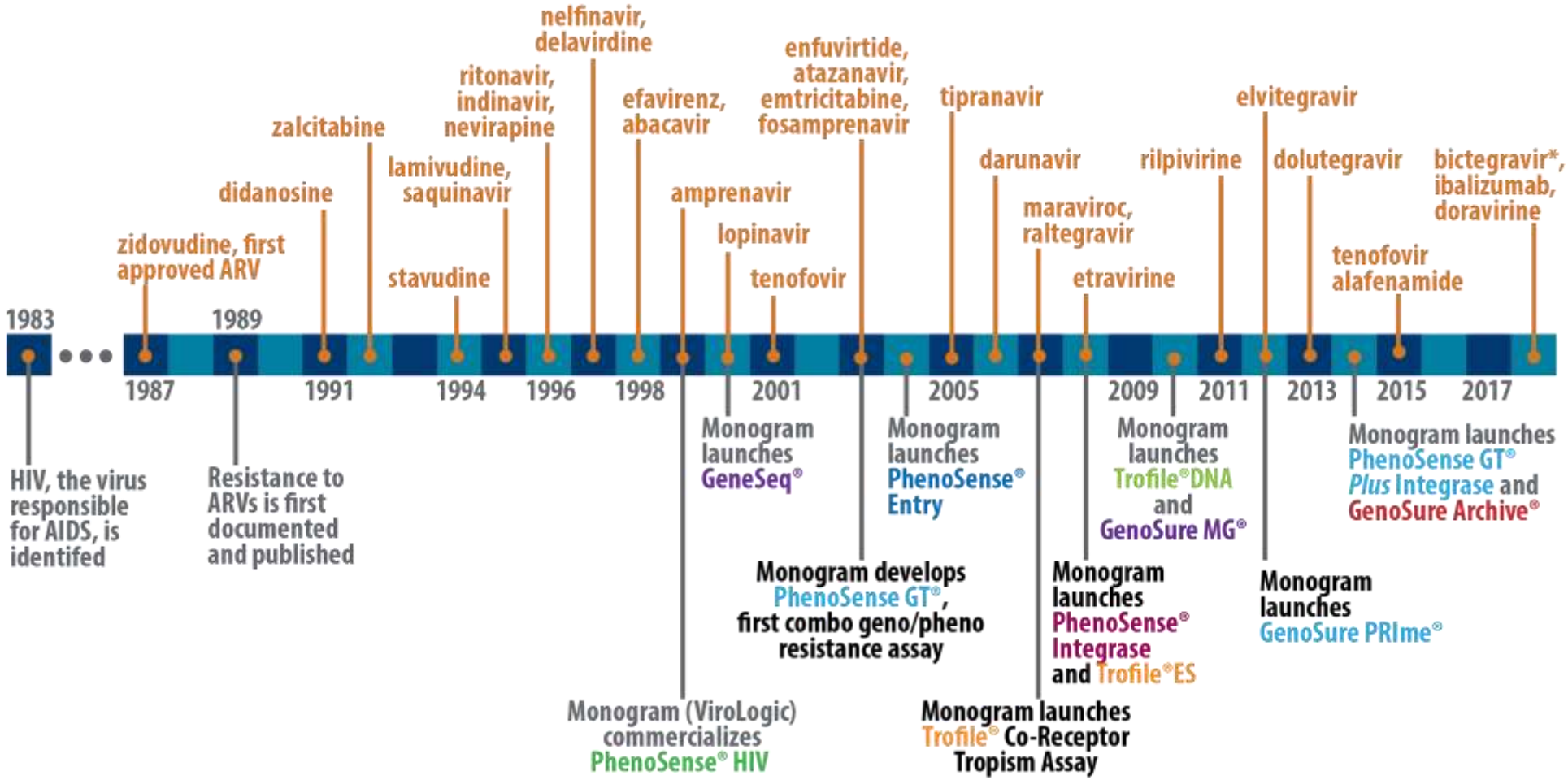
Pipeline of HIV: new drugs and new classes

Cristina Mussini

Disclosures

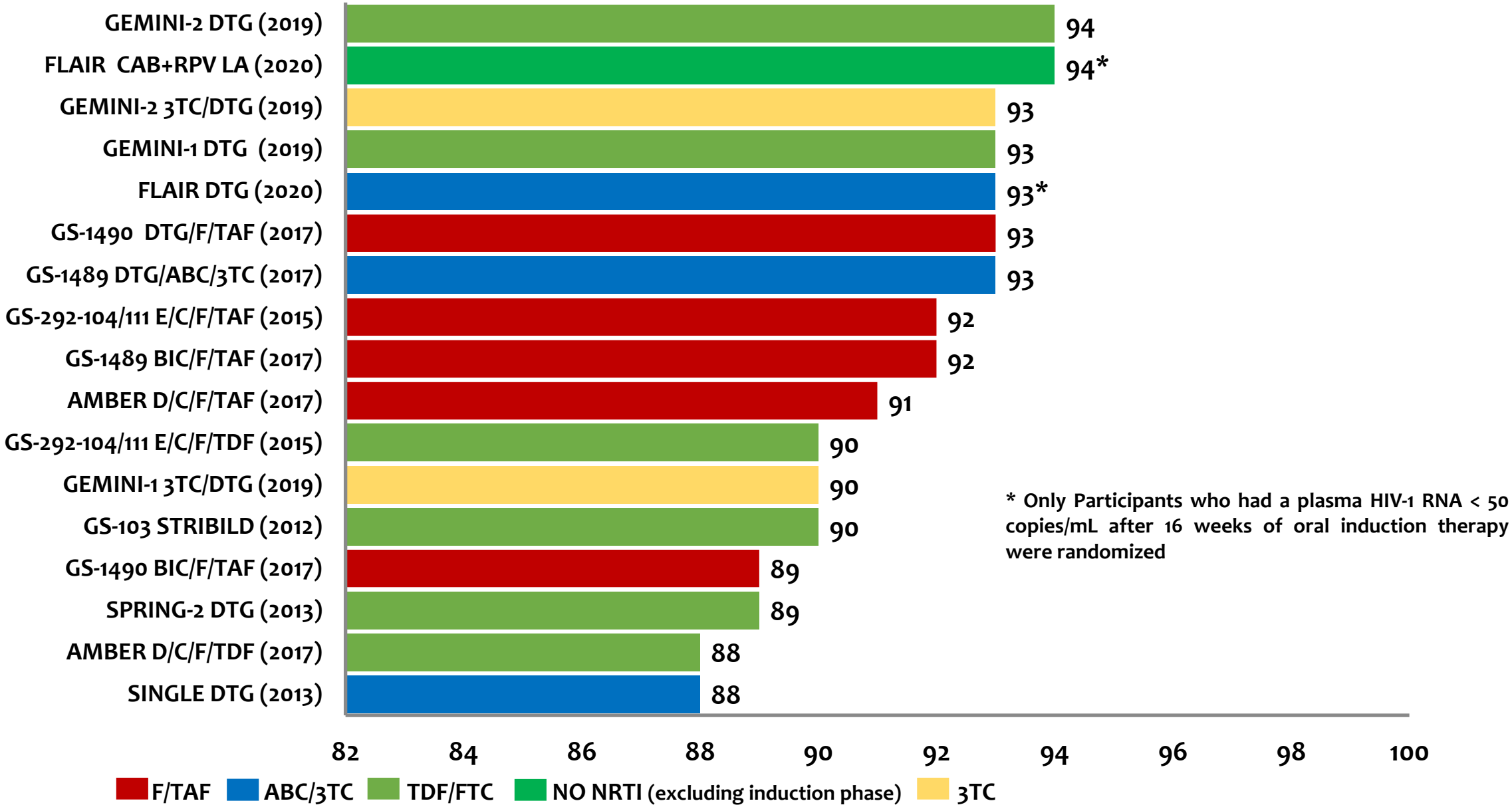
Cristina Mussini has served as a paid consultant to Gilead Sciences, Angelini, Abbvie, Pfizer, Janssen, MSD, ViiV Healthcare and received research fundings from Gilead Sciences, Janssen, MSD, Therateraperutics and ViiV Healthcare.


1983
1987
1989
1991
1994
1996
1998
2001
2005
2009
2011
2013
2015
2017
HIV, the virus responsible for AIDS, is identifed
zidovudine, first approved ARV
Resistance to ARVs is first documented and published
didanosine
zalcitabine
stavudine
lamivudine, saquinavir
ritonavir, indinavir, nevirapine
nelfinavir, delavirdine
efavirenz, abacavir
amprenavir
lopinavir
tenofovir
Monogram launches GeneSeq®
Monogram (ViroLogic) commercializes PhenoSense® HIV
enfuvirtide, atazanavir, emtricitabine, fosamprenavir
Monogram develops PhenoSense GT®, first combo geno/pheno resistance assay
Monogram launches PhenoSense® Entry
tipranavir
darunavir
maraviroc, raltegravir
Monogram launches Trofile® Co-Receptor Tropism Assay
etravirine
rilpivirine
Monogram launches Trofile®DNA and GenoSure MG®
Monogram launches PhenoSense® Integrase and Trofile®ES
elvitegravir
dolutegravir
Monogram launches GenoSure PRIme®
tenofovir alafenamide
bictegravir*, ibalizumab, doravirine
Monogram launches PhenoSense GT® Plus Integrase and GenoSure Archive®

What do we have now?

HIV-RNA < 50 cp/ml AT WEEK 48; ITT-E FDA Shapshot Analysis

Data from multiple studies (2012-2020). Not all regimens have been compared head to head in a clinical trial



* Only Participants who had a plasma HIV-1 RNA < 50 copies/mL after 16 weeks of oral induction therapy were randomized

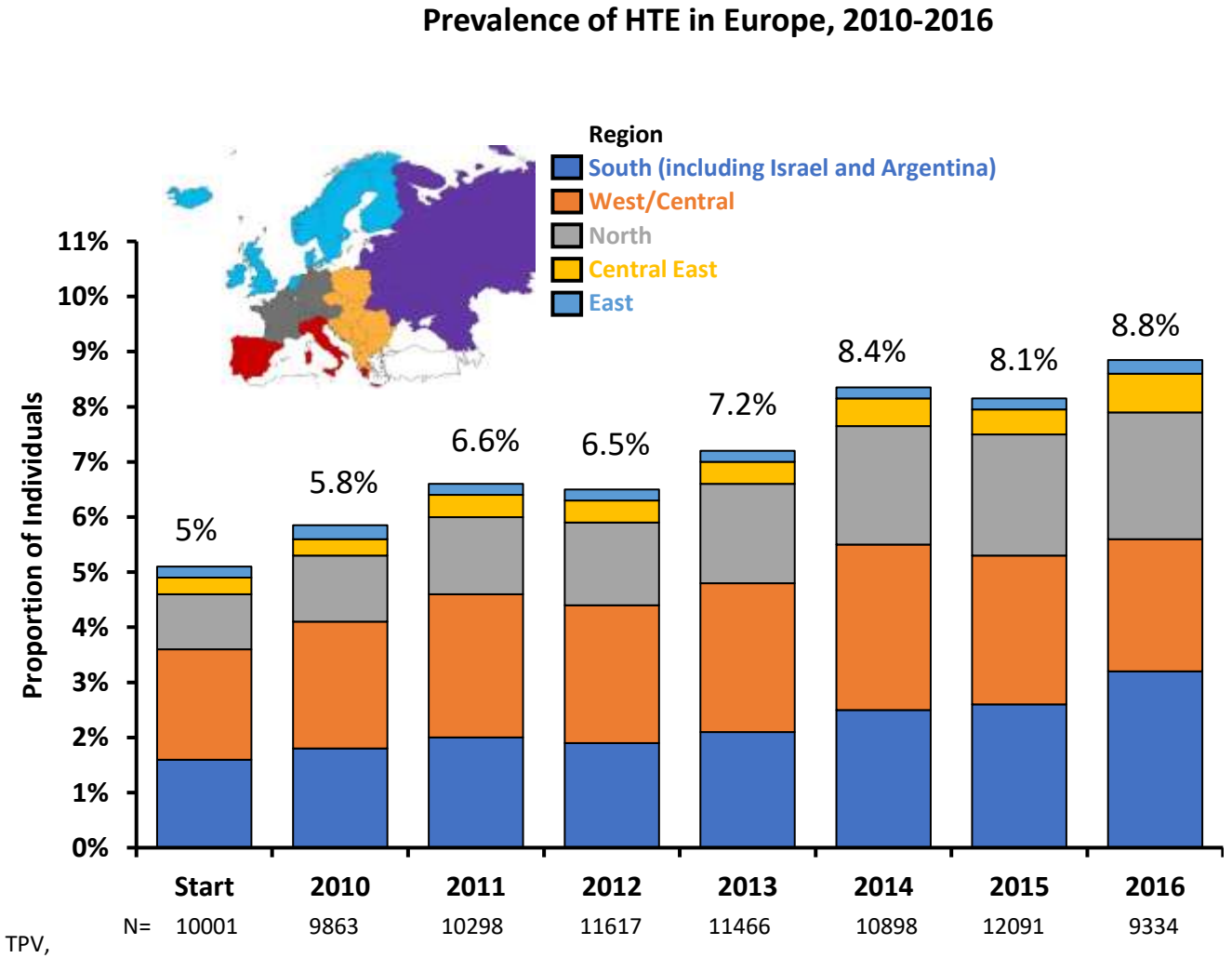
Comparing common recommended ARV third drugs

Characteristics	DTG	BIC	RAL	RPV	DOR	DRV/b
Virologic efficacy	+++	+++	++	+	++	++
Use in high VL/low CD4	+++	+++	+++	-	+++	+++
High barrier to resistance	+++	+++	++	+	+++	+++
Use in rapid ART initiation	+++	+++	+	+	++	+++
Effective in 2DR	+++	-	-	-	-	+
Clinical experience	+++	+	+++	+++	+	+++
Tolerability	+++	+++	+++	+++	+++	+++
Switch data on RCT	++	+++	++	++	++	++
Availabile as STR	+	+	-	+	+	+
Low metabolic impact	+++	++	+++	+++	+++	+
Lack of meal restrictions	+++	+++	+++	+	+++	+
Absence of DDIs	+++	++	+++	++	+++	+
Use in Tuberculosis	**++**	**-**	**++**	**-**	**-**	**+**
Use in pregnancy	+++	-	+++	++	-	+++
Use at conception	+	+++	+++	+++	+++	+++

Why do we need new drugs with different mechanisms?

Prevalence of HTE PLWH in Europe

- HTE composite definition included resistance to NRTIs, NNRTIs, and PIs or they met at least two of the following:
  - *Definition 1*: ≤ 2 drug classes available
  - *Definition 2*: ≥ 4 anchor agent switches and the 4th anchor agent was ENF, DRV, ETR, MVC, TPV, DTG or RAL
  - *Definition 3*: use of ≥ 4 of the following ARVs (DTG, DRV, ETR, RAL) together with a PI, MVC or ENF
- HTE prevalence around 8.8% in the EuroSIDA cohort
- HTE patients had a 2.4-fold and 1.3-fold higher incidence rate of new AIDS and non-AIDS clinical events, respectively

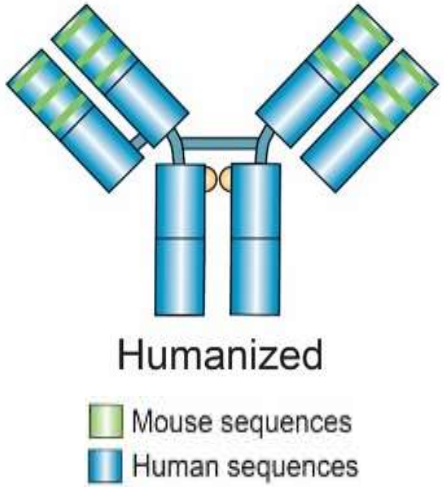


HTE, heavily treatment-experienced; ENF, enfuvirtide; DRV, darunavir; ETR, etravirine; MVC, maraviroc; TPV, tipranavir; DTG, dolutegravir; RAL, raltegravir

Pelchen-Matthews et al. JAIDS 2021; 87(2):806-817.

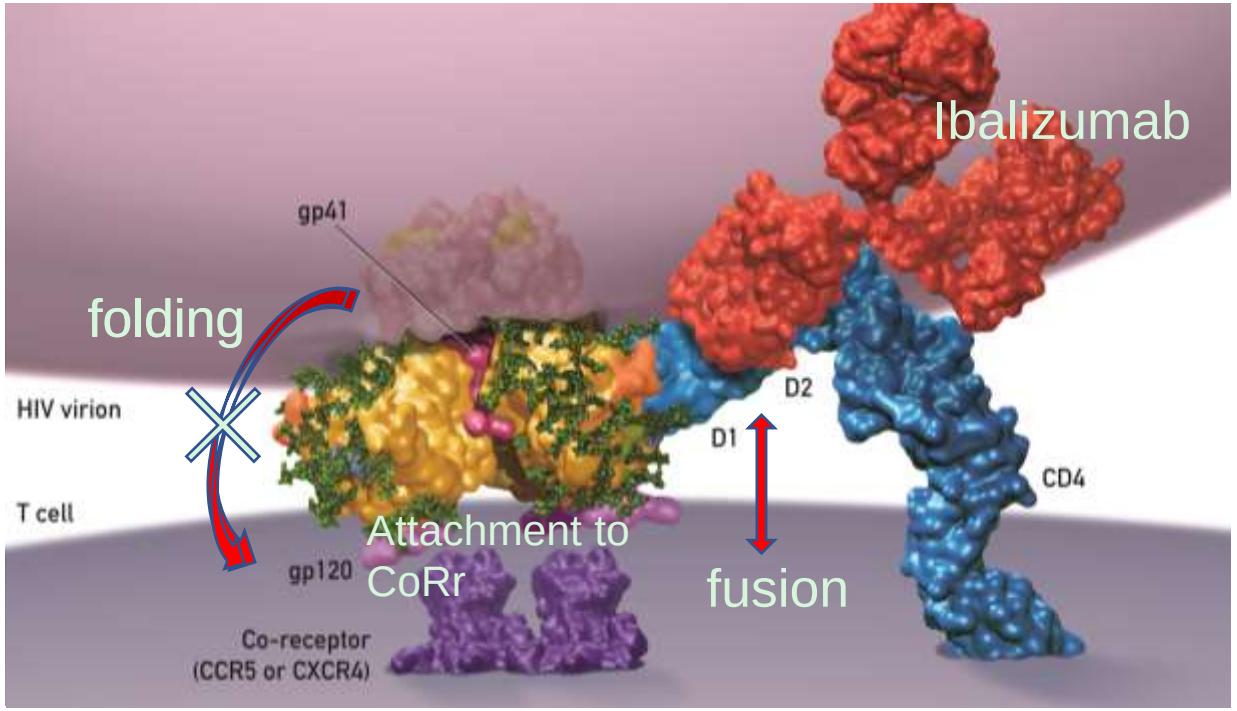
Ibalizumab: humanized monoclonal antibody

- Ibalizumab (IBA) is a humanized monoclonal antibody with a molecular weight of ~150 kDa targeting CD4
- Engineered from its murine progenitor (mu5A8)
- Antibody is 95% human
  - Lower immunogenicity than mouse/chimeric antibodies
- IgG4 backbone chosen for its limited effector functions:
  - antibody-dependent cellular toxicity (ADCC)
  - antibody-dependent cellular phagocytosis (ADCP)
  - complement activation



Mechanism of Action of Ibalizumab: CD4-directed antibody, “post attachment Inhibitor”

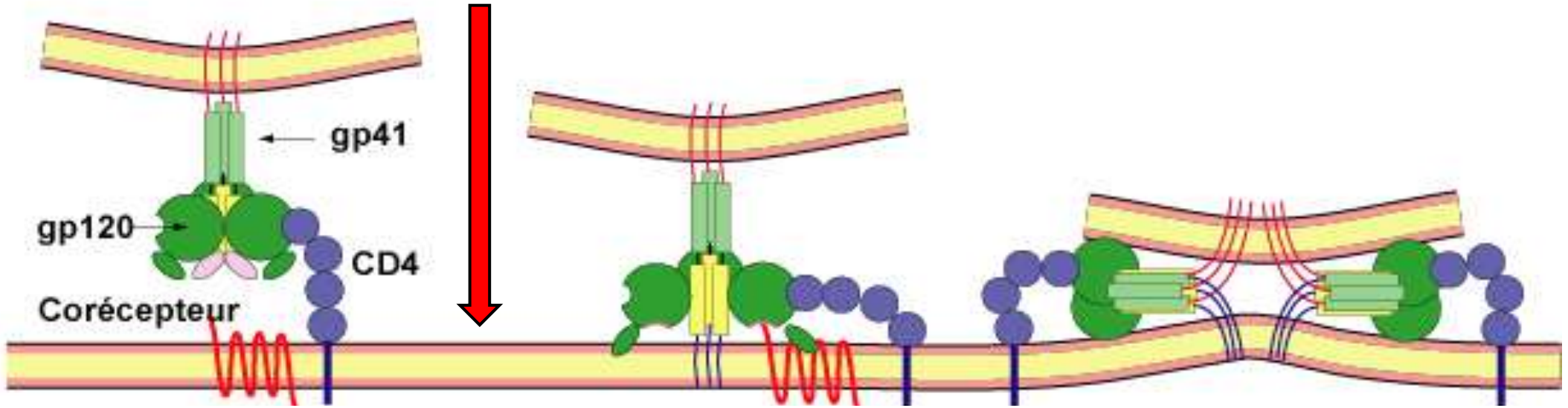
Image adapted from Song R, et al.



- IBA Prevents conformational changes induced by gp120-CD4 interaction via steric hindrance: → Prevents cell-to-cell fusion
- Non competitive inhibition mechanism : not same binding site than HIV on the CD4 (D2 and not D1) →MPI
- **No known polymorphisms at ibalizumab’s binding site (D2 of the CD4)**

Ibalizumab: post attachment inhibitor

Ibalizumab



Binds gp120

Fostemsavir

binds GP120

Binds CD4 and Prevents Folding of complex CD4/gp120

Ibalizumab

binds CD4

Binds CCR5 co-receptor

Maraviroc

binds CCR5

Binds gp 41 and Inhibiting Fusion cell membrane / viral envelope

Enfuvirtide

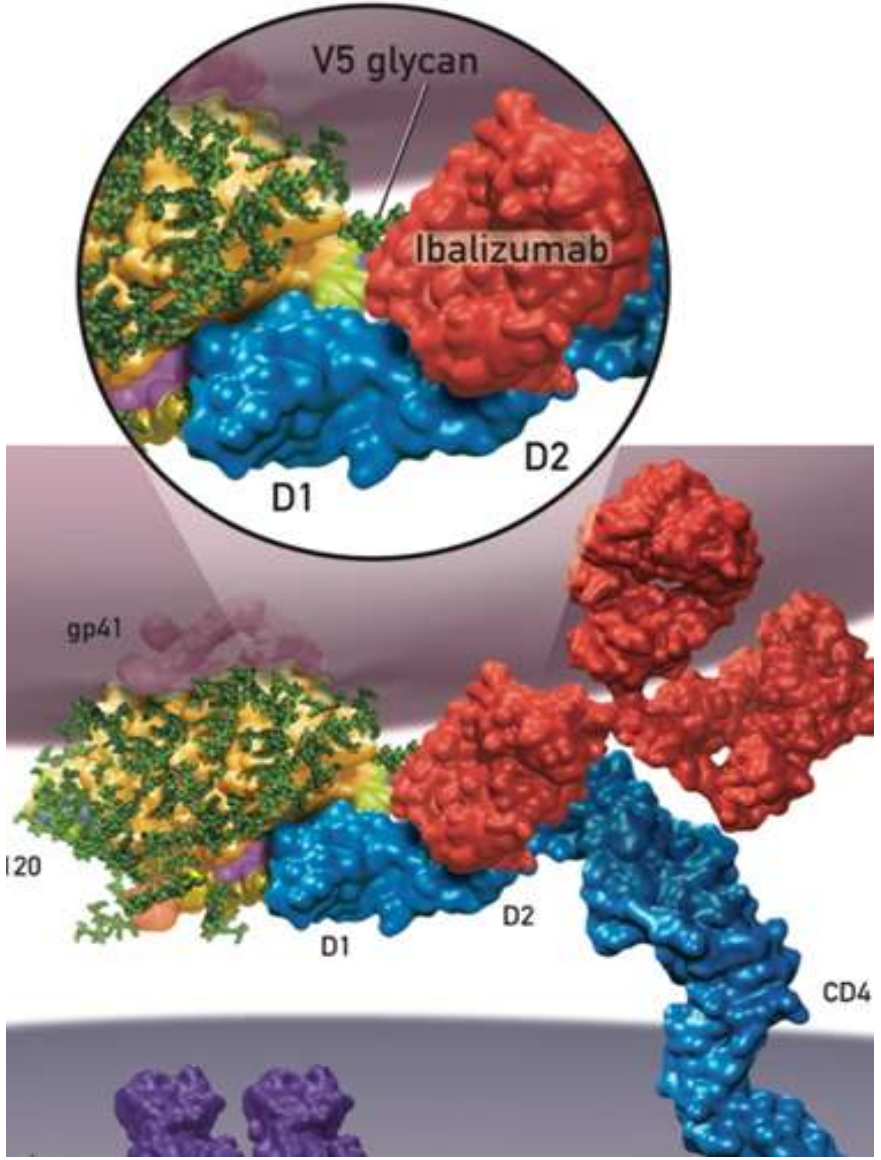
binds GP41

Mechanism of Reduced Susceptibility to Ibalizumab

Loss of N-Linked Glycans in V5 Loop of gp120

N-Glycans in the V5 loop of gp120 fill a void between the V5 loop and **Ibalizumab** causing steric hindrance and preventing conformational changes required for viral entry[1]

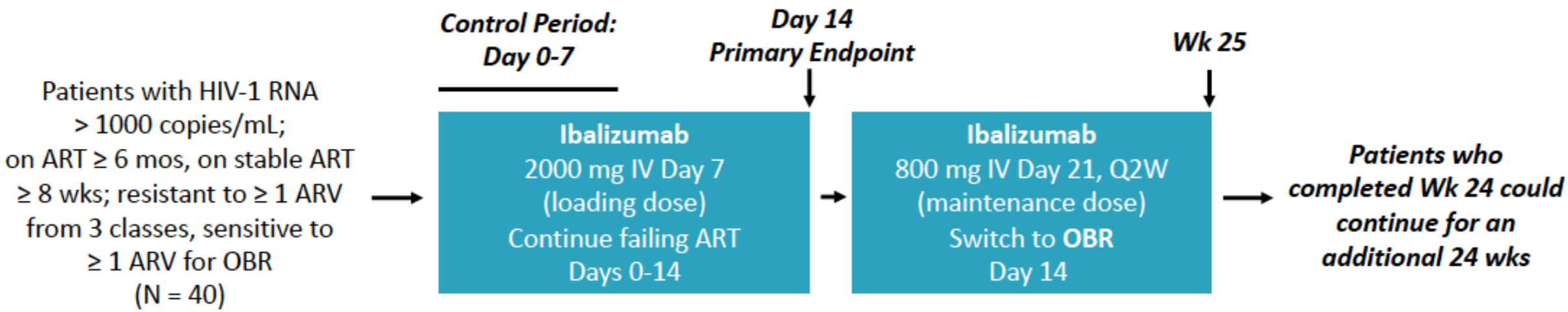
Decrease in susceptibility to ibalizumab has been associated to Loss of Potential N-linked Glycosylation Sites (=PNGS) in the V5 loop of HIV-1 gp120.[2,3]



1. Song R, et al. *Nat Biotechnol* 2013;31:1047-1052.
2. Toma et al. 2011
3. Pace et al 2013

TMB-301: Ibalizumab in Pretreated Patients Infected With Multidrug-Resistant HIV

- Single-arm, open-label phase III trial in patients with virologic failure
  - Primary endpoint: HIV-1 RNA decrease ≥ 0.5 $\log_{10}$ copies/mL from baseline to Day 14



- 53% with resistance to all drugs from ≥ 3 classes; 68% with INSTI resistance
- Mean BL VL 4.5 $\log_{10}$ copies/mL; mean BL CD4+ cell count: 150 cells/mm^3

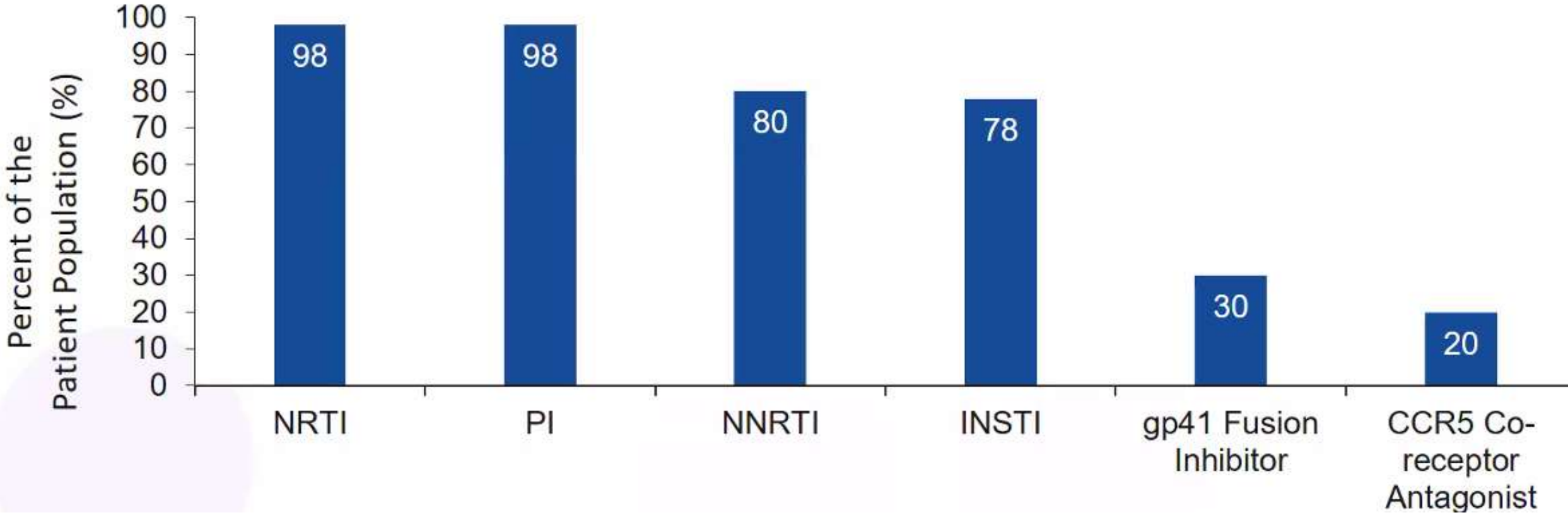
Emu. NEJM. 2018;379:645.

Slide credit: clinicaloptions.com

Baseline Previous ARV Treatment

53% had been treated with 10 or more ARVs prior to enrollment

Percentage of Participants Previously Treated With Any ARV From Class



TMB-301/-311: Virologic Outcomes Through 96 Wks

- TMB-311: patients enrolled in US and Puerto Rico who completed 25 wks in TMB-301 continued ibalizumab 800 mg Q2W for up to 96 wks

Virologic Outcome	Day 14[1] (N = 40)	Wk 25[1] (N = 40)	Wk 48[2,3] (N = 27)	Wk 96[4] (N = 27)
≥ 0.5 log_{10} HIV-1 RNA decrease, %	83*†	63	NR	NR
≥ 1.0 log_{10} HIV-1 RNA decrease, %	60	55	67	NR
Mean log_{10} HIV-1 RNA decrease	1.1	1.6	2.1	NR
Median log_{10} HIV-1 RNA decrease	NR	2.5	2.8	2.8
HIV-1 RNA < 50 copies/mL, %	NR	43	59	56
HIV-1 RNA < 200 copies/mL, %	NR	50	63	NR

*Primary endpoint; $P < .0001$ vs 3% at end of control period. †3 patients without ≥ 0.5 log_{10} HIV-1 RNA decrease at Day 14 later reached HIV-1 RNA < 50 copies/mL with ibalizumab + OBR.[5]

1. Emu. NEJM. 2018;379:645. 2. Emu. IDSA 2017. Abstr 1686. 3. Emu. HIV Glasgow 2018. Abstr O345.
4. Emu. CROI 2019. Abstr 485. 5. DeJesus. HIV Glasgow 2018. Abstr P064.

TMB-301/-311: Safety and Immunologic Outcomes Through 96 Wks

AEs Through Wk 25,[1] n (%)	Patients (N = 40)
Any AE	32 (80)
Assessed as related to ibalizumab	7 (18)
Leading to d/c of ibalizumab	5 (13)
Occurring in patients who died	4 (10)
Serious AE	9 (23)
AEs occurring in > 10% of patients	
▪ Diarrhea	8 (20)
▪ Dizziness	5 (13)
▪ Fatigue	5 (13)
▪ Nausea	5 (13)
▪ Pyrexia	5 (13)
▪ Rash	5 (13)

- No new safety signals emerged from Wk 25 to Wk 96[2]
  - 22 out of 27 patients completed treatment to 96 wks
  - Reasons for early d/c (none related to ibalizumab): Consent withdrawal: n = 2; physician decision: n = 1; death: n = 2 (advanced CVD, CMV progression)
- Median CD4+ cell count increases from baseline[2]:
  - Wk 25: 42 cells/mm^3 (n = 27)
  - Wk 96: 45 cells/mm^3 (n = 22)

1. Emu. NEJM. 2018;379:645. 2. Emu. CROI 2019. Abstr 485.

Fostemsavir

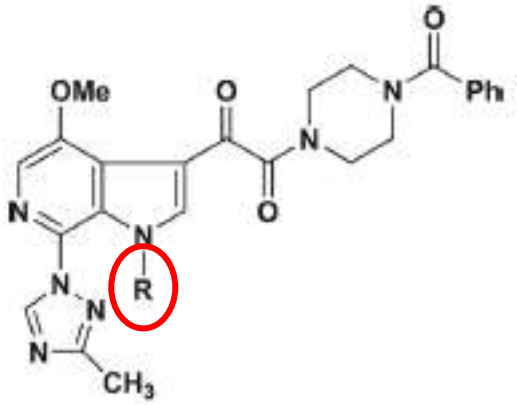
Fostemsavir: attachment inhibitor, active regardless of viral tropism, without cross-resistance to any of the existing ARV compounds.

z

Fostemsavir [BMS-663038 / GSK-3684934]

Mechanism of action

Phosphono-oxymethyl prodrug metabolised to **Temsavir** [BMS-626529], a first-in-class attachment inhibitor that binds to HIV-1 gp120, preventing initial viral attachment and entry into the host CD4+ T-cell

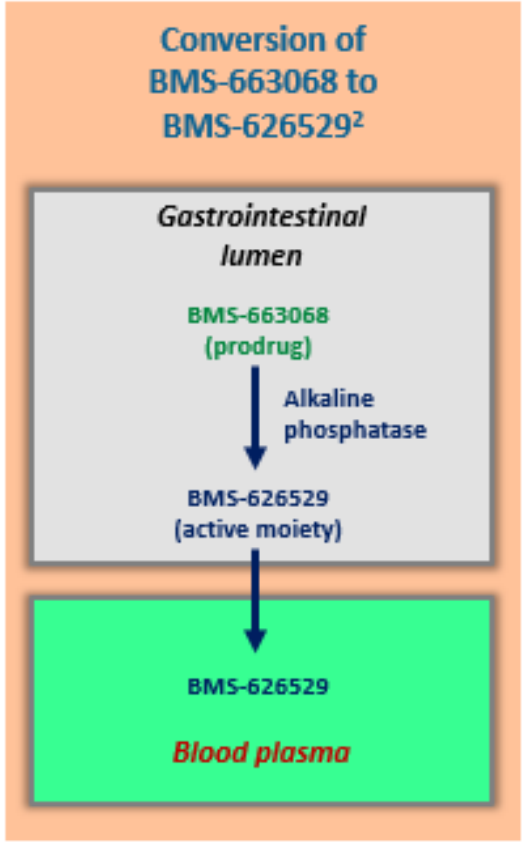


R = H: BMS-626529

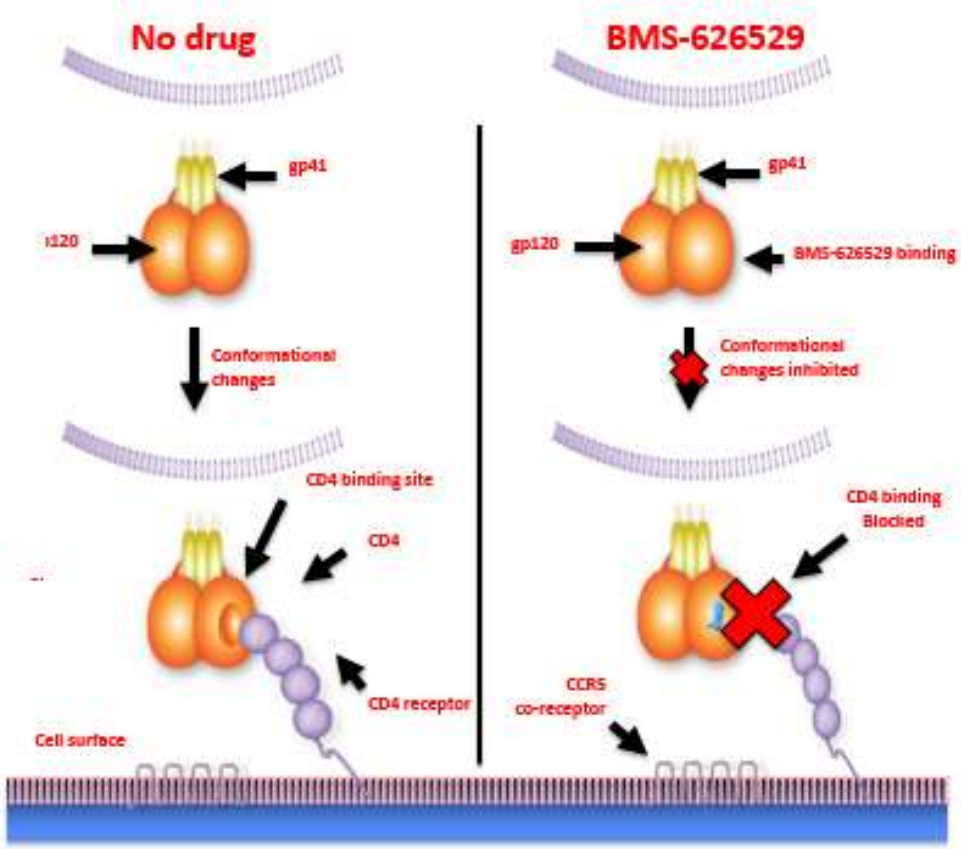
R = $CH_2OP(O)(OH)_2$: BMS-663068

Structures of BMS-626529 and the prodrug, BMS-663068.

1



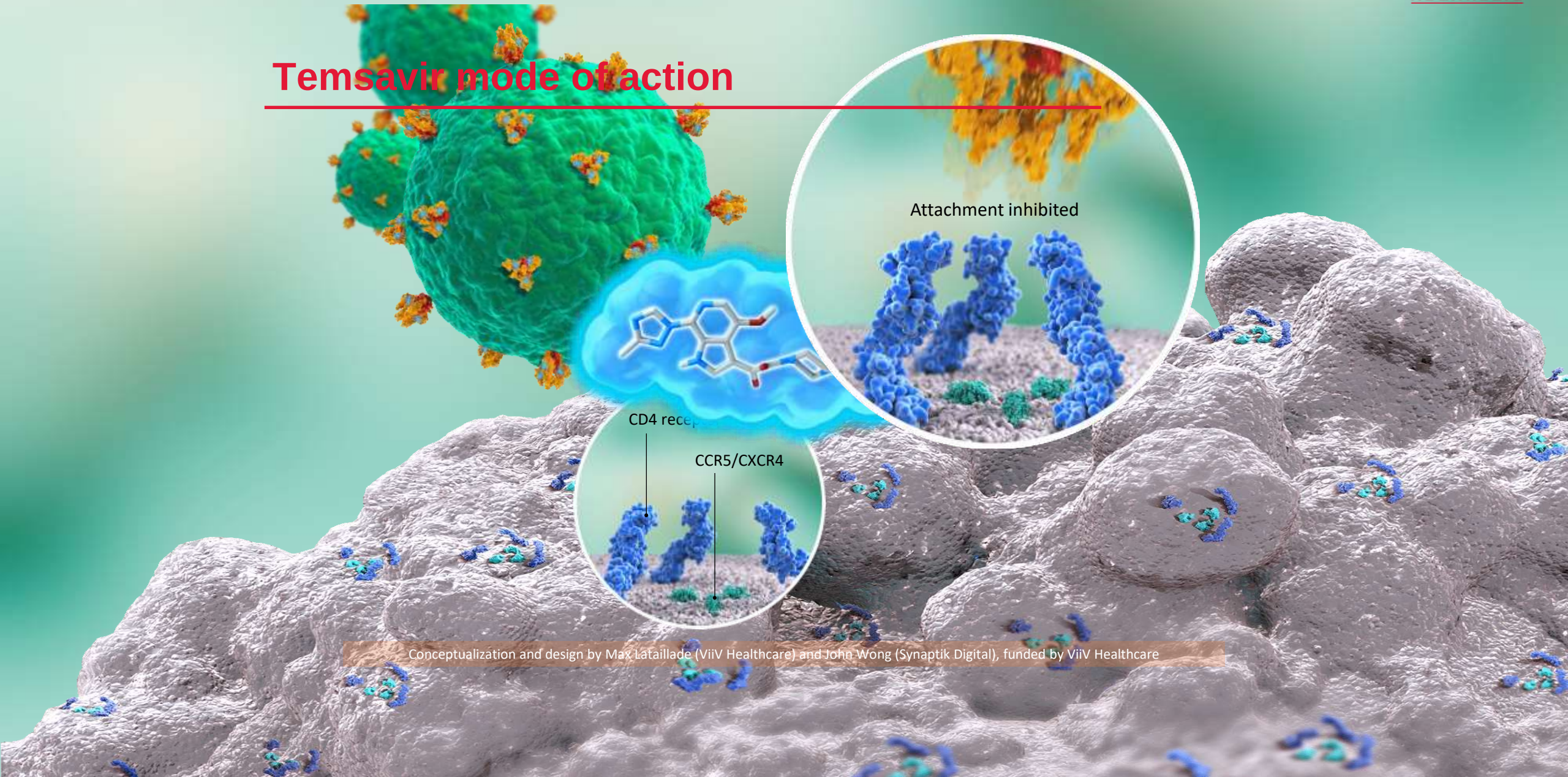
Proposed Mechanism of Action[3]



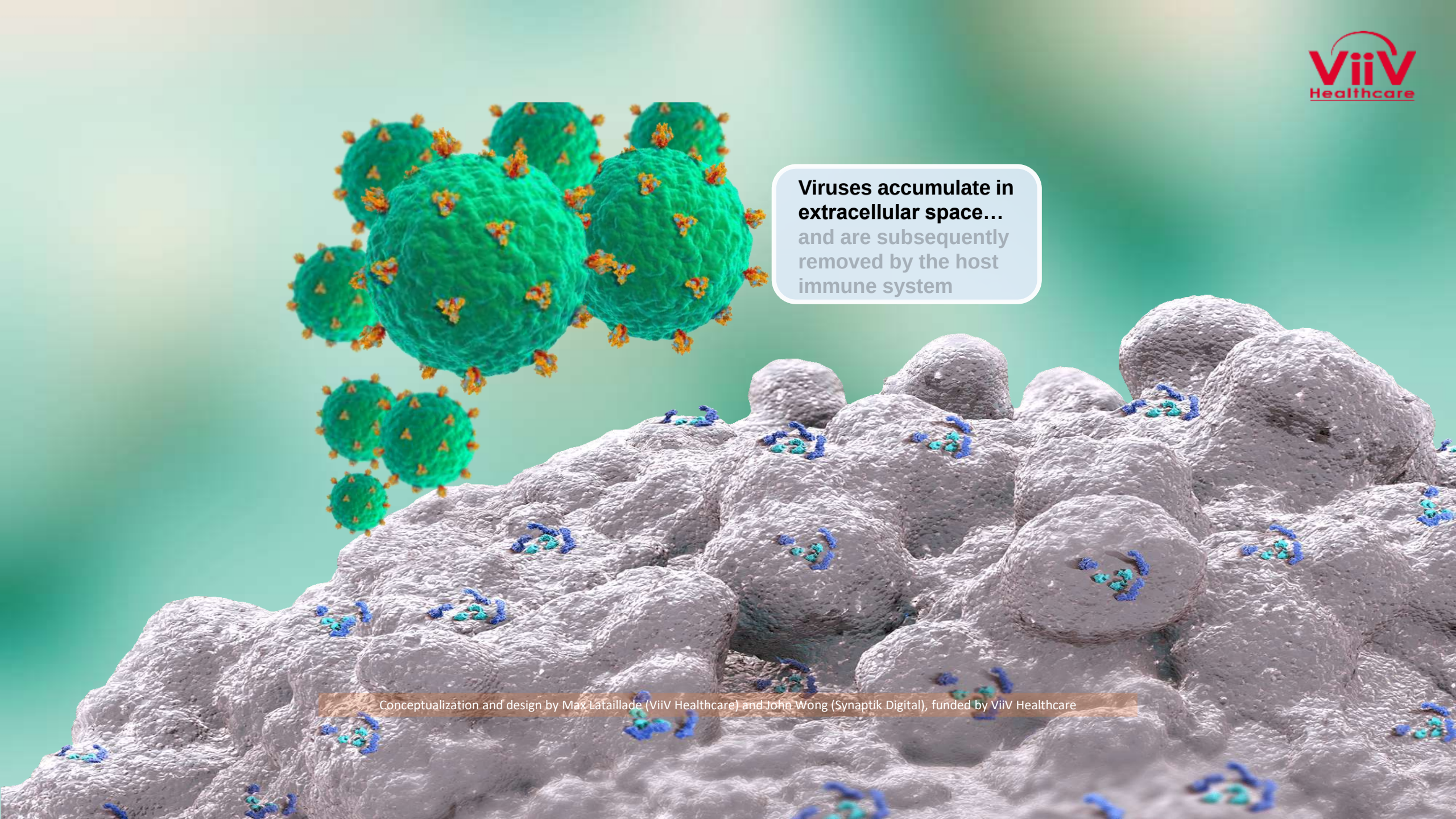
Viruses accumulate in extracellular space… and are subsequently removed by the host immune system

1. Nowicka-Sans B et al. AAC 2012; 56:3498–507; 2. Brown J et al. J Pharm Sci 2013; 102:142–511; 3. Langley DR, et al. Proteins. 2015; 83:331-50;

Temsavir mode of action



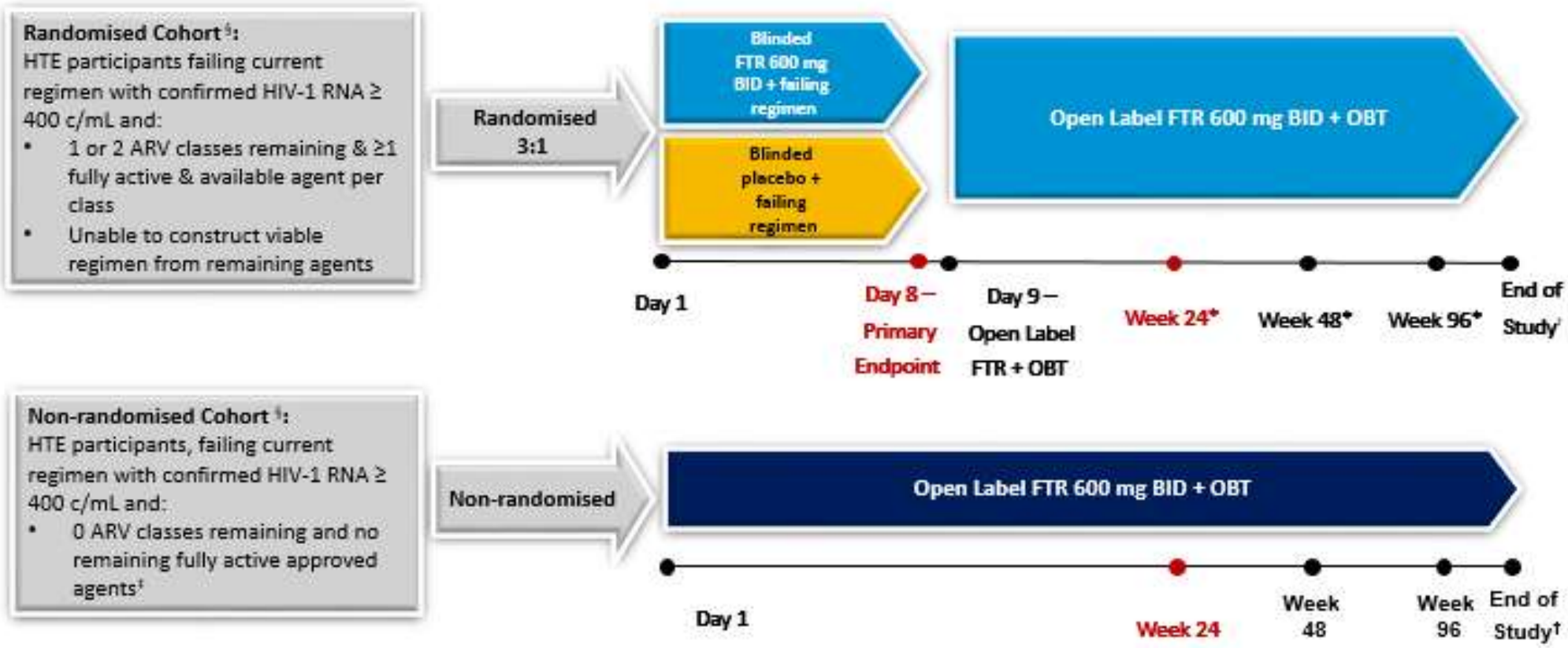
Conceptualization and design by Max Lataillade (ViiV Healthcare) and John Wong (Synaptik Digital), funded by ViiV Healthcare



Conceptualization and design by Max Lataillade (ViiV Healthcare) and John Wong (Synaptik Digital), funded by ViiV Healthcare

BRIGHTE Study

AI438-047: A Multi-arm, Phase 3, Randomized, Placebo Controlled, Double Blind Clinical Trial to Investigate the Efficacy and Safety of Fostemsavir (BMS-663068/GSK3684934) in Heavily Treatment Experienced Subjects Infected With Multi-drug Resistant HIV-1 (**BRIGHTE Study**)



Primary Objective:

- to compare the efficacy of fostemsavir [FTR] to placebo [PBO] (plus current failing regimen): mean change in $\log_{10}$ HIV-RNA from day 1 (baseline) to day 8 (in Randomized Cohort).

Secondary Objectives:

- to assess the durability of response (HIV-RNA <40 cp/ml) of FTR + OBT at weeks 24, 48 and 96
- to assess the safety and tolerability of FTR + OBT SAEs, AEs leading to discontinuation, Grade 3-4 laboratory abnormalities.
- to assess the emergence of antiretroviral drug resistance among subjects with PDVF

Kozal et al. EACS 2017; Milan, Italy. Oral PS8/5.

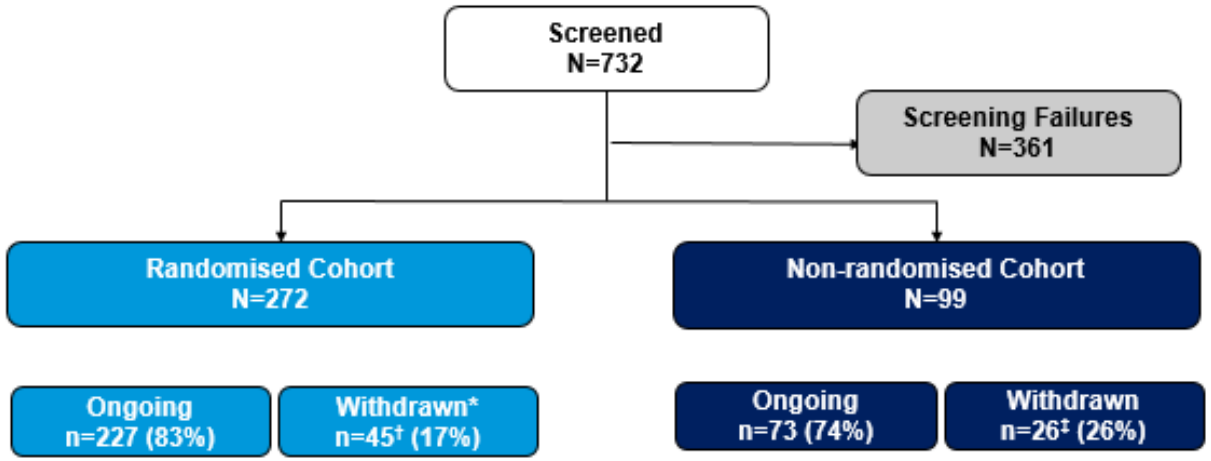
BRIGHTE Study

Baseline Characteristics[1]

Parameter	Randomised Cohort		Non-randomised Cohort	Total Treated Participants (N=371)
	Placebo BID (N=69)	FTR 600 mg BID (N=203)	FTR 600 mg BID (N=99)	
Age years, median (range)	45 (19–66)	48 (18–73)	50 (17–72)	49 (17–73)
<50 years, n (%)	46 (67)	116 (57)	44 (44)	206 (56)
Gender, n (%) Male	57 (83)	143 (70)	89 (90)	289 (78)
Race, n (%)				
White	47 (68)	137 (67)	73 (74)	257 (69)
Black/African American	18 (26)	42 (21)	23 (23)	83 (22)
HIV-1 RNA log_{10} c/mL, median (IQR)	4.5 (3.6–5.2)	4.7 (4.0–5.1)	4.3 (3.6–4.8)	4.6 (3.9–5.33
HIV-1 RNA c/mL, n (%)				
<400	7 (10)	14 (7)	5 (5)	26 (7)
400 to <1000	3 (4)	7 (3)	4 (4)	14 (4)
1000 to <100,000	35 (51)	126 (62)	75 (76)	236 (64)
≥100,000	24 (35)	56 (28)	15 (15)	95 (26)
CD4+ T-cells/µL, median (IQR)	100 (23–244)	99 (15–203)	41 (6–161)	80 (11–202)
CD4+ T-cells/µL, n (%)				
<20	17 (25)	55 (27)	40 (40)	112 (30)
20 to <50	6 (9)	19 (9)	14 (14)	39 (11)
50 to <200	26 (38)	76 (37)	25 (25)	127 (34)
200 to <500	16 (23)	42 (21)	18 (18)	76 (20)
≥500	4 (6)	11 (5)	2 (2)	17 (5)

Relative to the Randomised Cohort, a greater proportion of participants in the Non-Randomised Cohort had a CD4+ T-cell count <20 cells/µL

Study Disposition[2]



*6 participants (FTR n=5; placebo n=1) discontinued during the double-blind period of the study.

† Withdrawal reasons (n, %): AEs (13, 5%), lack of efficacy (9, 3%), non-adherence (7, 3%), withdrawn consent (5, 2%), lost to follow-up (5, 2%), met stopping criteria (3, 1%), death (1, <1%), pregnancy (1, <1%) and other (1, <1%).

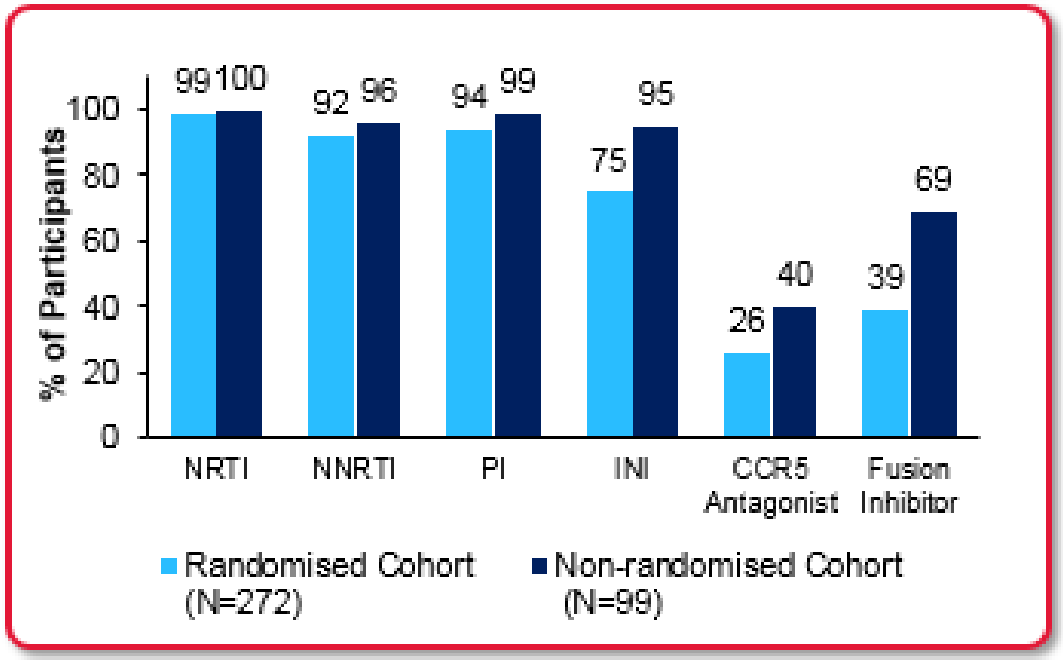
§ Withdrawal reasons (n, %): AEs (9, 9%), lack of efficacy (4, 4%), non-adherence (3, 3%), withdrawn consent (2, 2%), lost to follow-up (1, 1%), met stopping criteria (3, 3%), death (1, 1%) and other (3, 3%).

1. Aberg J et al. HIV Glasgow 2018; Glasgow, UK. Oral 334A & 334B;
2. Kozal et al. EACS 2017; Milan, Italy. Oral PS8/5.

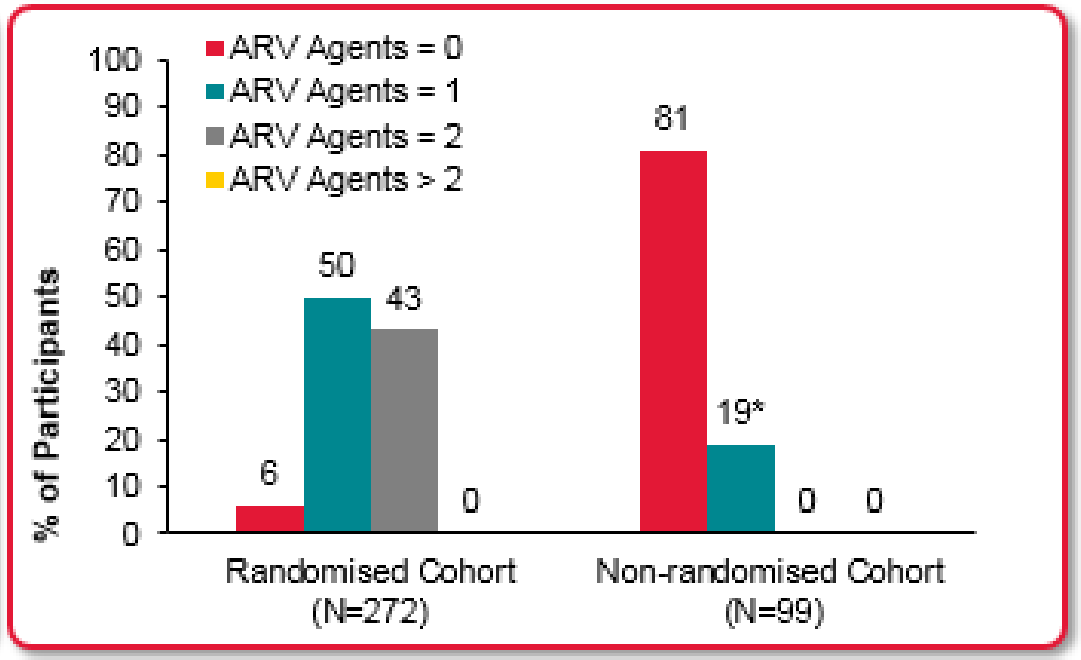
BRIGHTE Study

Baseline Characteristics

Prior Exposure to ARVs



Fully Active and Available ARV Agents in Initial OBT



- Overall, 71% (262/371) of participants were treated for HIV-1 infection for>15 years, 85% (316/371) had prior experience with ≥5 ARV regimens (80% and 96% were INSTI and PI experienced, respectively), and 86% (320/371) had a history of AIDS
- In the Randomised Cohort, 50% (137/272) and 43% had 1 or 2 FAAs in their initial OBT, respectively
  - Of the 99 Non-randomized participants, 81 had no approved FAAs or investigational ARVs in their initial OBT and 15 had investigational ibalizumab in their initial OBT

*15/19 received investigational ARV Ibalizumab.

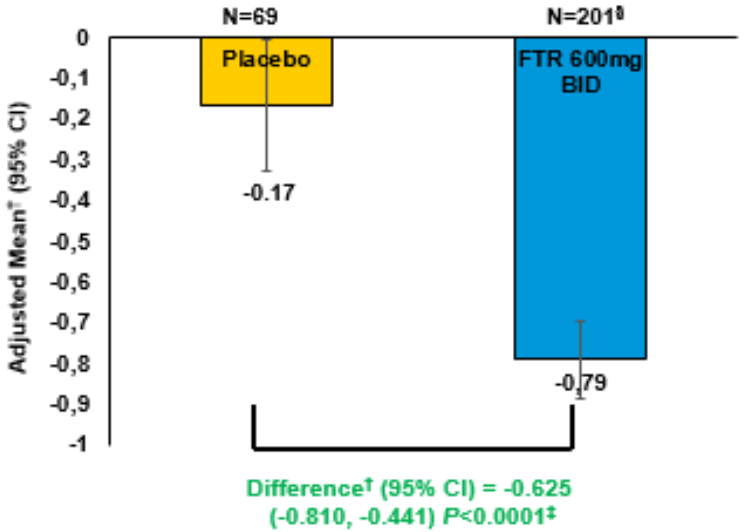
INI, integrase inhibitor; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-NRTI; PI, protease inhibitor; FAA: Full Active Agents.

Kozal et al. EACS 2017; Milan, Italy. Oral PS8/5.

BRIGHTE Study

Primary Endpoint

The primary endpoint was the adjusted mean plasma HIV-1 RNA $\log_{10}$ change from Day 1 at Day 8* in the Randomised Cohort (ITT-E)



FTR participants (ITT-E)

- >0.5 $\log_{10}$ decrease - **65%**
- >1 $\log_{10}$ decrease - **46%**

Subgroup: Baseline HIV-1 RNA >1000 c/mL (n=182), FTR demonstrated:

- Median decrease of **1 $\log_{10}$**
- Adjusted mean decrease of **0.9 $\log_{10}$**
- >0.5 $\log_{10}$ decrease - **68%**
- >1 $\log_{10}$ decrease - **50%**

Virologic Response at Week 24 (Snapshot Analysis)

Outcome	Randomized Cohort (N=272)	Non-randomized Cohort (N=99)
Virologic Success, n (%) (HIV-1 RNA <40 c/mL)	146 (54)	36 (36)
Virologic Failure, n (%)	108 (40)	55 (56)
Data in window not below threshold	87 (32)	44 (44)
D/C for lack of efficacy	1 (0)	0
D/C for other reason while not below threshold	5 (2)	2 (2)
Change in ART	15 (6)	9 (9)
No Virologic Data	18 (7)	8 (8)
D/C study due to AE or Death	11 (4)	4 (4)
D/C study for Other Reasons	4 (1)	0
Missing data during window but on study	3 (1)	4 (4)

Kozal et al. EACS 2017; Milan, Italy. Oral PS8/5.

Fostemsavir: Indications and Recommendations

- July 2020: FDA approved as twice daily oral tablet for heavily treatment–experienced adults with multidrug-resistant HIV infection and regimen failure[1]
- Recommendations from guidelines
  - DHHS ART guidelines not yet updated to reflect FDA approval of fostemsavir[2]
  - IAS-USA: *"…fostemsavir can be used when creating a salvage regimen* ***for individuals with extremely limited treatment options."***[3]
- Needs to be combined with other active agents to achieve viral suppression

1. Fostemsavir PI. 2. DHHS ART Guidelines. December 2019. 3. Saag. JAMA. 2020;[Epub].

Slide credit: clinicaloptions.com

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

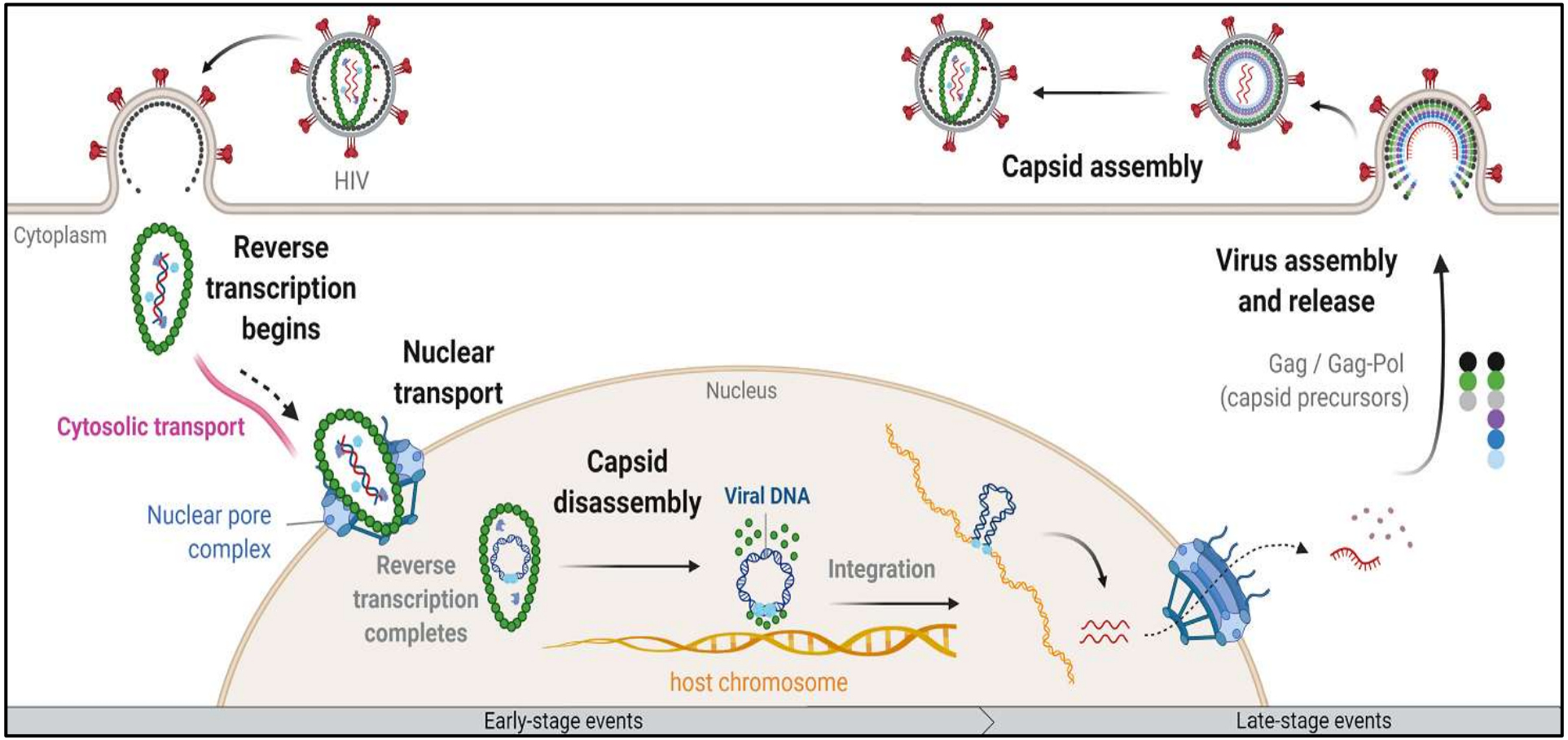
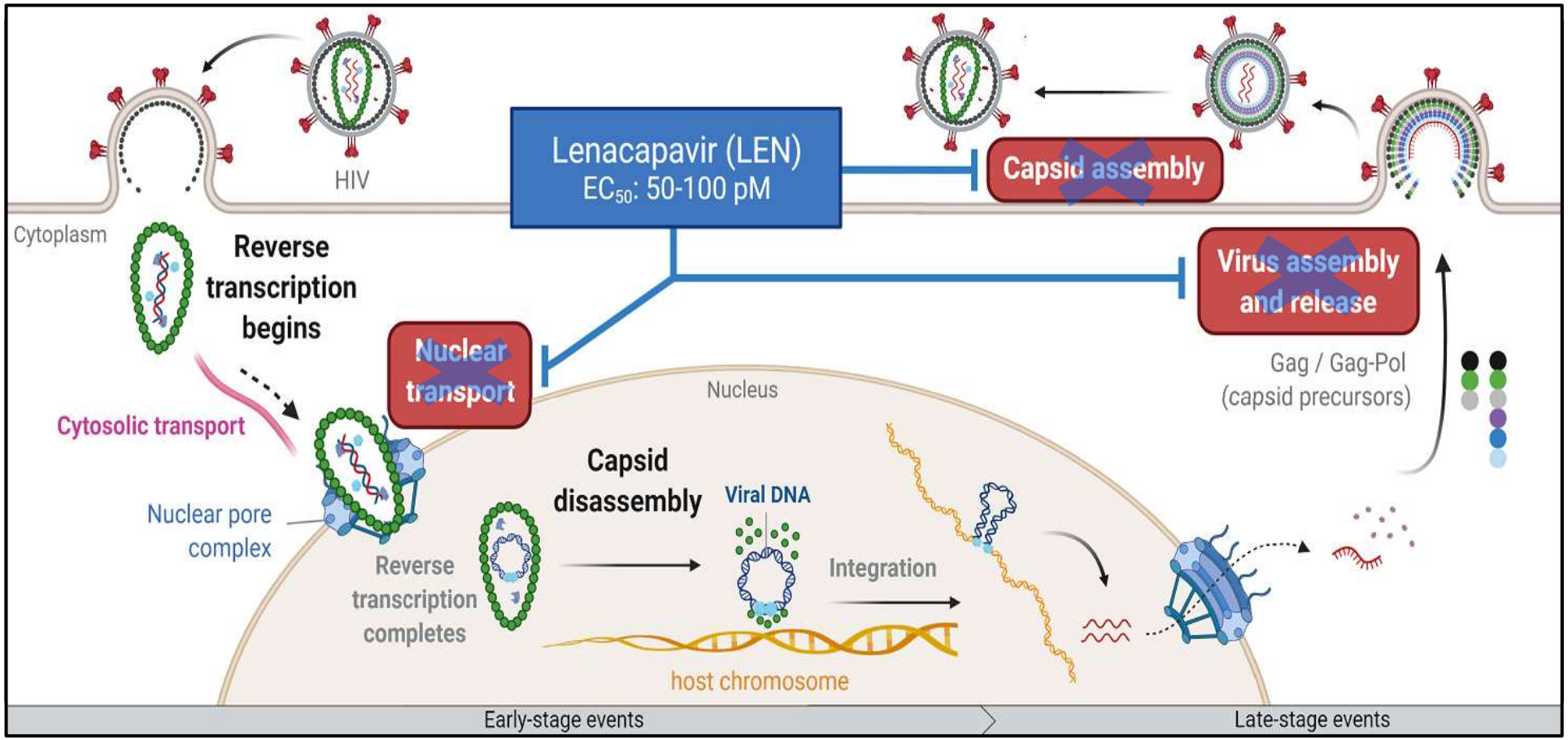


Figure generated based on the following references: Link J, et al. Nature 2020;584:614-618; Bester SM, et al. Science 2020;370:360-364; Cihlar T. vCROI 2021. Oral #22; Muller B. vCROI 2021. Oral #19; Pathak VK. vCROI 2021. Oral #20; Ganser-Pornillos B. vCROI 2021. Oral #21

LEN Targets Multiple Stages of the HIV Replication Cycle

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

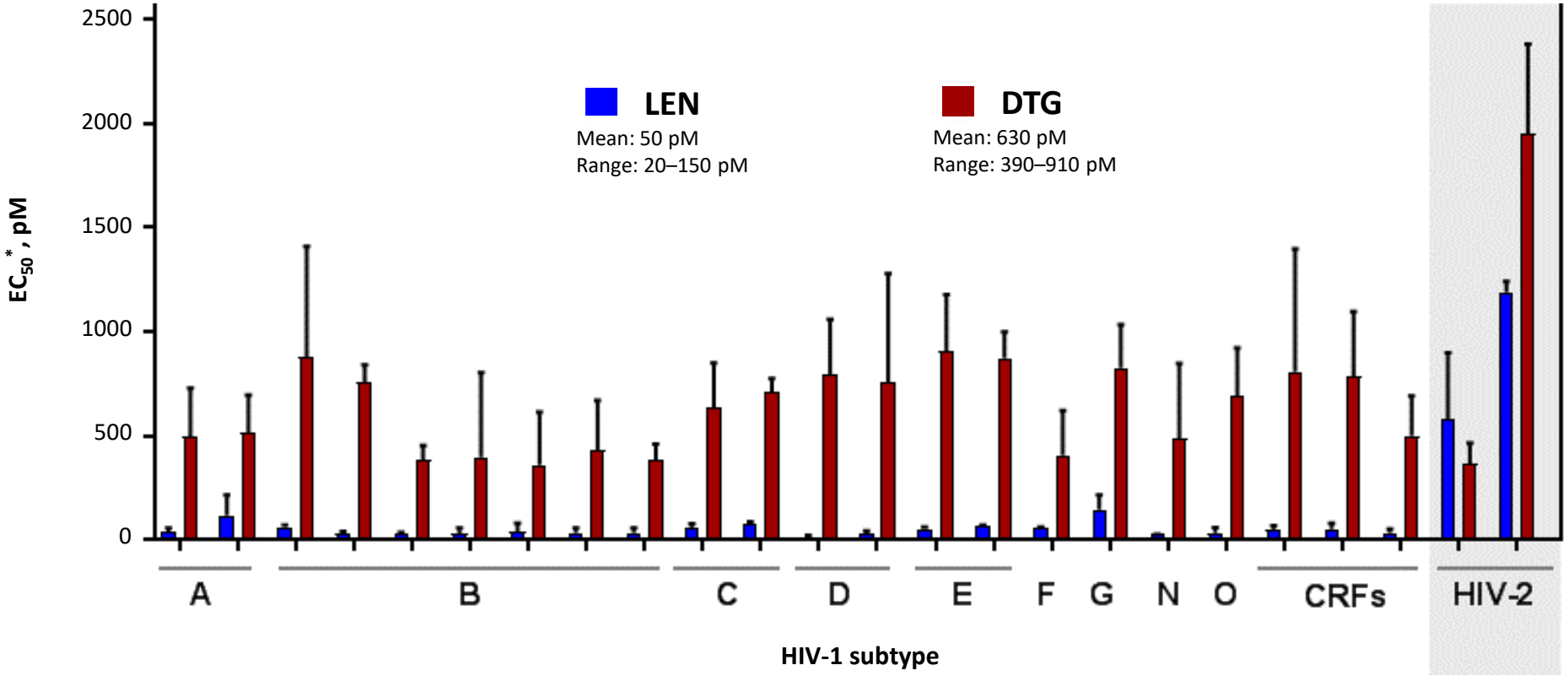
1. Capsid-mediated nuclear uptake of HIV proviral DNA
2. Virus assembly and release
3. Capsid core formation



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

Potency Against HIV-1 and HIV-2 in Human PBMCs



LEN is a more potent inhibitor of all major HIV-1 subtypes than DTG;
LEN also has activity against HIV-2

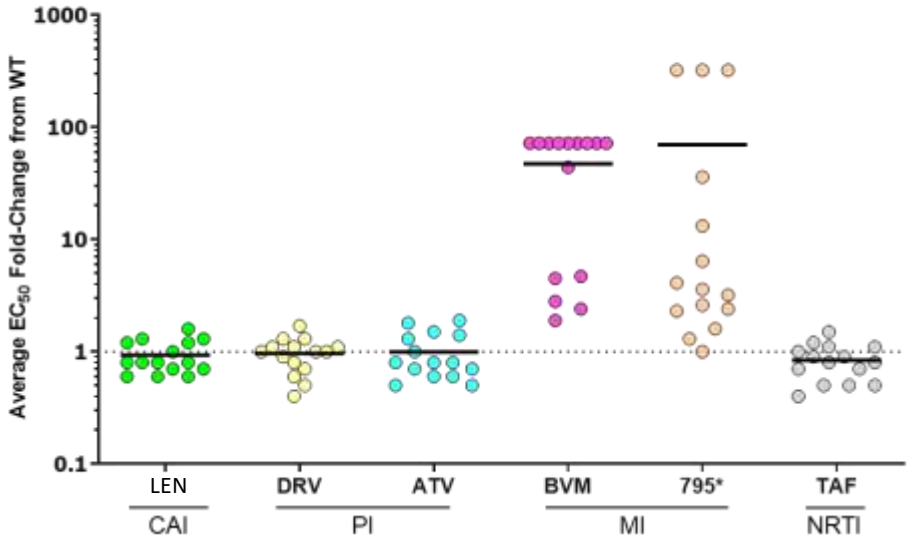
*In PBMC against clinical isolates.
CRF, circulating recombinant forms; EC_{50}, half maximal effective concentration; PBMC, peripheral blood mononuclear cell.

‡

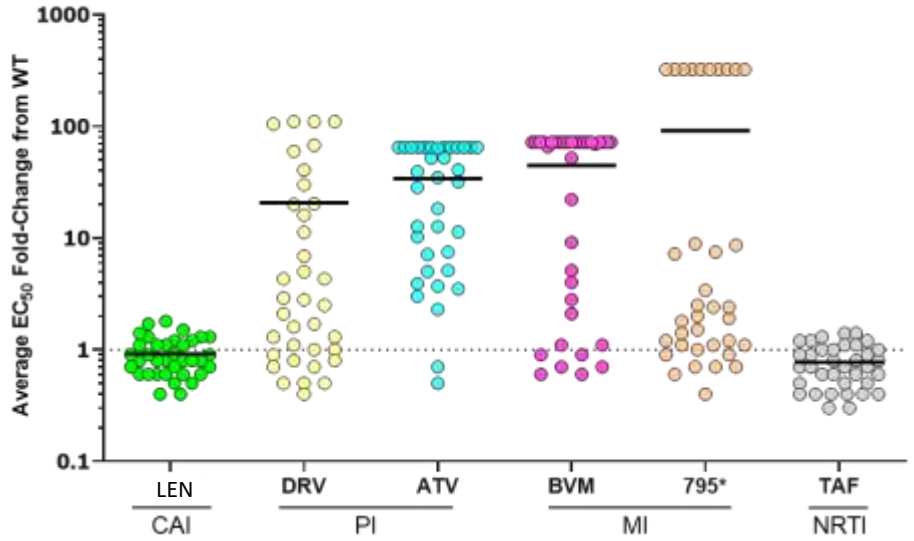
Potency in Isolates from TN & TE PLWH

Antiviral activity of LEN in HIV-1 primary isolates from PLWH

Treatment-Naïve (TN) (n=15)



Treatment-Experienced (TE) (n=36)



LEN activity not affected by naturally occurring polymorphisms in gag and/or protease mutations

High potency of LEN demonstrated with picomolar activity against all isolates tested

* GSK-3532795/BMS-955176

BVM, bevirimat; CAI, capsid inhibitor; MI, maturation inhibitor; TN, treatment-naïve; TE, treatment-experienced

Margot N, et al. CROI 2020. Boston, MA. 529

‡

Activity and Resistance Characterization of LEN

Background[1]

- LEN mutations 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

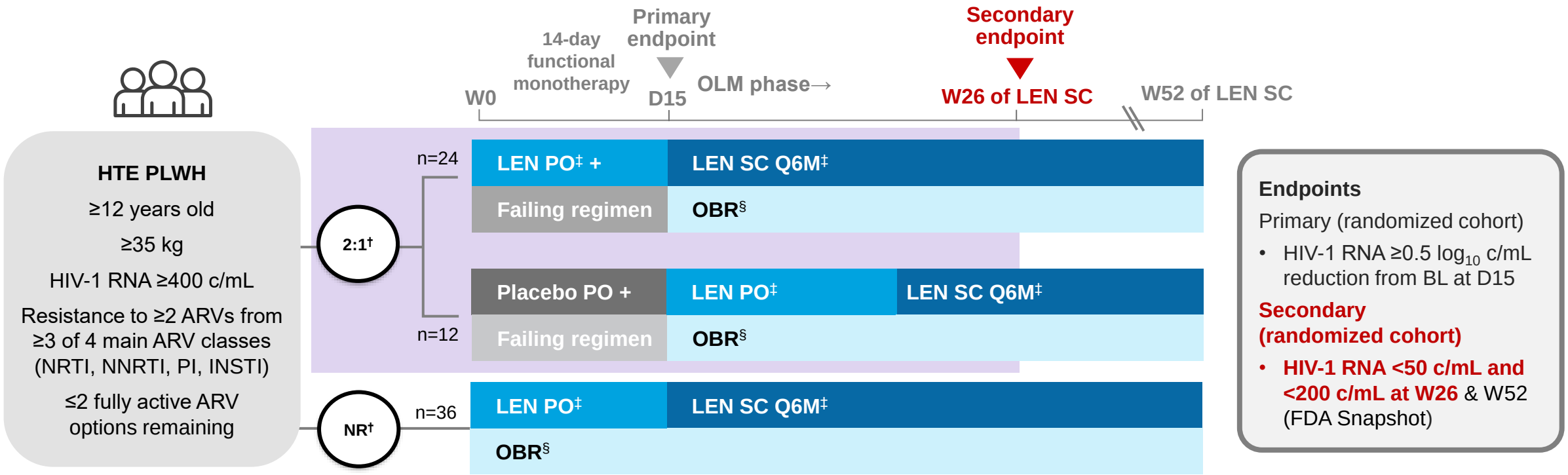
WT, wild-type; ND, not determined
* Results were consistent across single- and multi-cycle assay formats, and across primary cells and cell lines
† Ratio of Mutant/WT EC_{50}, determined with SC reporter HIV-1 in PhenoSense Gag-Pro assay
‡ Percentage of reference strain, determined with SC reporter HIV-1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

Phase 2/3, Blinded, Placebo-controlled Study in HTE PLWH with MDR

Study Design



‡**LEN dosing:** Oral initiation (**Day 1:** 600 mg [2 × 300 mg tablet]; **Day 2:** 600 mg [2 × 300 mg tablet]; **Day 8:** 300 mg), followed by maintenance dose of 927 mg (2 × 1.5 mL) SC into the abdomen **Q6M (Q26 weeks)**

Participants with <0.5 log_{10} decline in HIV-1 RNA during screening entered the randomized cohort; participants with ≥0.5 log_{10} decline in HIV-1 RNA during screening entered the non-randomized cohort

Molina JM, et al. vIAS 2021, OALX01LB02

Baseline Characteristics

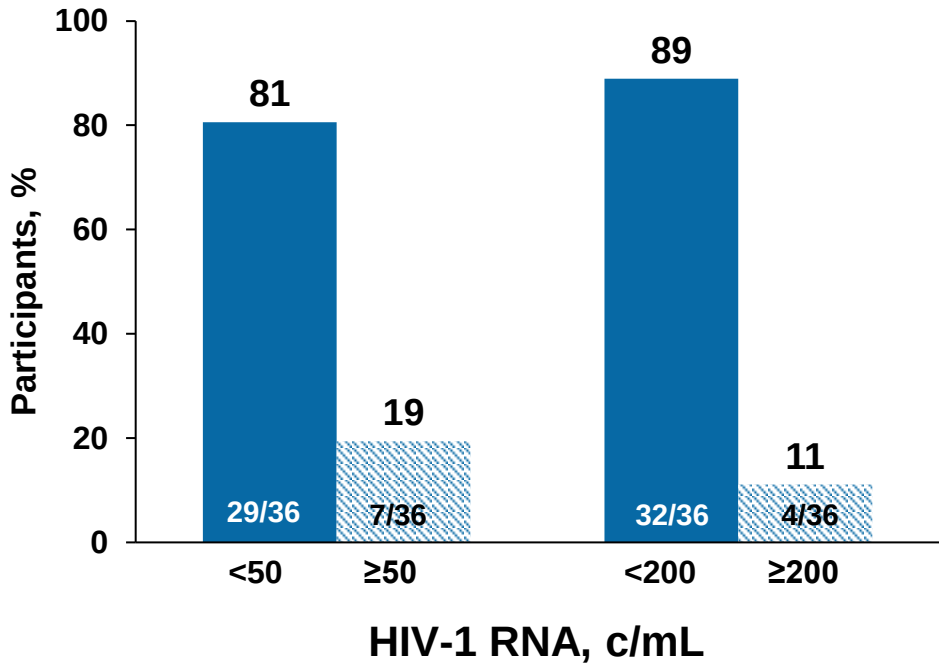
	Randomized		Nonrandomized	Total LEN N=72
	LEN n=24	Placebo n=12	LEN n=36	
Age, median (range), years	55 (24–71)	54 (27–59)	49 (23–78)	52 (23–78)
Sex, % female at birth	29	25	22	25
Race, % Black	42	55	31	38
Ethnicity, % Hispanic/Latinx	25	36	14	21
HIV-1 RNA, median (range), log_{10} c/mL	4.2 (2.3–5.4)	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 (3–1,296)	150 (3–1,296)
≤200 cells/μL, %	67	92	53	64
Time since HIV diagnosis, median (range), years	27 (13–39)	26 (14–35)	23 (9–44)	24 (9–44)
Number of prior ARV agents, median (range)	9 (2–24)	9 (3–22)	13 (3–25)	11 (2–25)
Number of ARV agents in failing regimen, median (range)	3 (1–7)	3 (2–6)	4 (2–7)	3 (1–7)
Known resistance to ≥2 drugs in class, %				
NRTI	96	100	100	99
NNRTI	92	100	100	97
PI	83	67	83	81
INSTI	83	58	64	69

HTE, heavily treatment-experienced; MDR, multidrug resistance

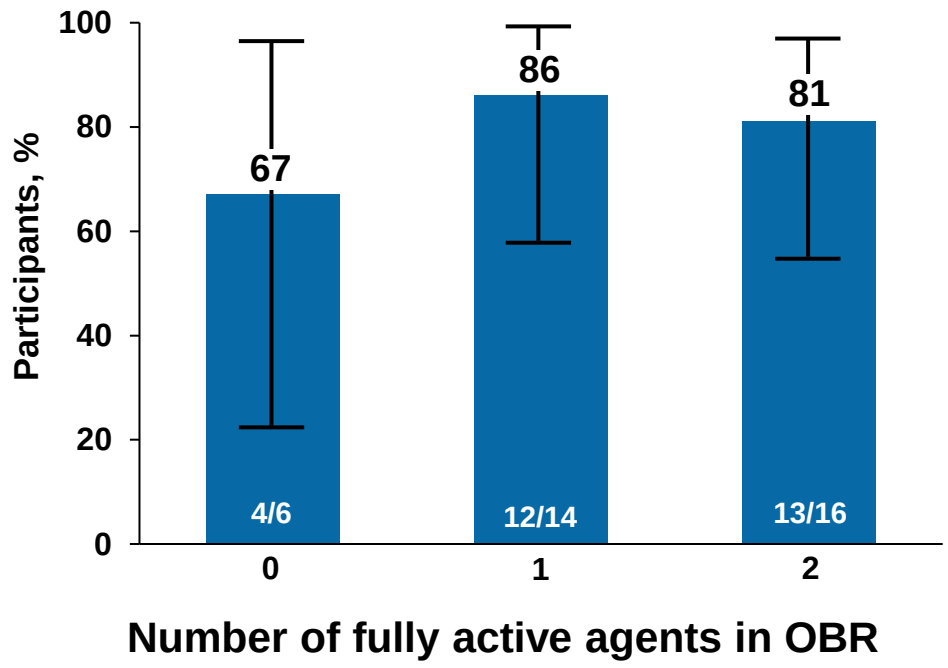
Molina JM, et al. vIAS 2021, OALX01LB02

Efficacy at W26 in the LEN Arm, Randomized Cohort (n=36)

FDA Snapshot Algorithm (n=36)



HIV-1 RNA <50 c/mL



Mean CD4 Change at W26

+ 81 cells/µL

CD4 (<50 cells/µL)

- Baseline: 22% (8/36)
- W26: 0% (0/34)

LEN in combination with OBR led to high rates of virologic suppression in HTE PLWH

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

Molina JM, et al. vIAS 2021, OALX01LB02

Emergent LEN Resistance, Randomized Cohort

	Randomized cohort n=36
Participants meeting criteria for resistance testing, n (%)	11 (31)
No emergent LEN resistance, n (%)	7 (19)
Emergent LEN resistance, n (%)	4 (11)
M66I	4
Q67H	1
K70N/R/S	1
N74D	1

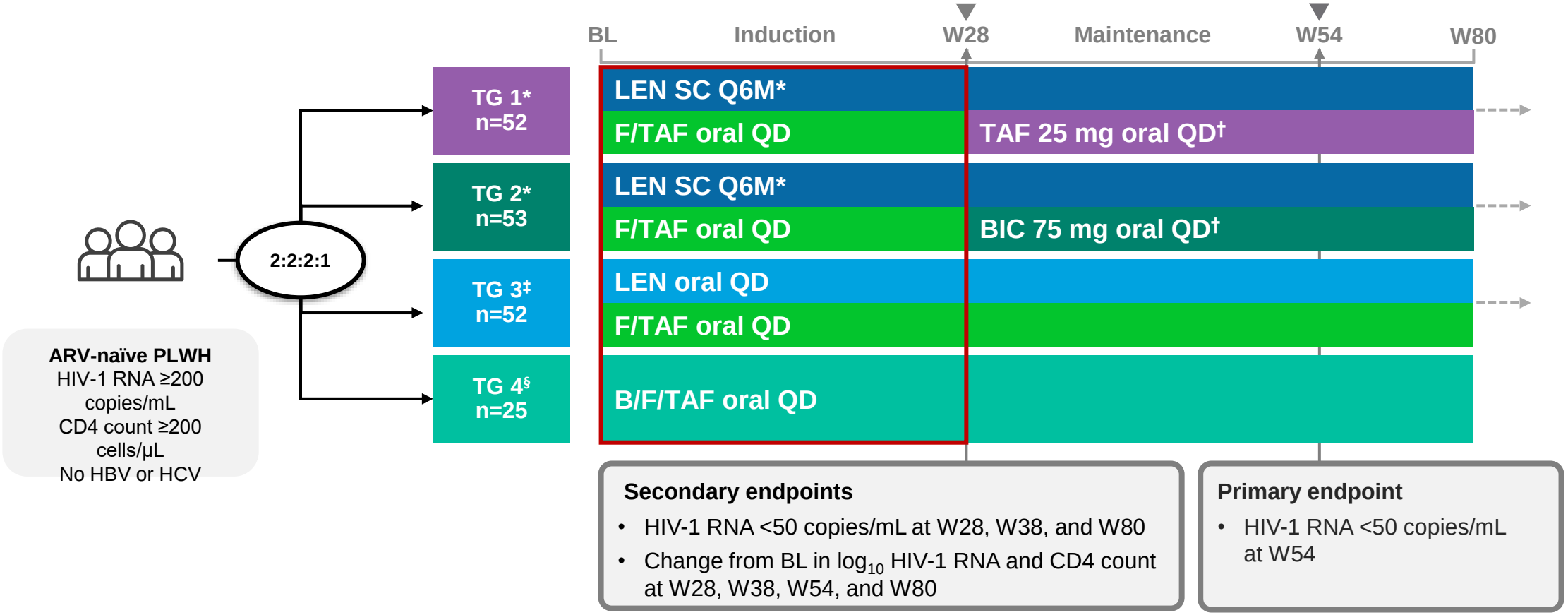
All 4 participants with emergent LEN resistance remained on LEN

- **3 participants resuppressed at a later visit: 1 with OBR change and 2 without an OBR change**
- 1 participant with no fully active agent never suppressed (max 1.7 $\log_{10}$ c/mL decline in HIV-1 RNA)
- No participant developed additional resistance to the agents in the OBR

Capsid genotypic and phenotypic resistance testing was 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 4 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.

LEN in Treatment-Naïve PLWH

Phase 2, randomized, open-label, active controlled study in treatment-naïve PLWH to evaluate antiviral efficacy of SC LEN (N=182)



*LEN oral lead-in (600 mg on D1 and D2, 300 mg on D8) followed by LEN SC 927 mg on D15; F/TAF, 200/25 mg; †Participants in TG 1 and 2 required HIV-1 RNA <50 copies/mL at W16 and W22 to initiate either TAF or BIC at W28; those with HIV-1 RNA ≥50 copies/mL discontinued study at W28 ; ‡LEN 600 mg on D1 and D2, followed by LEN 50 mg from D3; F/TAF, 200/25 mg; §B/F/TAF, 50/200/25 mg
BL, baseline; LEN, lenacapavir; Q6M, every 6 months (Q26 weeks); QD, once daily; SC, subcutaneously; TG, Treatment Group

CALIBRATE INTERIM ANALYSIS: VIROLOGIC OUTCOMES AT WEEK 28

Characteristic, %	LEN SC + FTC/TAF → TAF (n = 52)	LEN SC + FTC/TAF → BIC (n = 53)	LEN Oral + FTC/TAF (n = 52)	BIC/FTC/TAF (n = 25)
Virologic Outcome by FDA Snapshot (ITT)				
▪ HIV-1 RNA <50 copies/mL	94	92	94	100
▪ HIV-1 RNA ≥50 copies/mL	0	4	0	0
▪ No data	6	4	6	0
Virologic Outcome by Missing = Failure Analysis				
▪ HIV-1 RNA <50 copies/mL at Week 4	83	79	87	84
▪ HIV-1 RNA <50 copies/mL at Week 28	94	92	94	100

- **One patient receiving LEN SC + FTC/TAF → BIC developed resistance mutations at Week 10 conferring a 20-fold change in LEN susceptibility**
  - **CA: Q67H + K70R; RT: M184M/I**
- Plasma concentrations of LEN remained in target range throughout

Gupta. IAS 2021. Abstr OAB0302.

Based on CCO HIV

CALIBRATE INTERIM ANALYSIS: MUTATIONAL PROFILE OF SINGLE PATIENT WITH EMERGENT LEN RESISTANCE

Timeline of Events	Patient Assigned to LEN SC + FTC/TAF (→ BIC)
Wk 0	Capsid: No RAMs RT: No RAMs
Wk 1	Capsid: No RAMs RT: No RAMs
Wk 2	Capsid: No RAMs RT: M184I (4%), M184V (6%)
Wk 4	Capsid: Q67H (19%) RT: M184I (27%), M184V (64%)
Wk 10	Capsid: Q67H + K70R – **LEN resistance** RT: M184M/I
Wk 22	Patient switched to ZDV + 3TC, TDF, DTG

- No missed LEN doses and plasma LEN concentrations consistently in target range
- Plasma FTC and TFV concentrations consistent with expected PK
- M184 mutations preceded emergence of LEN RAMs

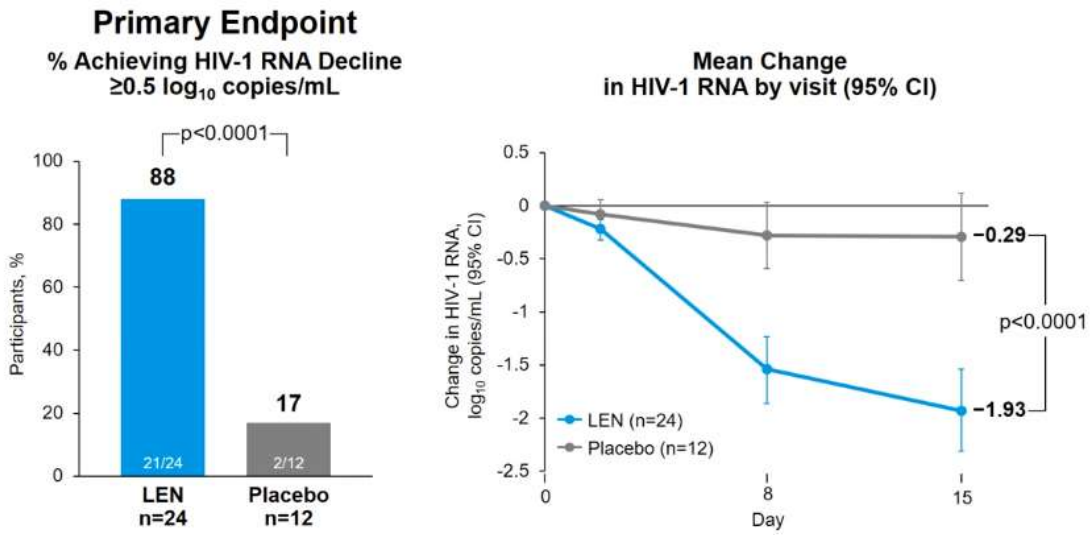
Phenotypic Analysis, EC_{50} FC	Capsid	RT	
	LEN	TFV	FTC
Baseline	1.2	ND	ND
Wk 10	20	0.46	>58

VanderVeen. IDWeek 2021. Abstr 73.

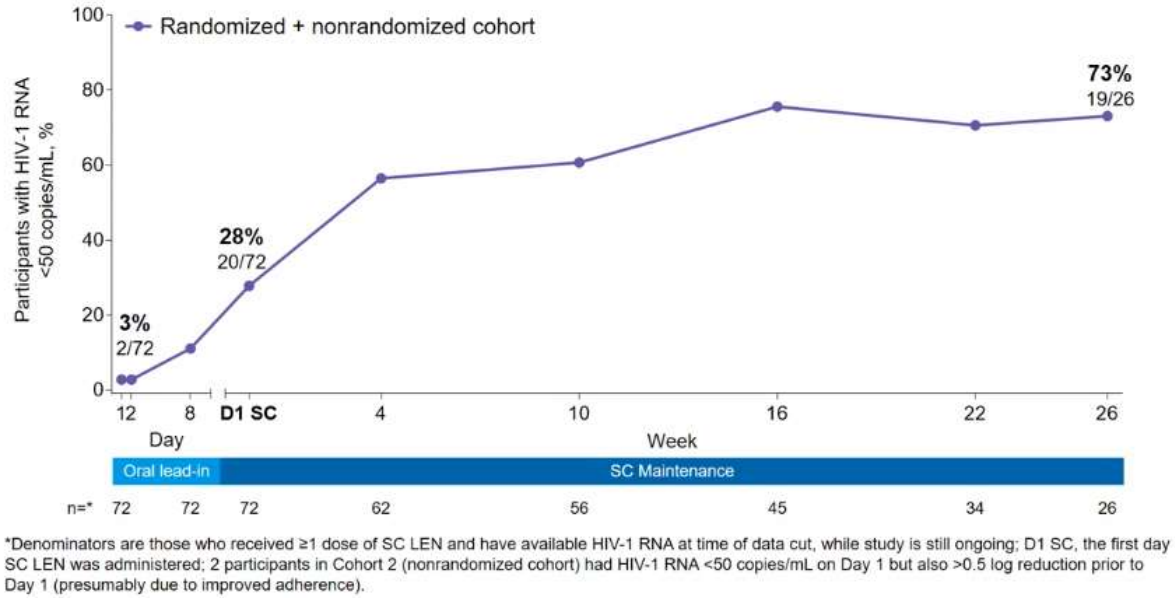
Based on CCO HIV

Lenacapavir- Results

Functional Monotherapy



With OBR



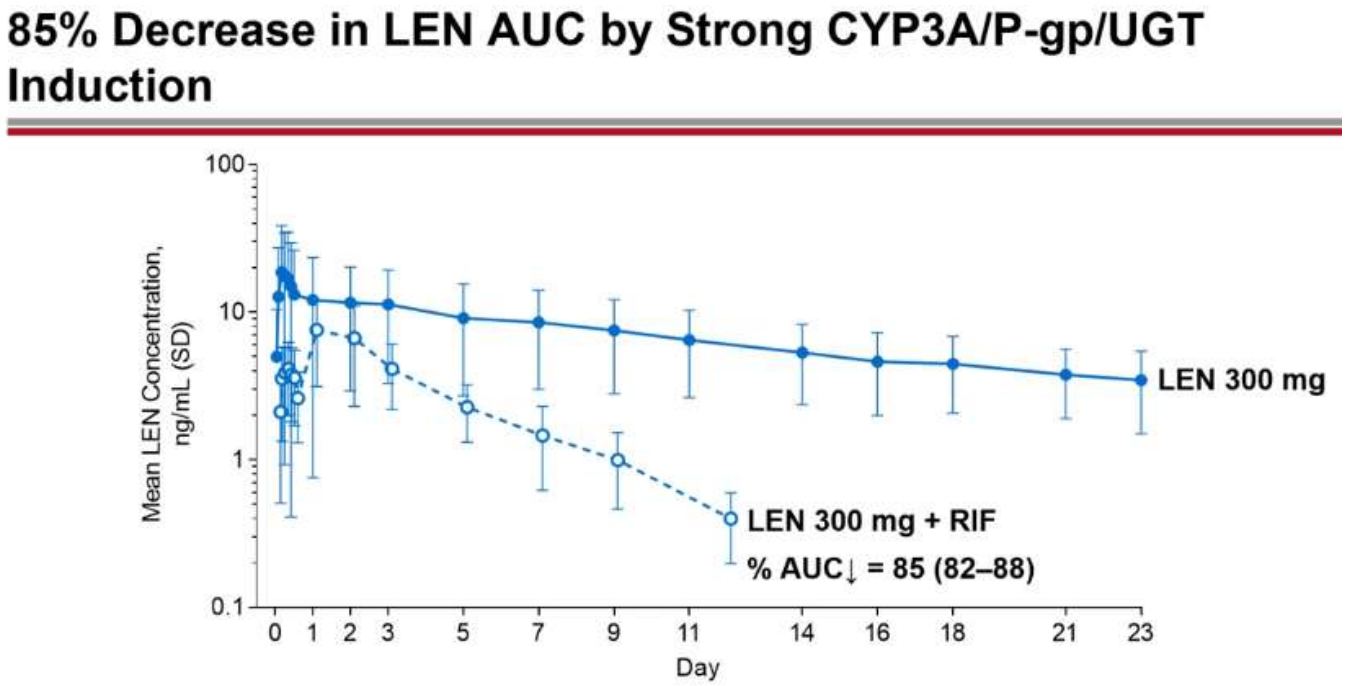
*Denominators are those who received ≥1 dose of SC LEN and have available HIV-1 RNA at time of data cut, while study is still ongoing; D1 SC, the first day SC LEN was administered; 2 participants in Cohort 2 (nonrandomized cohort) had HIV-1 RNA <50 copies/mL on Day 1 but also >0.5 log reduction prior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

- Injection Site Reactions in 33/72, mostly mild
- 2/72 participants developed LEN resistance

Segal-Maurer CROI 2021

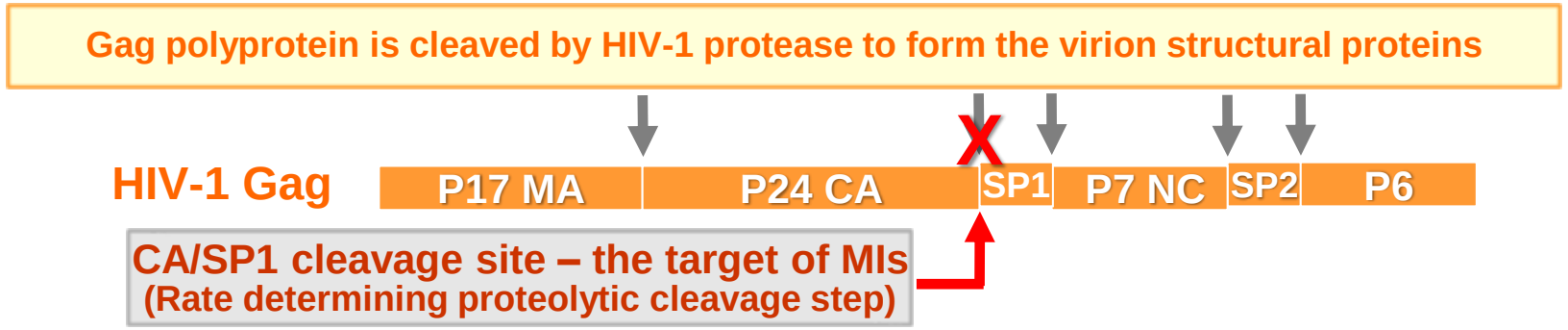
Lenacapavir – Drug interaction

- Administered with DRV/r (3A4 inhibitor), ATV/r (UGT1A1 + PgP inhibition), Rifampin (3A4/PgP/UGT inducer), Famotidine
- Minimal effect with PI, acid reducer
- Do not use Rifampin with Lenacapavir

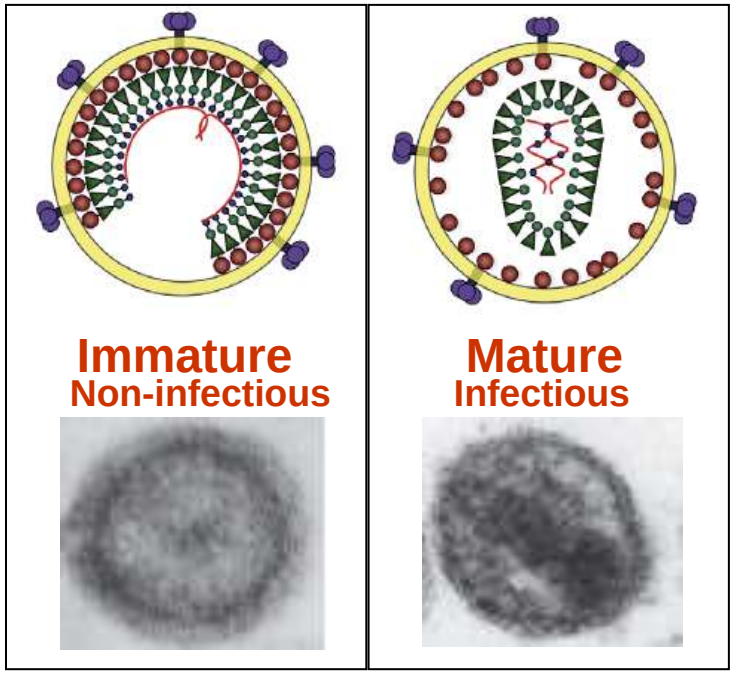


Lutz CROI 2021

Maturation inhibitors



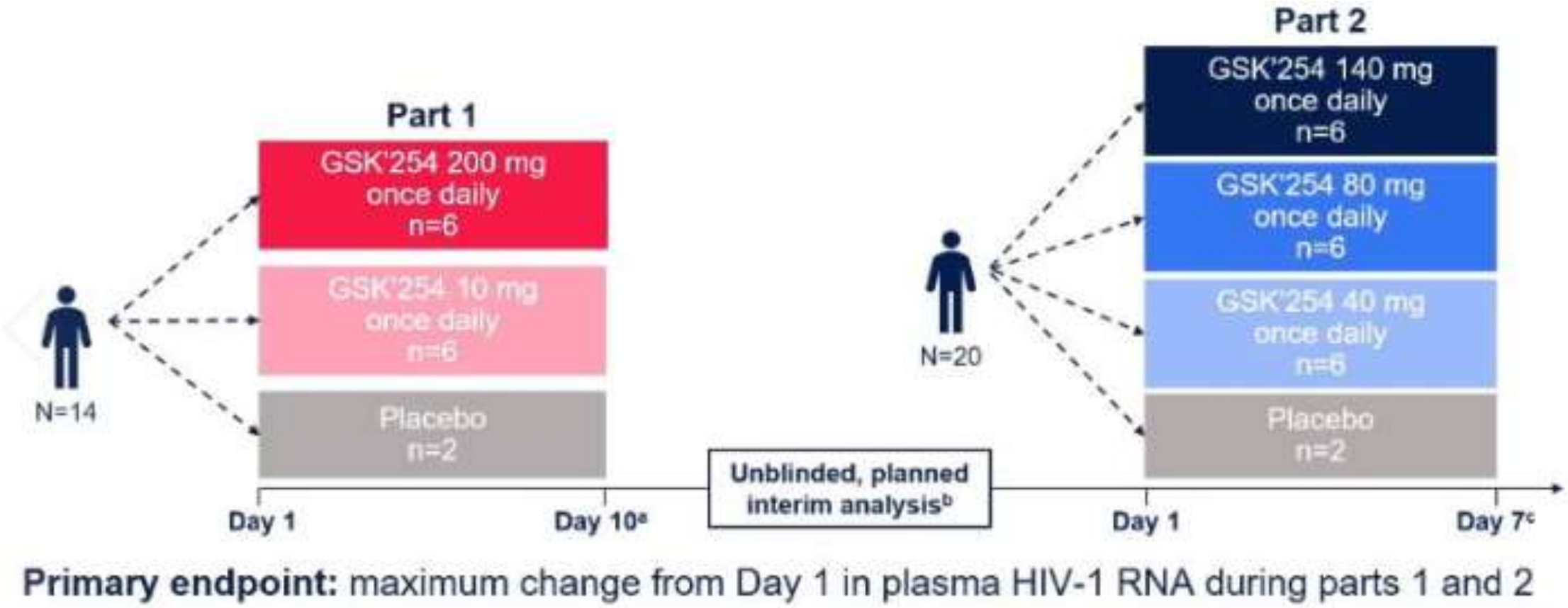
- HIV-1 protease cleaves Gag in a stepwise fashion into six pieces; Gag polyprotein is the main structural protein of HIV-1
- **MI's inhibit the last protease cleavage between the CA-SP1 subunit (effect similar to protease block); non-infectious, immature HIV-1 particles result**
- Pursuing further optimized MIs for oral or long acting regimens
  - **GSK '254** for oral, FDC w/ DTG and monoentity
  - **GSK '937** for long acting injectable, SQ and IM



DE/HIV/0088/18; 06.2018; NCT03231943

GSK 3640254 – Maturation Inhibitor

- Small Phase IIA dose-ranging study in 6 patients per dose

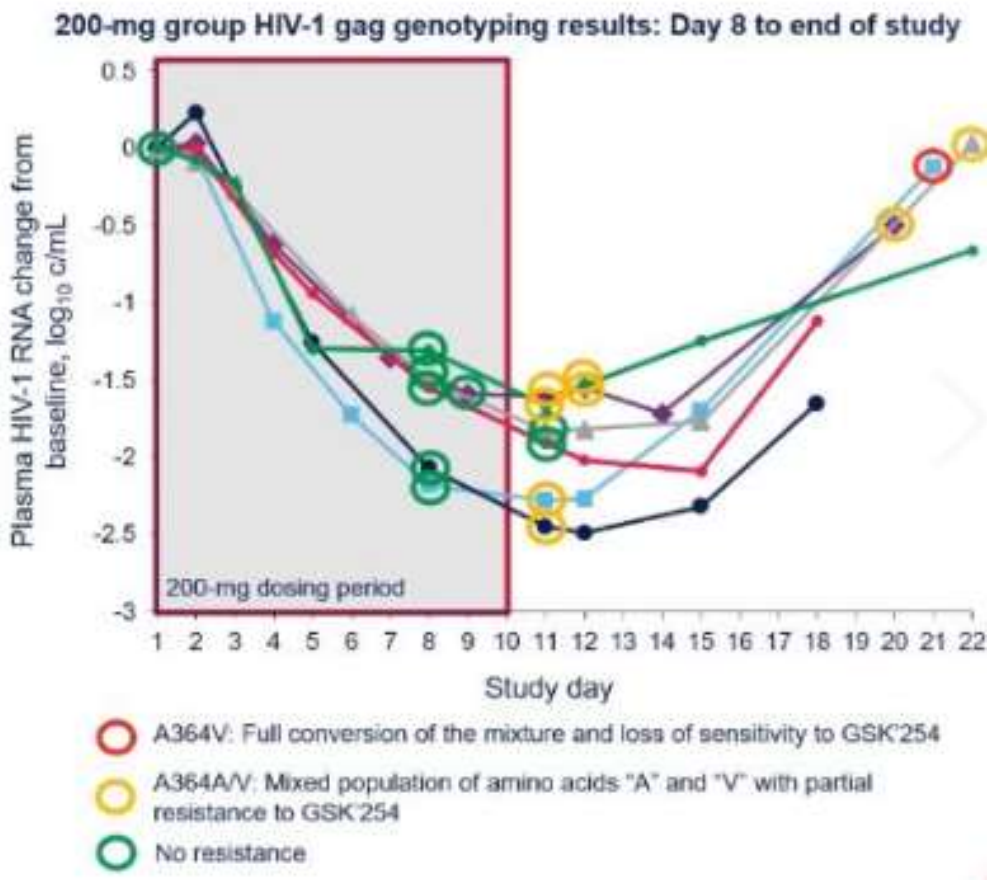


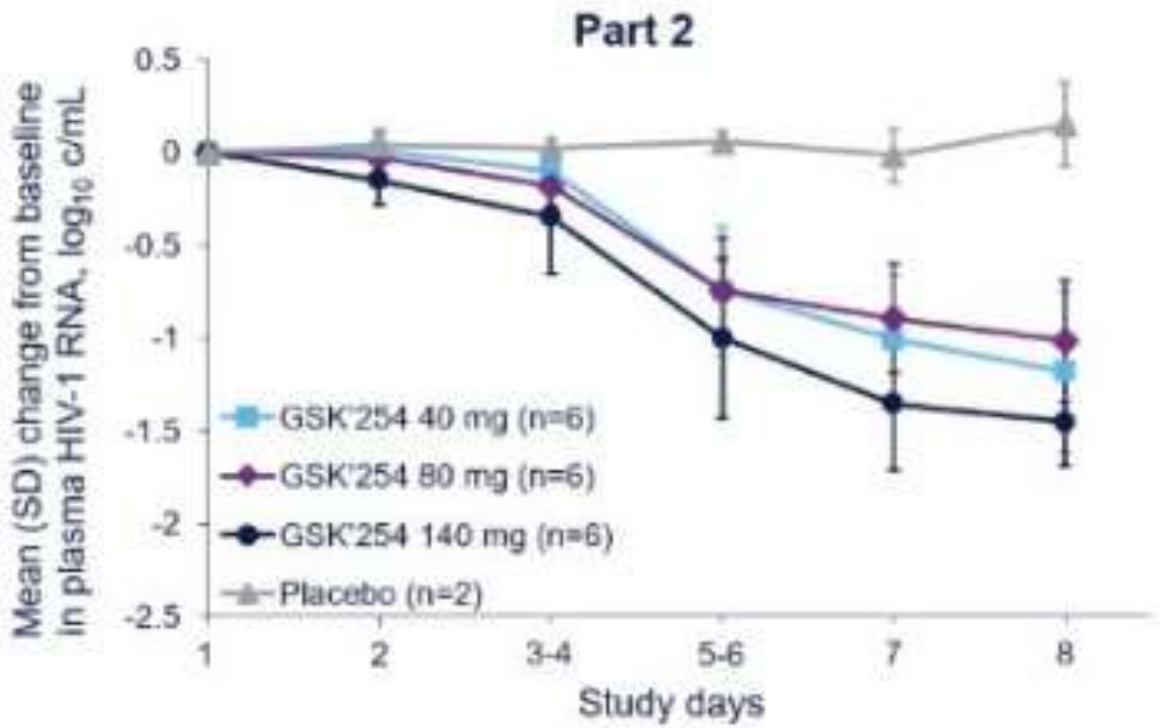
Primary endpoint: maximum change from Day 1 in plasma HIV-1 RNA during parts 1 and 2

Spinner CROI 2021

GSK 3640254 – Maturation Inhibitor

- Phase 1: resistance emerged in the high dose, 10-day arm
- Phase 2: No resistance in 7-day arm, good antiviral activity





Spinner CROI 2021

BEVIRIMAT

Resistance

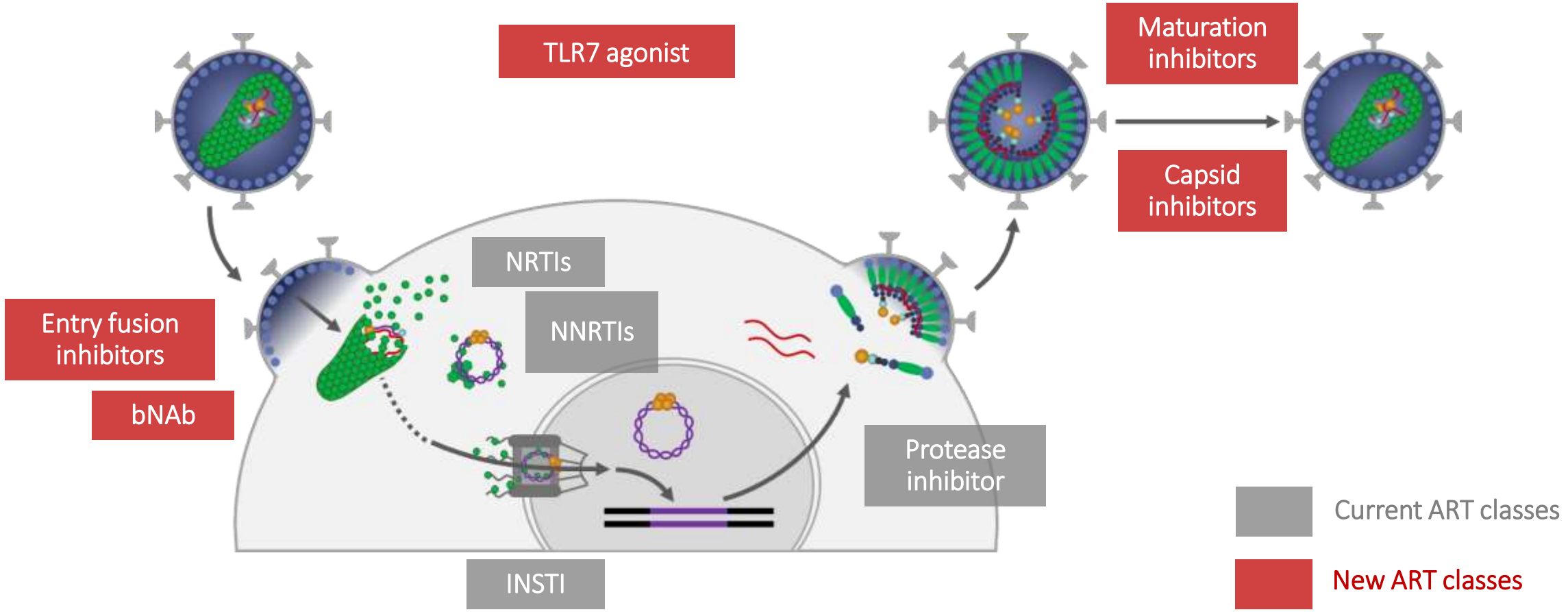
In vitro studies have shown that presence of a number of single nucleotide polymorphisms in the CA/SP1 cleavage site have resulted in resistance to bevirimat. However, mutations at these sites were not found in phase I and II clinical trials. Instead, mutations in the glutamine-valine-threonine (QVT) motif of the SP1 peptide are also known to cause bevirimat resistance. In addition, V362I mutations have been shown to confer strong resistance to bevirimat, where the S373P and I376V mutations may confer low resistance to bevirimat. A further complication of the use of bevirimat is that, since bevirimat targets the CA/SP1 cleavage site, it could also be used in the treatment of protease inhibitor resistant patients. Except for A364V, mutations in the CA/SP1 cleavage site have showed to result in fitness deficits when combined with protease inhibitor resistance. This proposes that these mutations may develop slowly. It has been shown that protease inhibitor resistance can result in an increase in the occurrence of mutations within the downstream QVT motif.[10][11][12][13]

Clinical trials

In December 2007, some results of the Phase IIb trial were released. Thomson Financial News reported that, "some patients respond 'very well' to the drug, while another population 'does not respond as well at current dose levels.'" Panacos said it intends to add a group to the study at a higher dosage.[14] The drug manufacturer, Panacos, has stated that success with bevirimat hinges on a patient's particular HIV not having a specific group of genetic mutations in HIV's Gag protein. When they evaluated the study participants' virus and found that the participant's virologic response depended greatly on whether or not the Gag protein of a participant's virus had polymorphisms—multiple mutations in the protein's structure. After sampling the virus of 100 patients in the company's database, they found that about 50 percent did not have Gag polymorphisms, meaning that about 50 percent would likely respond well to the drug.[15]

The other need is to have long acting regimens other than CARLA

Current and new ART drug classes and effects on HIV lifecycle



Current and new ART drug classes are being investigated for LA and non-oral delivery

ART, antiretroviral therapy; bNAb, broadly neutralising antibodies; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; TLR7, toll-like receptor-7.
Orkin C, et al. Presented at EACS 2019, 6-9 November 2019, Basel, Switzerland; #PL2.

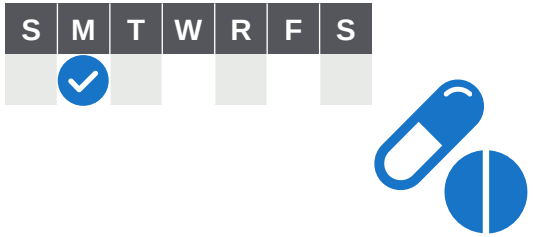
A New Dual Option with LEN

Capsid inhibitor
LEN

+

Islatravir

Oral capsid inhibitor
LEN



+

Islatravir oral

LEN and ISL are not approved for use by any regulatory body globally

IS, islatravir; LEM, lenacapavir

BioSpace. Gilead and Merck Announce Agreement to Jointly Develop and Commercialize Long-Acting, Investigational Treatment Combinations of Lenacapavir and Islatravir in HIV. Published: Mar 15, 2021. Available at: www.biospace.com/article/releases/gilead-and-merck-announce-agreement-to-jointly-develop-and-commercialize-long-acting-investigational-treatment-combinations-of-lenacapavir-and-islatravir-in-hiv-/.

ILLUMINATE Clinical Development Program

Comprehensive clinical development program evaluating DOR 100 mg/ISL 0.75 mg across a diverse population of PLWH

	Trial Name (Protocol No.)	Population	Study Design/ Comparator	ClinicalTrials.gov Identifier
Ph 3	Illuminate HTE (P019)	Heavily treatment experienced (HTE)	Double-blind OBT	NCT04233216
	Illuminate Switch A (P017)	Virologically suppressed	Open-label baseline ART	NCT04223778
	Illuminate Switch B (P018)	Virologically suppressed	Double-blind BIC/FTC/TAF	NCT04223791
	Illuminate Naïve (P020)	Treatment-naïve	Double-blind BIC/FTC/TAF	NCT04233879
Ph 2	Illuminate Adolescents (P028)	Treatment-naïve or virologically suppressed adolescents	Single-arm	NCT04295772

MERCK

Search everyth

Merck Announces Clinical Holds on Studies Evaluating Islatravir for the Treatment and Prevention of HIV-1 Infection

Save

December 13, 2021 5:00 pm ET

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) has placed clinical holds on the investigational new drug applications (INDs) for the oral and implant formulations of islatravir (MK-8591) for HIV-1 pre-exposure prophylaxis (PrEP); the injectable formulation of islatravir for HIV-1 treatment and prophylaxis; and the oral doravirine/islatravir (DOR/ISL) HIV-1 once-daily treatment. The FDA's clinical hold is based on previously announced observations of decreases in total lymphocyte and CD4+ T-cell counts in some participants receiving islatravir in clinical studies. As previously announced, Merck has stopped dosing in the Phase 2 IMAGINE-DR clinical trial of islatravir in combination with MK-8507 (MK-8591-013) and paused enrollment in the once-monthly Phase 3 PrEP studies, (MK-8591-022 and MK-8591-024) (see announcements here and here). With the FDA's clinical hold, no new studies may be initiated. Participants who are currently receiving islatravir as part of the studies for PrEP, including

Long-Acting Cabotegravir Plus VRC-HIVMAB075-00-AB (VRC07-523LS) for Viral Suppression in Adults Living With HIV-1

NIAID, open label, phase II study, recruiting

Arm
Experimental: CAB LA + VRC07-523LS Step 1: CAB administered orally as one 30 mg tablet once daily, plus two NRTIs, for 5 weeks. Step 2: CAB LA loading dose (600 mg) administered as one IM injection at Step 2 entry study visit, and maintenance dose (400 mg), starting at 4 weeks after CAB LA loading dose, and then every 4 weeks through Week R2+44. VRC07-523LS (40 mg/kg) administered as an IV infusion starting at Step 2 entry and then every 8 weeks through Week R2+40. Step 3: SOC oral ART regimen for approximately 48 weeks.

bNAbs

- broadly Neutralising monoclonal Antibodies
- Generated from HIV-positive people who develop strong antibodies to HIV (after several years).
- Been known since early HIV research but only recently isolated and cloned for use as treatment.
- Need to use in combination – some trispecific.
- Many other treatments – cancer, immune disorders.
- Priced as very expensive drugs: £5K - >£200,000/year.

HIV bNAbs

- Two mechanisms:
  - direct antiretroviral (entry inhibitors)
  (can have ~1.5 log mono, 2 log dual on VL
  - immune modulating vaccine-type effect (after drug levels have left)

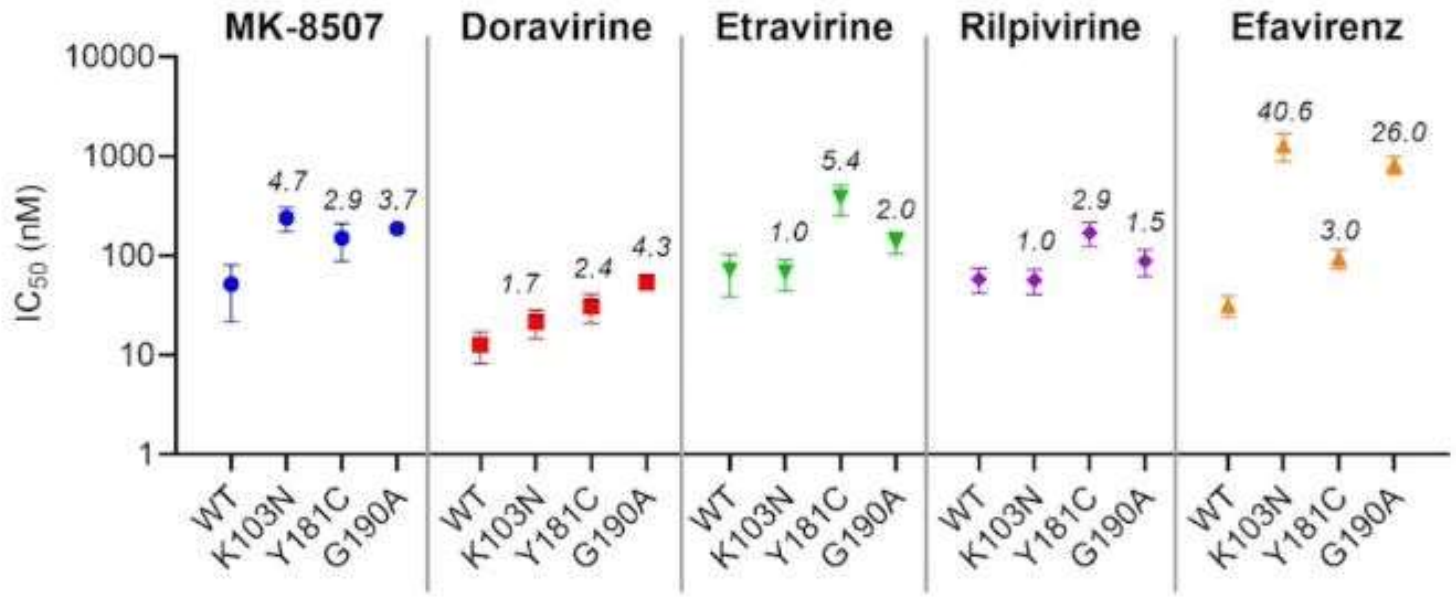
- Long acting LS formulations (ie from M428L and N434S) extends half life x 4 – allows 6-monthly dosing.

New drugs from old classes but with longer half-lives are coming

MK8507 – NNRTI

- Resistance profile similar to Doravirine
- Plasma t1/2~70 hours **suitable for once weekly dosing**

MK-8507 has potency changes <5-fold against common NNRTI resistance-associated variants (K103N, Y181C, G190A)

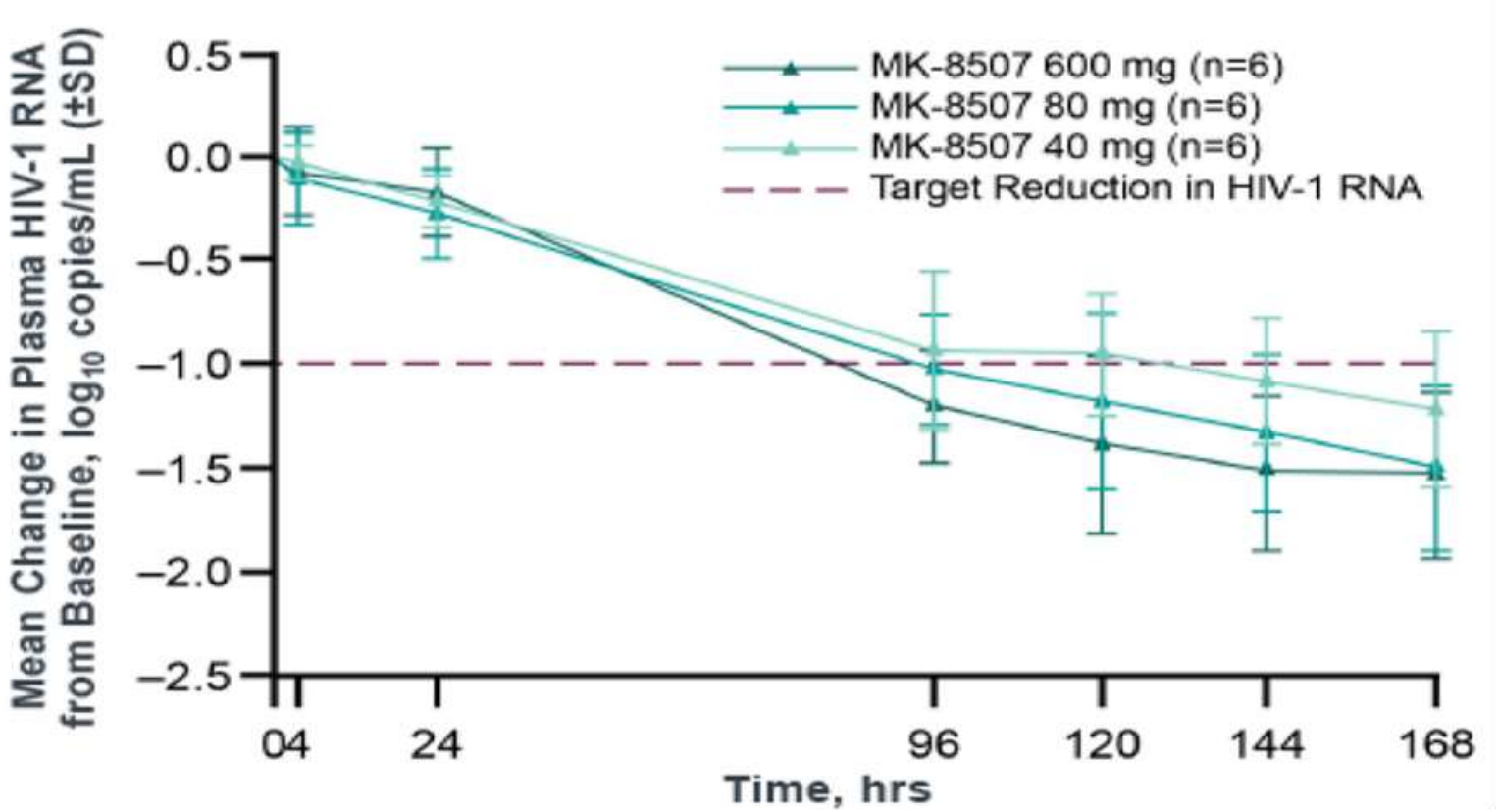


IC_{50} values graphed with fold change vs WT values shown above each point.

MT4-GFP cells (100% NHS)
IC_{50}, half-maximal inhibitory concentration; NHS, normal human serum; WT, wild-type

Diamond CROI 2021

MK8507 – Single Dose Antiviral Potency



- Plan – Once weekly Islatravir + MK8507 for HIV treatment

Diamond CROI 2021

S-365598

ViiV Healthcare announces exclusive license agreement with Shionogi to develop third-generation HIV integrase inhibitor with potential for ultra long-acting dosing intervals

28 september 2021

NOVEL HIV PI WITH HIGH RESISTANCE BARRIER AND POTENTIAL FOR UNBOOSTED QD ORAL DOSING

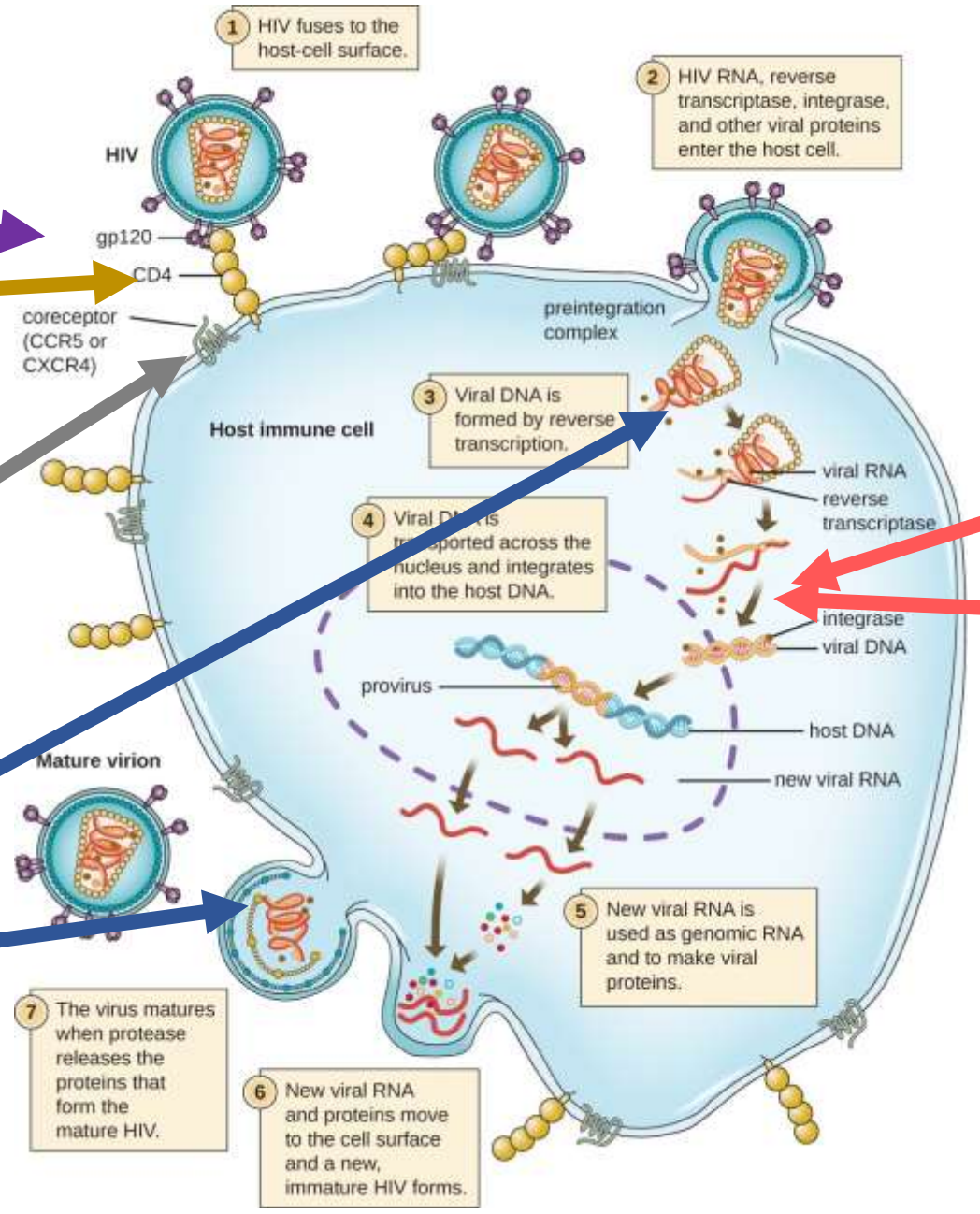
Long-acting antiretrovirals as new options for MDR HIV

Anti-gp120:
Fostemsavir

Anti-CD4:
Ibalizumab

Anti-CCR5:
Leronlimab
(PRO 140)

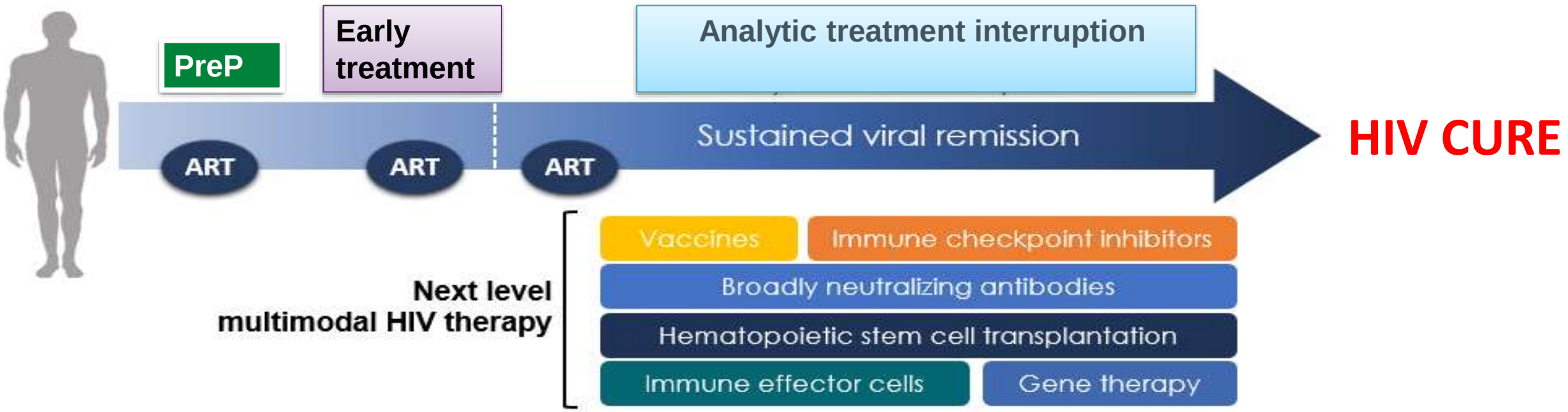
Capsid inhibitors:
Lenacapavir
(GS-6207)



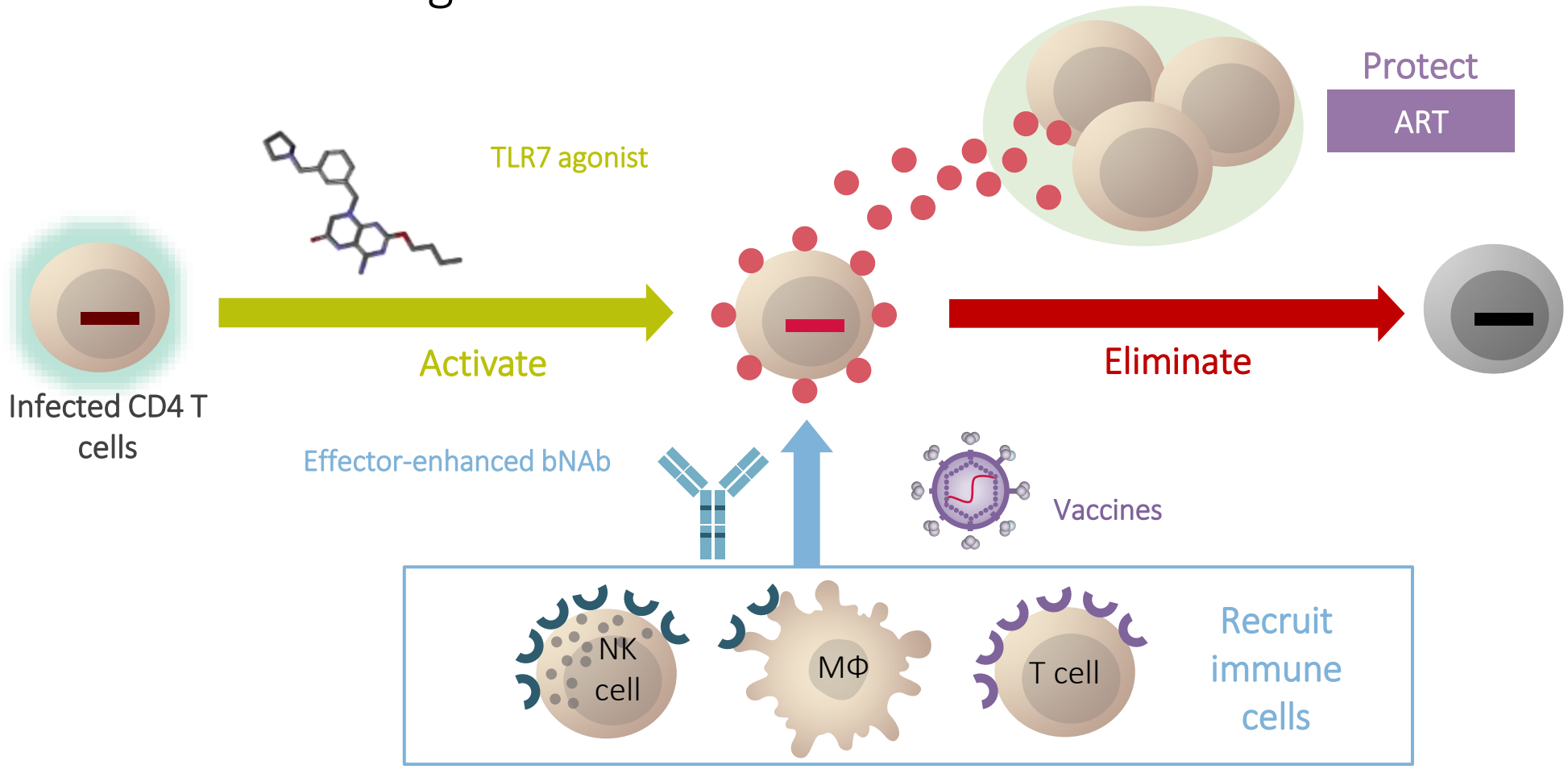
Nucleoside reverse transcriptase translocation inhibitors (NRTTIs):
Islatravir

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):
MK-8507

HIV PERSISTANCE as a MAJOR TREATMENT GAP



Gilead's approach to HIV Cure:
Immune-based strategies to activate and eliminate the HIV reservoir



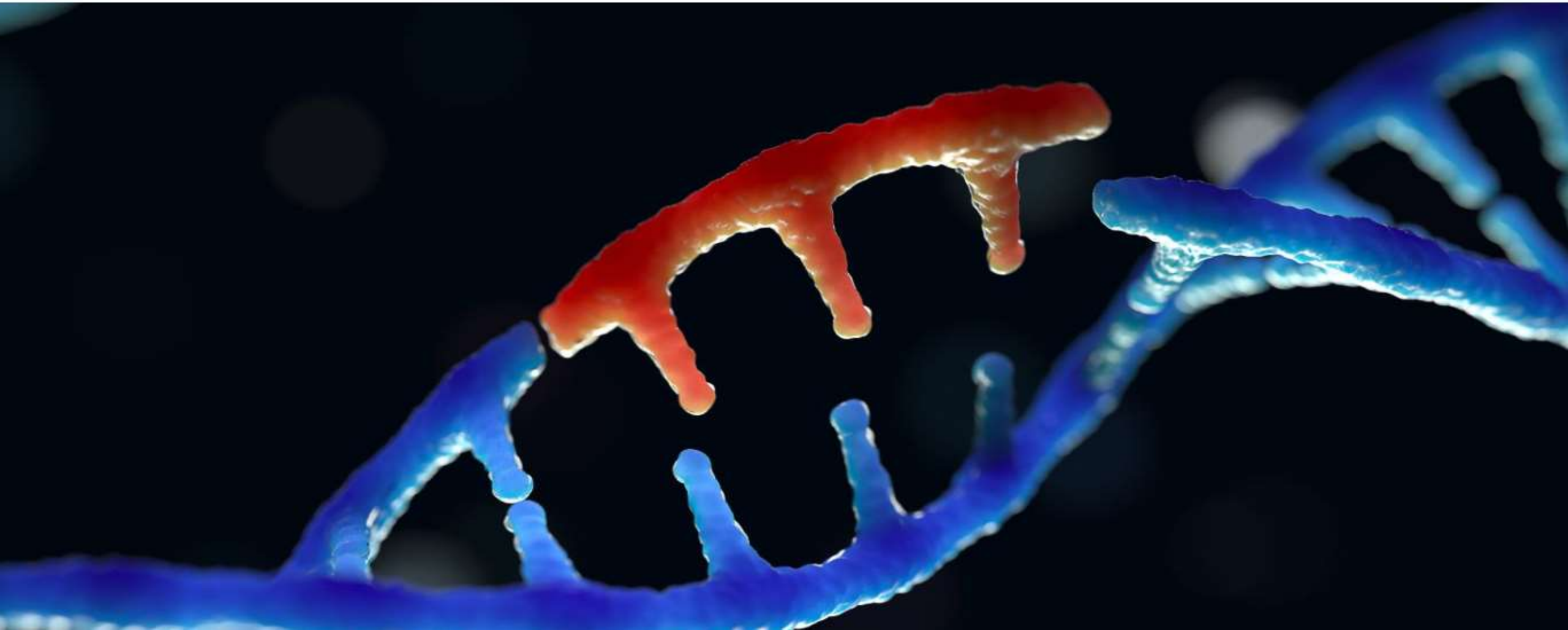
ART, antiretroviral therapy; bNAb, broadly neutralising antibody; CD, cluster of differentiation; MΦ, macrophage; NK, natural killer; TLR7, toll-like receptor-7.

Nature Research HIV: Progress and future challenges in treatment, prevention and cure. Available at: https://www.nature.com/articles/d42473-018-00280-0. Last accessed: December 2019.

FDA approves first trial investigating CRISPR gene editing as HIV cure

By Kezia Parkins | 16 Sep 2021

A new paradigm for HIV treatment is on the horizon as FDA gives nod for startup to begin trials of CRISPR-based gene therapy.



Article | Published: 09 December 2021

A multiclade *env–gag* VLP mRNA vaccine elicits tier-2 HIV-1-neutralizing antibodies and reduces the risk of heterologous SHIV infection in macaques

Peng Zhang, Elisabeth Narayanan, ... Paolo Lusso + Show authors

Nature Medicine **27**, 2234–2245 (2021) | Cite this article

Vaccinated animals had a 79% per-exposure risk reduction upon repeated low-dose mucosal challenges with heterologous tier-2 simian–human immunodeficiency virus (SHIV AD8). Thus, the multiclade *env–gag* VLP mRNA platform represents a promising approach for the development of an HIV-1 vaccine.

Conclusions

The field of HIV treament is continuosly evolving and more agents will come. Dual long acting treatment will be the standard of care, but the road to reach the ideal treatment is not an easy one.