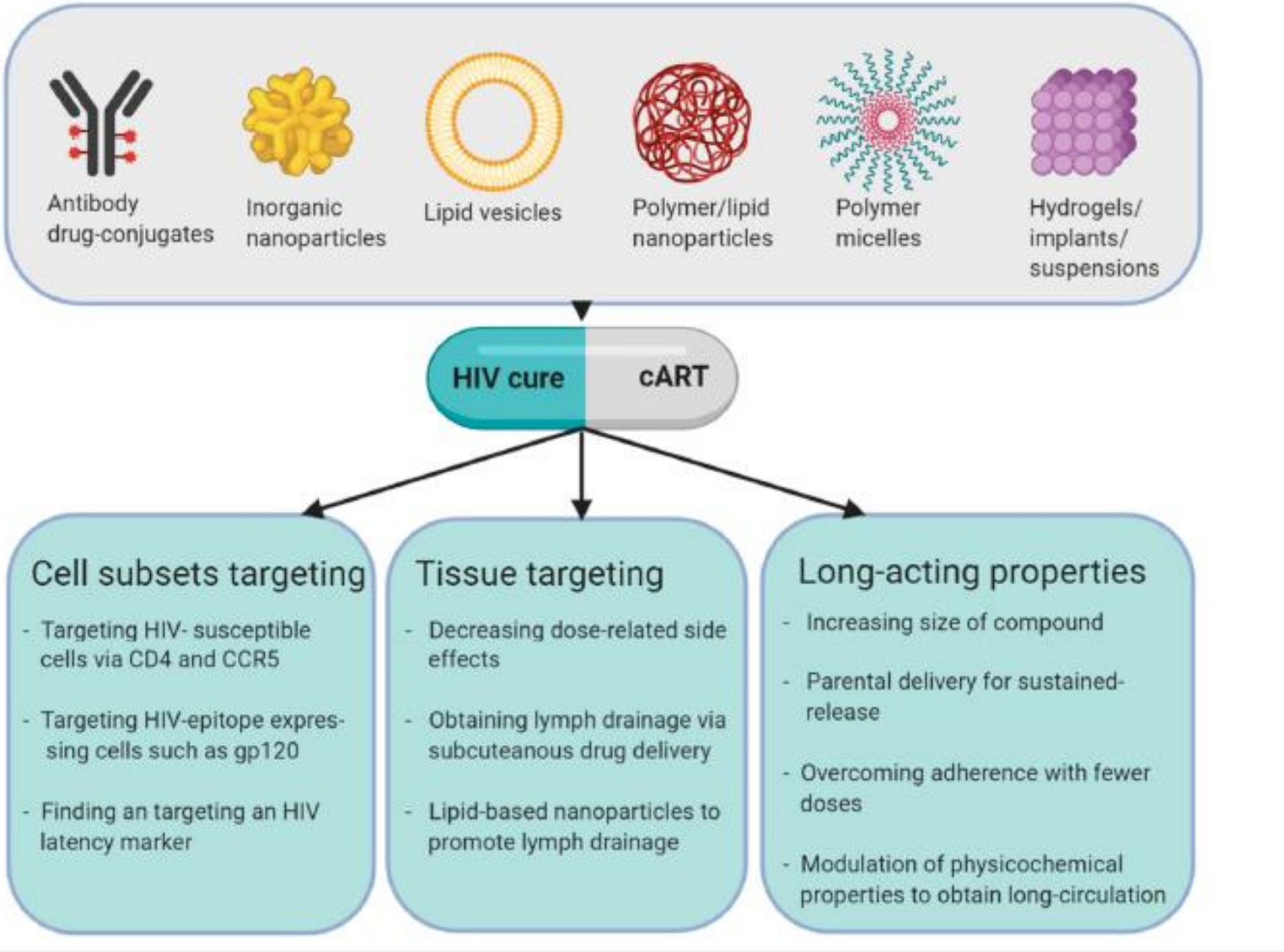
viruses

MDPI

Review

The Potential of Long-Acting, Tissue-Targeted Synthetic Nanotherapy for Delivery of Antiviral Therapy Against HIV Infection

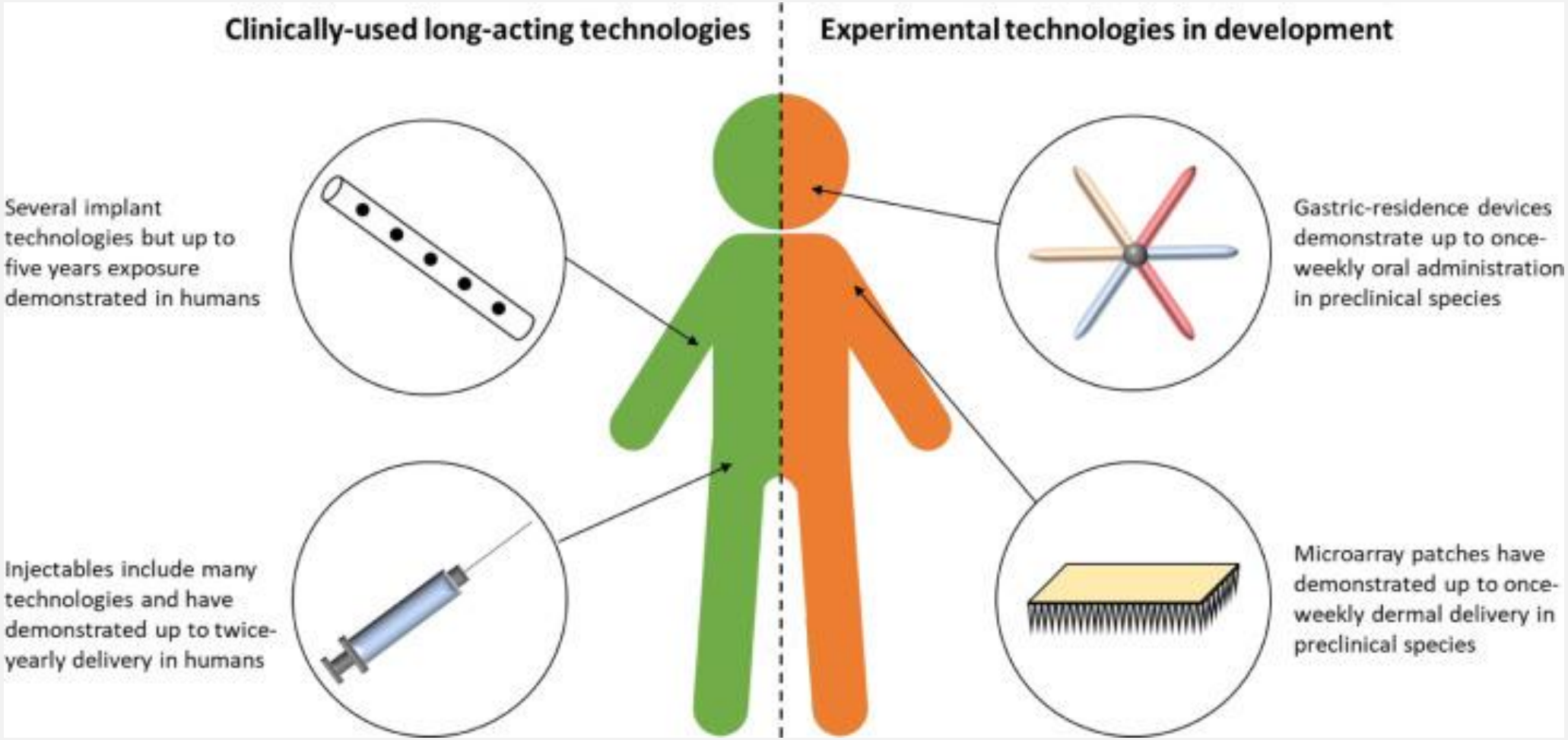
Anna Halling Folkmar Andersen [1,2,*] and Martin Tolstrup [1,2]



Examples of types of nanotherapy and their application in HIV treatment and cure

Viruses **2020**, *12*, 412; doi:10.3390/v12040412

THE NEW ERA


Clinically-used long-acting technologies
Experimental technologies in development
Several implant technologies but up to five years exposure demonstrated in humans
Injectables include many technologies and have demonstrated up to twice-yearly delivery in humans
Gastric-residence devices demonstrate up to once-weekly oral administration in preclinical species
Microarray patches have demonstrated up to once-weekly dermal delivery in preclinical species