XII Workshop Nazionale
Innovazione e Ricerca per la Pratica Clinica
TERAPIE INNOVATIVE DELLE EPATITI CRONICHE VIRALI E DELLE INFEZIONI VIRALI
Firenze, 10-11 Gennaio 2022

Il ruolo delle nuove opzioni terapeutiche

Sergio Lo Caputo
Malattie Infettive
A.O.U Policlinico Foggia
Università di Foggia

Disclosure of potential conflicts of interest

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

Drug names		Recommended adult dose *	Total daily pills
Fixed dose combinations	0 5 10 15 20mm *Approximate to actual size.*		
Atripla (efavirenz + emtricitabine + tenofovir DF)		One tablet, once-daily. Take at night and not with a high fat meal. See info on separate drugs.	1
Biktarvy (bictegravir + TAF + emtricitabine)		One tablet, once-daily. Take with or without food. See info on separate drugs.	1
Eviplera (rilpivirine + emtricitabine + tenofovir DF)		One tablet, once-daily, with food (400 kcal). See separate drug info.	1
Odefsey (rilpivirine + emtricitabine + TAF)		One tablet, once-daily, take with food. See info on separate drugs.	1
Triumeq (dolutegravir + abacavir + lamivudine)		One tablet, once-daily. Take with or without food. See info on separate drugs.	1
Genvoya (elvitegravir + cobicistat + emtricitabine + TAF)		One tablet, once-daily. Take with food. See info on separate drugs.	1
Stribild (elvitegravir + cobicistat + emtricitabine + tenofovir DF)		One tablet, once-daily, take with food. See info on separate drugs.	1
Symtuza (darunavir + cobicistat + emtricitabine + TAF)		One tablet, once-daily, take with food. See info on separate drugs.	1
Delstrigo (doravirine + lamivudine + tenofovir DF)		One tablet, once-daily, with or without food. See info on each drug.	1
Dovato (dolutegravir + lamivudine)		One tablet, once-daily, with or without food. See info on each drug.	1
Juluca (dolutegravir + rilpivirine)		One tablet, once-daily, take with food. See info on separate drugs.	1
Dual nukes: nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)			
tenofovir DF 300 mg + emtricitabine 200 mg (Truvada [pictured] or generic) ++		One tablet, once-daily.	1
TAF (10 mg white or 25 mg blue) + emtricitabine (200 mg), Descovy		One tablet, once-daily.	1
abacavir 600 mg + lamivudine 300 mg (Kivexa or generic) ++		One tablet, once-daily.	1
Single nukes (NRTIs)			
Single nukes are only used in a few situations. See back page of this leaflet for single versions of tenofovir DF, emtricitabine, abacavir and lamivudine.			

* Different doses or formulations might be used - always check doses with your pharmacist.

++ Generic versions might be a different colour and shape. § EU approval pending.

NNRTIs: non-nucleoside reverse transcriptase inhibitors (non-nukes)			
efavirenz 600 mg or 200 mg (Sustiva, [pictured] or generic) ++		1 x 600 tablet (or 3 x 200 caps) once-daily; at night, not with high fat meal.	1 tablet (or 3 capsules)
nevirapine PR 400 mg (Viramune [pictured] or generic ++		1 x 400 mg once a day. Take with or without food.	1 x 400 mg
etravirine (100 mg or 200 mg) (Intelence)		2 x 100 mg OR 1 x 200 mg, twice daily, take with food. Dispersible in water.	2 or 4
rilpivirine (Edurant)		1 x 25 mg tablet, once-daily, take with main meal (500 kcal).	1
doravirine (Pifeltro)		1 x 100 mg tablet, once-daily, take with or without food.	1
INIs or INSTIs: integrase inhibitors			
raltegravir 400 mg (pink) & 600 mg (yellow) (Isentress)		1 x 400 mg, twice-daily OR 2 x 600 mg tablet, once-daily. Take with or without food.	2
dolutegravir (Tivicay) *		1 x 50 mg tablet, once-daily (or 1 x 50 mg twice -daily). With food if twice-daily but with or without otherwise.	1 or 2
elvitegravir and bictegravir are only in combination pills – see Stribild, Genvoya and Biktarvy.			1
CCR5 inhibitors (entry inhibitor)			
maraviroc * (Celsentri)		150 mg or 300 mg or 600 mg, as directed, depending on other ARVs in the combination.	1 or 2 or 4
b/PI: boosted protease inhibitors			
atazanavir * (Reyataz)		1 x 300 mg cap + booster, once-daily. Take with food. 150 mg and 200 mg capsules also available.	1 (+ 1 booster)
darunavir 600 mg (orange) & 800 mg (red), (Prezista) *		1 x 800 mg + booster once-daily (OR 1 x 600 mg + 100 mg booster twice-daily with resistance). Take with food.	1 or 2 (+ 1 or 2 boosters)
atazanavir/cobicistat (Evotaz)		1 tablet, once-daily. Take with food.	1
darunavir/cobicistat (Rezolsta)		1 tablet, once-daily. Take with food.	1
PK (pharmacokinetic) boosters			
cobicistat (/c) (Tybost)		150 mg tablet, once daily. Used to boost atazanavir, darunavir and elvitegravir.	depends on boosted drug
ritonavir (/r) * (Norvir)		100 mg tablets used at different doses to boost other PIs.	depends on PI

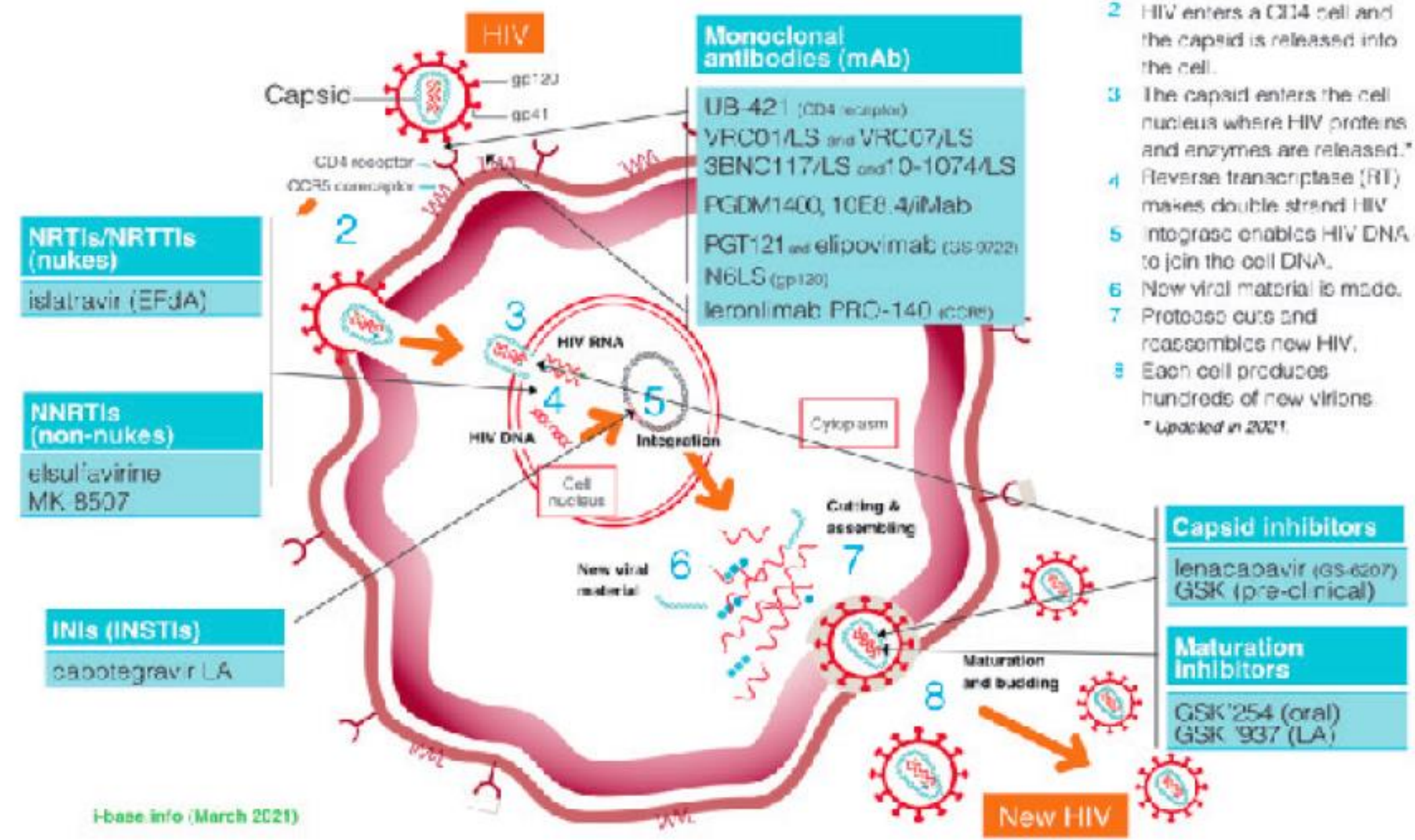
Table 1: Recent regulatory approvals and submissions

Compound/formulation	Class	Approved / submitted	Company
cabotegravir LA and rilpivirine LA injections	INSTI + NNRTI injections.	Approved US: January 2021. Approved EU: January 2021.	ViiV Healthcare Janssen
fostemsavir	gp120 attachment inhibitor.	Approved US: July 2020. Approved EU: January 2021.	ViiV Healthcare
paediatric dolutegravir	integrase inhibitor.	Approved US: July 2020. Approved EU: November 2020.	ViiV Healthcare
lenacapavir	capsid inhibitor for MDR HIV.	Submitted US: July 2021. Submitted EU: August 2021	Gilead Sciences

Table 2: HIV pipeline compounds by development phase (excluding individual bNAbs)

Compound/Company	Class	Notes	Phase
islatravir (EFdA) Merck/MSD	NRTTI	Highly potent, low dose, active against NRTI resistance. Long half-life, potential as oral (dosed daily, weekly and perhaps monthly) and an implant (annual). Monthly and annual formulations are for PrEP.	Phase 2/3
islatravir / 3TC / doravirine Merck/MSD	FDC: NRTTI + NRTI + NNRTI	FDC with generic 3TC and NNRTI doravirine. Current studies used triple combination for initial ART and switch to islatravir/doravirine for dual maintenance ART.	Phase 3
islatravir / doravirine Merck/MSD	FDC: NRTTI + NNRTI	Dual FDC with NNRTI doravirine. Currently studies look at a switch option after viral suppression with triple drug ART.	Phase 3
MK-8507 Merck/MSD	NNRTI	New NNTRI being studied with weekly dosing of islatravir.	Phase 2
Lenacapavir Gilead	capsid inhibitor	Activity at multiple stages of viral lifecycle. Sub-cutaneous injection every six months. Phase 3 data in MDR presented at CROI 2021 and IAS 2021. Phase 2 results in naive at IAS 2021. Phase 3 PrEP studies just starting.	Phase 2 and 3
Maturation inhibitors: GSK3640254 and GSK3739937	maturation inhibitor	Maturation inhibitor in phase 2 studies.	Phase 2
albuvirtide	fusions inhibitor	Similar to enfuvirtide (T-20). Long-acting weekly formualtion. Already approved in China but phase 3 data only recently reported at IAS 2021. Developed by Frontier Biotechnologies. US studied listed with bNAb for MDR HIV.	Phase 3
bNAbs: leronlimab, UB-421, VRC01, 3BNC117, 10-1074,10E8, N6, PGDM1400 and PGT121 etc.	bNAb's: Multiple targets include CD4 binding, v3 loop etc	Many bNAbs are in development for prevention, treatment and cure research - often in long-acting LS formulations and in dual or triple combinations. Many public and private research institutes (NIH, Rockefeller etc) and pharmaceutical research companies (Gilead, ViiV etc). See Table 3.	Preclincal, Phase 1 to 3

HIV pipeline 2021: targets in the HIV lifecycle



Stages in the HIV lifecycle

1. HIV attaches to a CD4 cell
2. HIV enters a CD4 cell and the capsid is released into the cell.
3. The capsid enters the cell nucleus where HIV proteins and enzymes are released.*
4. Reverse transcriptase (RT) makes double strand HIV
5. Integrase enables HIV DNA to join the cell DNA.
6. New viral material is made.
7. Protease cuts and reassembles new HIV.
8. Each cell produces hundreds of new virions

* Updated in 2021

MERCK

NEWS RELEASE

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

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.

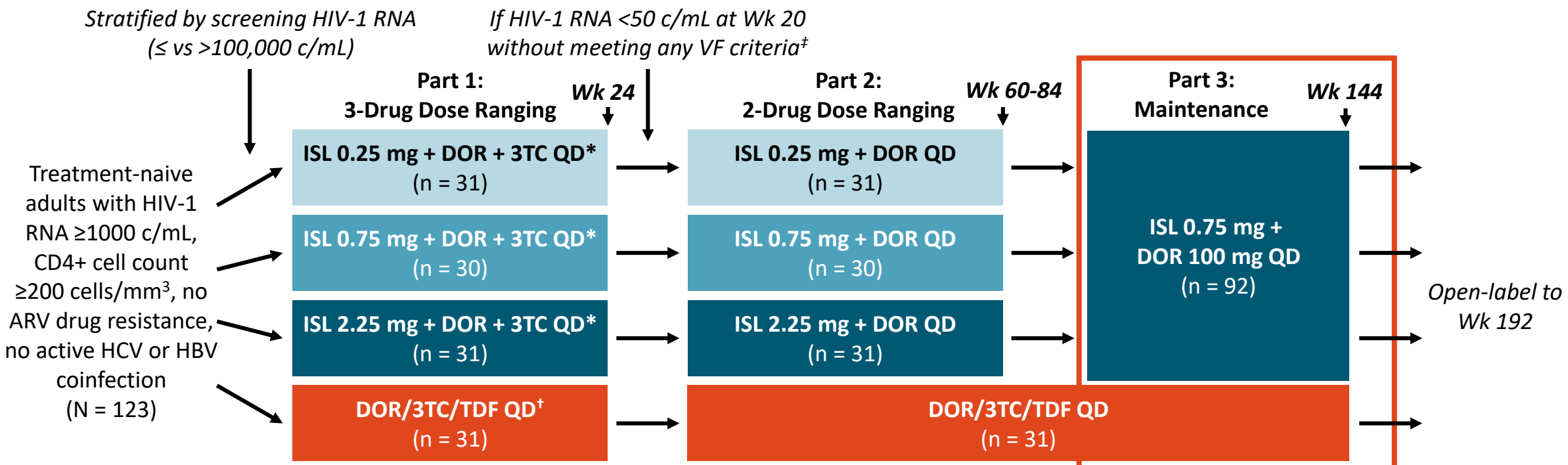
The FDA's clinical hold is based on previously announced observations of decreases in total lymphocyte and CD4+ T-cell counts in some participants receiving islatravir in clinical studies

Gilead and Merck have made the decision to stop all dosing of participants in the Phase 2 clinical study 2 (NCT05052996) evaluating an oral-weekly combination treatment regimen of Merck's investigational islatravir and Gilead's investigational lenacapavir in people living with HIV who are virologically suppressed on antiretroviral therapy.

13/12/2021

P011: Islatravir + Doravirine in Treatment-Naive PWH

- International, randomized, double-blind phase IIb trial[1,2]



*Received placebo for DOR/3TC/TDF QD. †Received placebo for ISL + DOR + 3TC QD.
‡If HIV-1 RNA ≥50 c/mL at Wk 20, continued Part 1 until HIV-1 RNA <50 c/mL and, if not meeting any VF criteria, transitioned to Part 2.

- High rates of efficacy and tolerability through Wk 96; no patients met criteria for resistance testing[2]

1. Molina. EACS 2021. Abstr OS 1/5. 2. Molina. Glasgow 2020. Abstr O415.

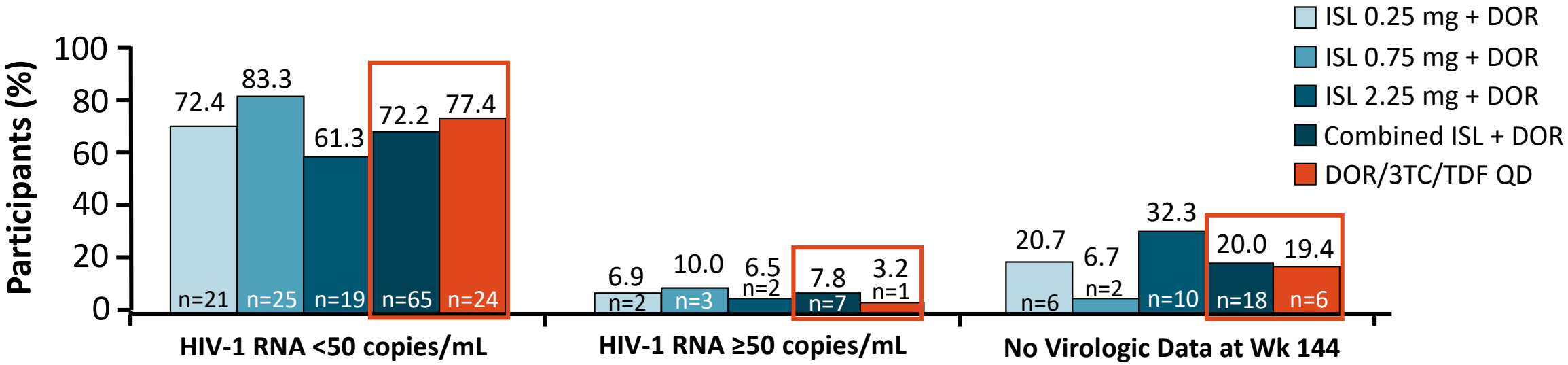
Slide credit: clinicaloptions.com

P011: Baseline Demographics

Characteristic	ISL 0.25 mg + DOR* QD (n = 31)	ISL 0.75 mg + DOR* QD (n = 30)	ISL 2.25 mg + DOR* QD (n = 31)	Combined ISL + DOR (n = 92)	DOR/3TC/TDF QD (n = 31)
Male, n (%)	30 (96.8)	27 (90.0)	28 (90.3)	85 (92.4)	28 (90.3)
Median age, yr (range)	27.0 (19-75)	28.0 (18-51)	29.0 (19-67)	28.5 (18-75)	27.0 (18, 56)
Race/ethnicity, n (%) ▪ Black ▪ White ▪ Hispanic/Latinx	 ▪ 6 (19.4) ▪ 24 (77.4) ▪ 14 (45.2)	 ▪ 6 (20.0) ▪ 24 (80.0) ▪ 19 (63.3)	 ▪ 8 (25.8) ▪ 21 (67.7) ▪ 12 (38.7)	 ▪ 20 (21.7) ▪ 69 (75.0) ▪ 45 (48.9)	 ▪ 5 (16.1) ▪ 24 (77.4) ▪ 15 (48.4)
Median CD4+ count, cells/mm^3 (range)	415.0 (199-889)	535.5 (178-828)	416.0 (185-1122)	445.5 (178-1122)	473.0 (224-1321)
Median HIV-1 RNA, log_{10} copies/mL (range)	4.6 (3.5-6.2)	4.5 (3.0-5.8)	4.7 (3.1-5.8)	4.6 (3.0-6.2)	4.2 (3.3-6.1)
▪ ≤100,000 copies/mL, n (%)	22 (71.0)	24 (80.0)	22 (71.0)	68 (73.9)	26 (83.9)
▪ >100,000 copies/mL, n (%)	7 (22.6)	6 (20.0)	9 (29.0)	22 (23.9)	5 (16.1)

*Participants initially received ISL + DOR + 3TC and switched to ISL + DOR during Part 2 of the study.

P011: Virologic Outcomes at Wk 144



- Protocol-defined virologic failure (PDVF, confirmed HIV-1 RNA ≥50 copies/mL) in n = 7 patients
  - All discontinued trial with confirmatory HIV-1 RNA <80 copies/mL
- No instances of clinically significant confirmed viremia (HIV-1 RNA ≥200 copies/mL) or viral drug resistance analysis

Molina. EACS 2021. Abstr OS 1/5.

Slide credit: clinicaloptions.com

P011: Safety Outcomes Through Wk 144

Adverse Event, n (%)	ISL 0.25 mg + DOR* QD (n = 29)	ISL 0.75 mg + DOR* QD (n = 30)	ISL 2.25 mg + DOR* QD (n = 31)	Combined ISL + DOR Groups (n = 90)	DOR/3TC/TDF QD (n = 31)
Drug-related AE	0	3 (10.0)	4 (12.9)	7 (7.8)	7 (22.6)
Serious AE	2 (6.9)	6 (20.0)	2 (6.5)	10 (11.1)	4 (12.9)
Serious drug-related AE	0	0	0	0	1 (3.2)
Discontinued due to AE	1 (3.4)	0	2 (6.5)	3 (3.3)	1 (3.2)
Discontinued due to drug-related AE	0	0	2 (6.5)	2 (2.2)	1 (3.2)

*Participants initially received ISL + DOR + 3TC and switched to ISL + DOR during Part 2 of the study.

- Most common drug-related adverse events: diarrhea, nausea, headache, abnormal dreams
- Lower rate of drug-related AEs in the ISL + DOR groups (7.8%) than in the DOR/3TC/TDF group (22.6%)
- All discontinuations due to drug-related AEs occurred prior to Wk 48
  - ISL 2.25 mg group, n = 2 (diarrhea/nausea/vomiting, n = 1; HBV reactivation, n = 1)
  - DOR/3TC/TDF group (worsening of congenital long QT syndrome, n = 1)
- No deaths or serious drug-related AEs across ISL + DOR groups

Molina. EACS 2021. Abstr OS 1/5.

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

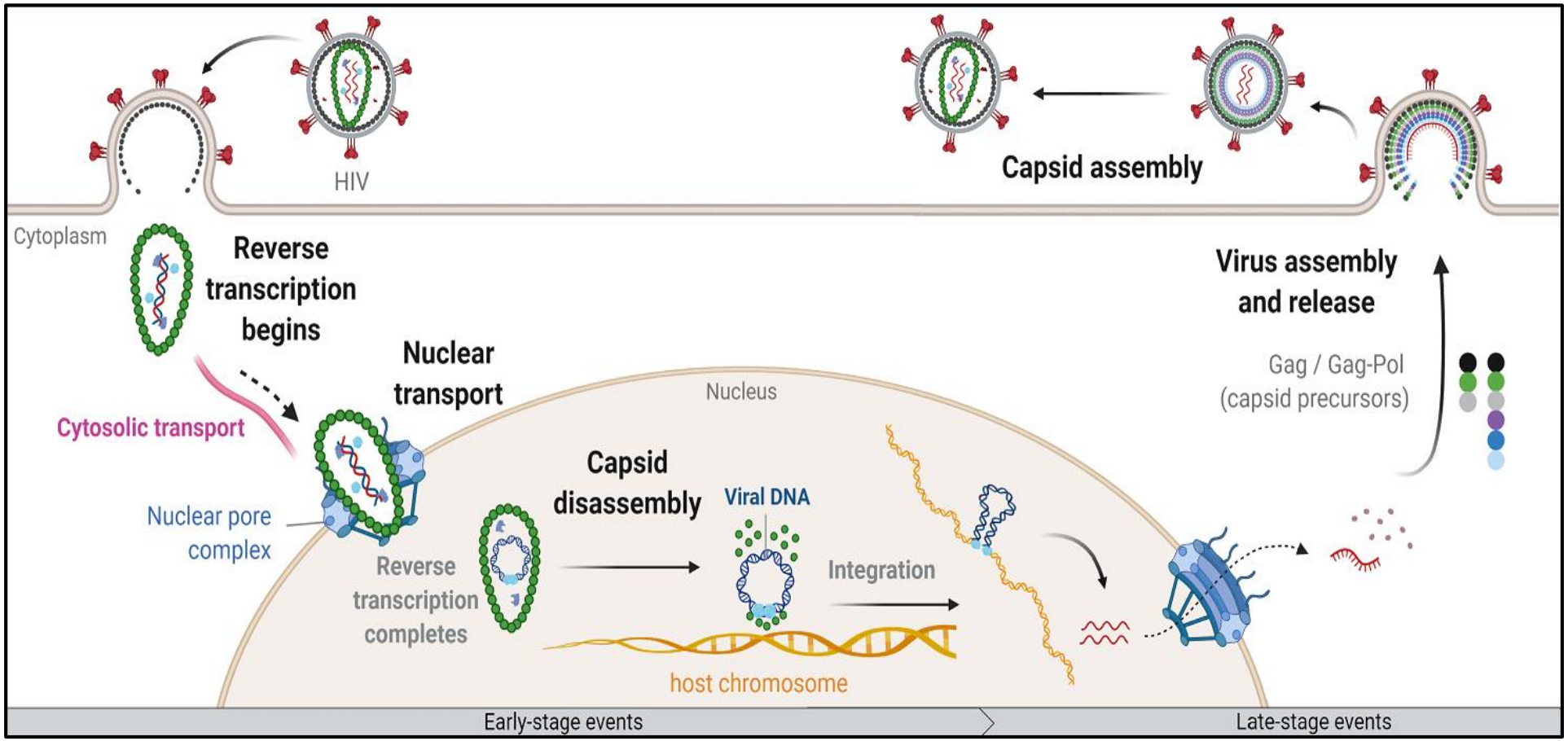
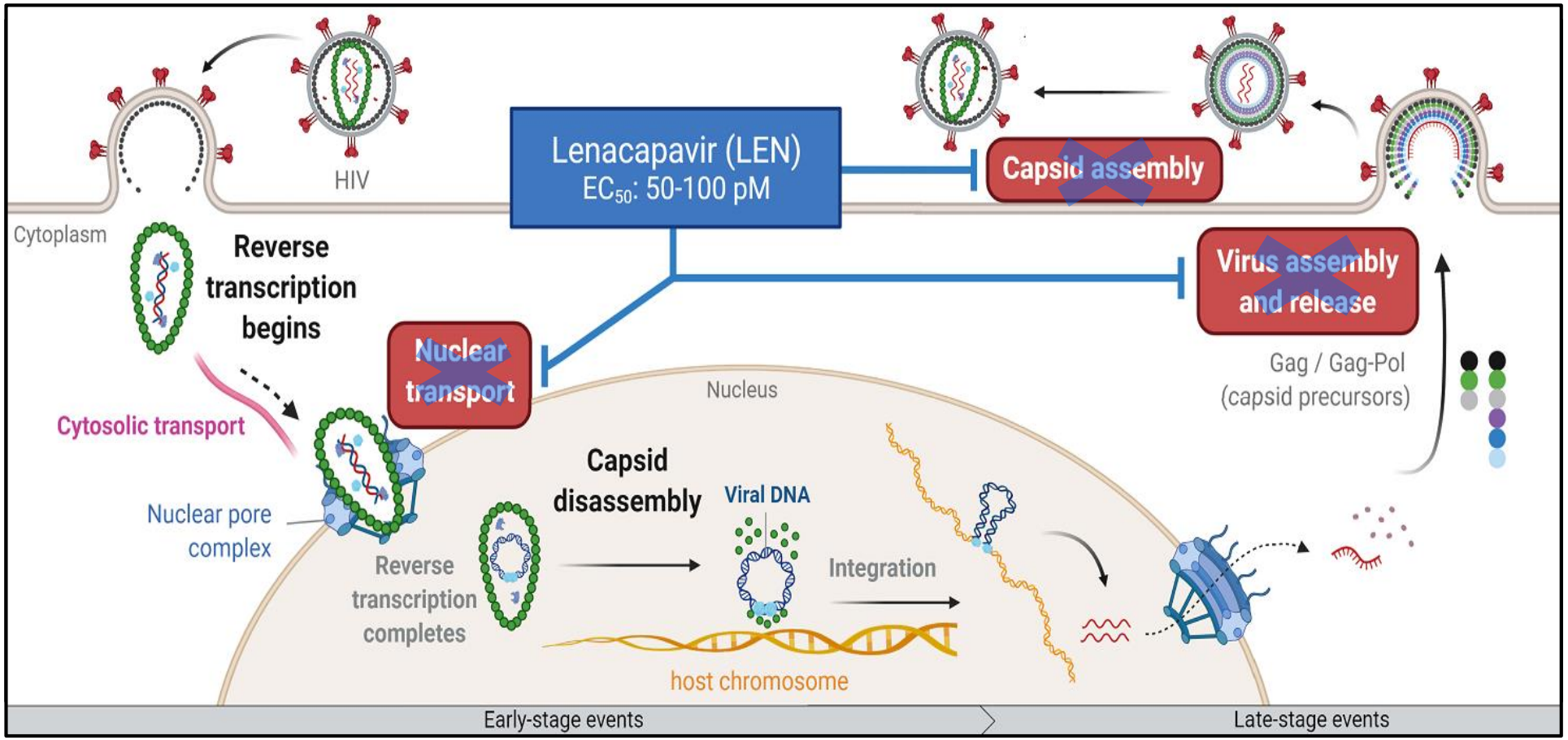


Figure generated based on the following references: Link J, et al. Nature 2020;584:614-618; Bester SM, et al. Science 2020;370:360-364; Cihlar T. vCROI 2021. Oral #22; Muller B. vCROI 2021. Oral #19; Pathak VK. vCROI 2021. Oral #20; Ganser-Pornillos B. vCROI 2021. Oral #21

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

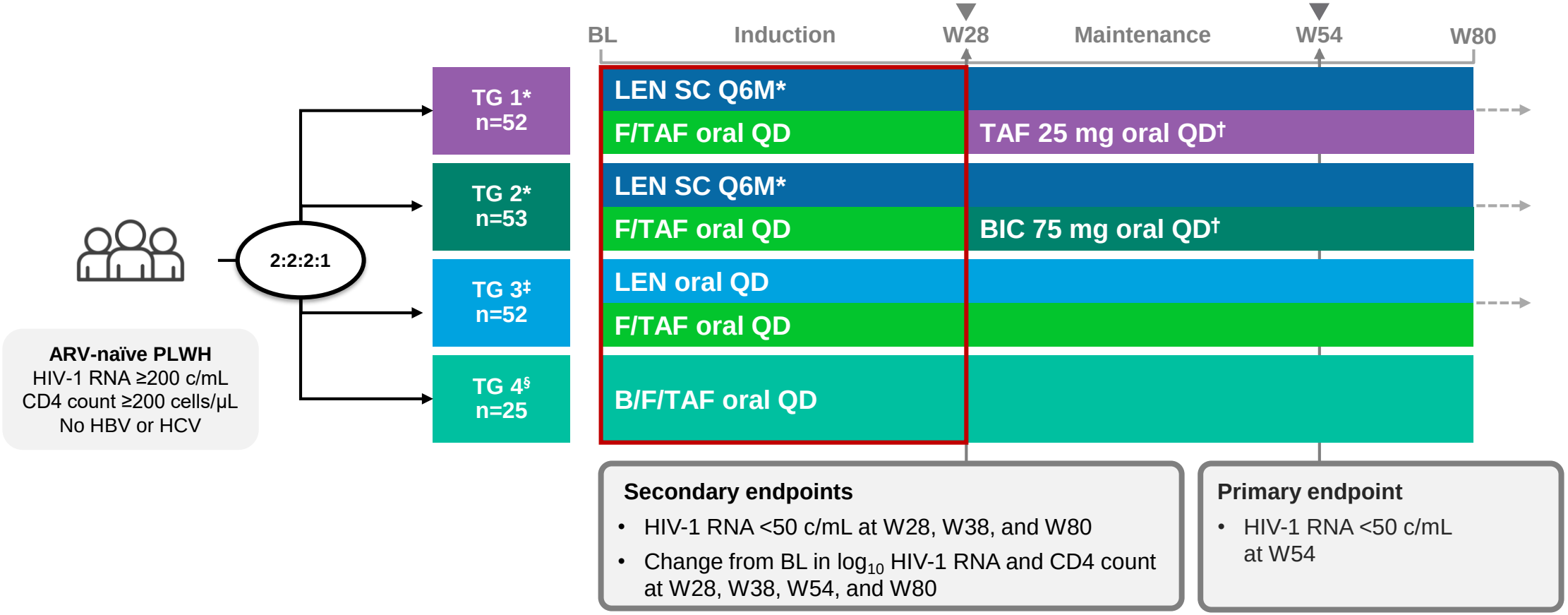


LEN modulates the stability and/or transport of capsid complexes, leading to inhibition of multiple processes in the HIV lifecycle

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

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 initiation (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 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 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

Gupta S, et al. vIAS 2021, OALB0302

Baseline Characteristics

Demographics

	LEN SC + F/TAF (→ TAF) n=52	LEN SC + F/TAF (→ BIC) n=53	LEN QD + F/TAF n=52	B/F/TAF n=25
Median age, years (range)	31 (19–61)	28 (19–56)	28 (19–72)	29 (21–61)
Female at birth, %	10	2	12	0
Black race, %	46	45	60	64
Hispanic/ Latinx, %	48	40	46	48

Clinical Characteristics

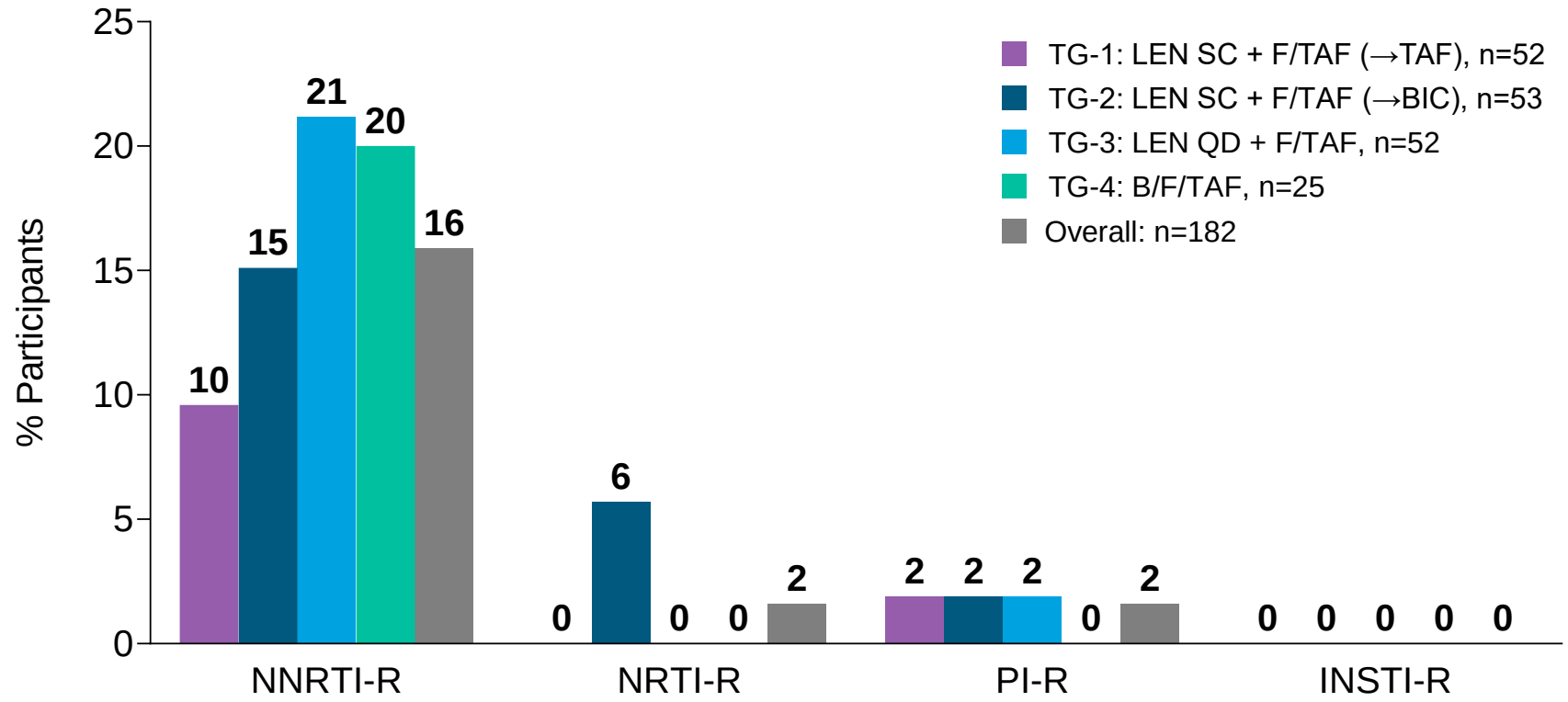
	LEN SC + F/TAF (→ TAF) n=52	LEN SC + F/TAF (→ BIC) n=53	LEN QD + F/TAF n=52	B/F/TAF n=25
Median HIV-1 RNA, log_{10} c/mL (Q1, Q3)	4.27 (3.77, 4.63)	4.32 (3.96, 4.74)	4.53 (3.82, 4.83)	4.37 (4.09, 4.77)
HIV-1 RNA >100,000 c/mL, %	10	17	17	16
Median CD4 count, cells/μL (Q1, Q3)	404 (320, 599)	450 (332, 599)	409 (301, 600)	482 (393, 527)
CD4 count <200 cells/μL, %	0	2	6	0

LEN, lenacapavir; Q, quartile; QD, once daily; SC, subcutaneously

Gupta S, et al. vIAS 2021, OALB0302

Frequency of Preexisting Baseline Resistance Substitutions

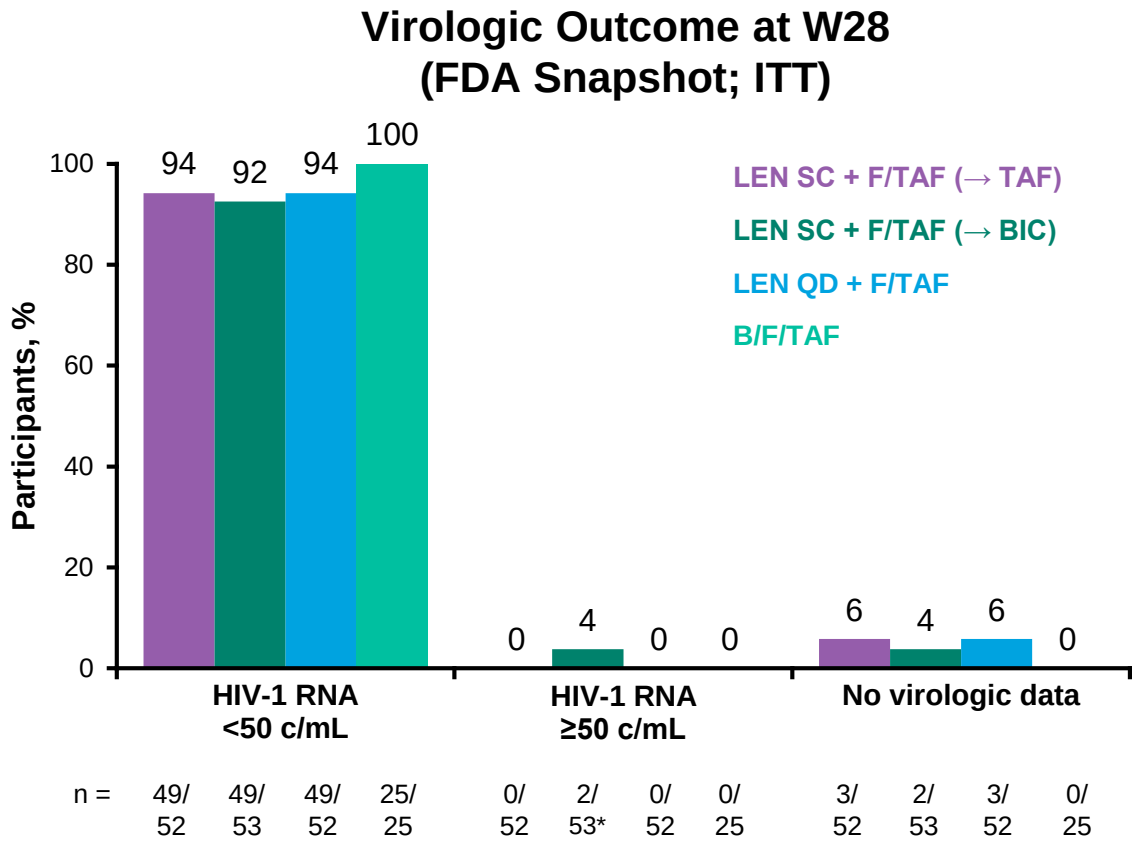
- LEN resistance mutations previously identified in vitro were not found in study population at baseline
- Primary NNRTI-R mutations were primarily K103N/S (8%), followed by E138A/G/K/Q/R (4%)
- Primary NRTI-R mutations were infrequent and consisted of TAMs

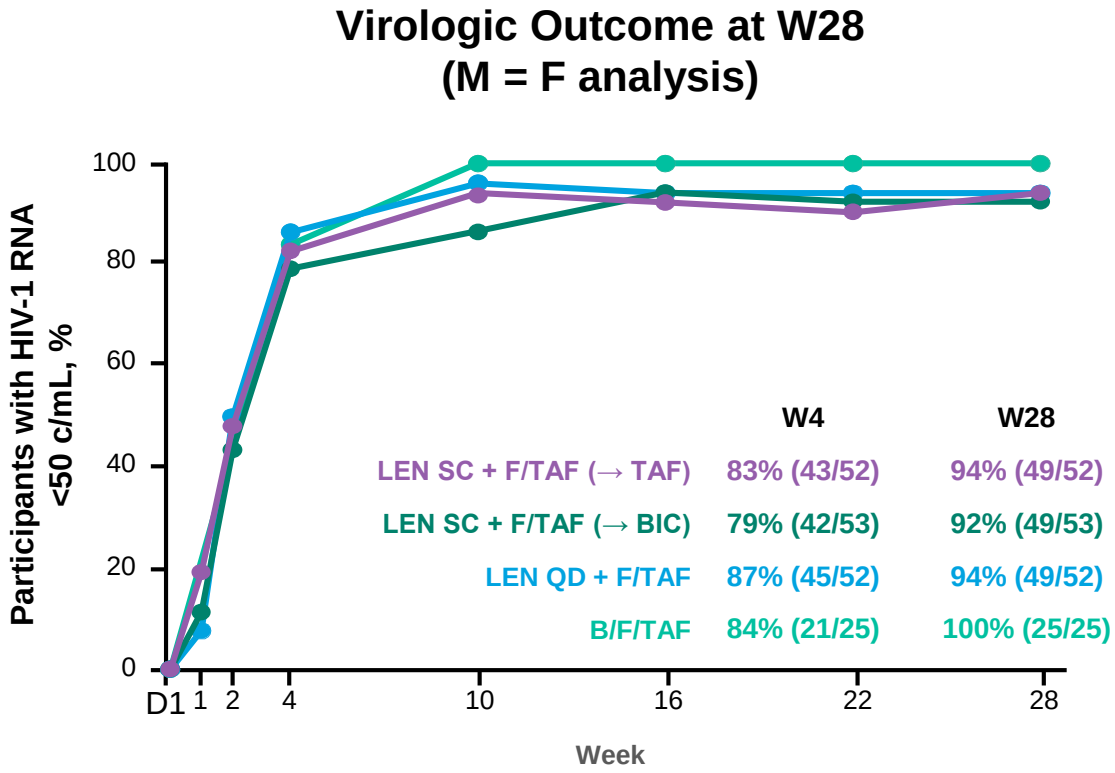


NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; R, resistance; TAM, thymidine analogue mutation.

VanderVeen et al. IDWeek2021. Oral 73

Virologic Outcomes at W28



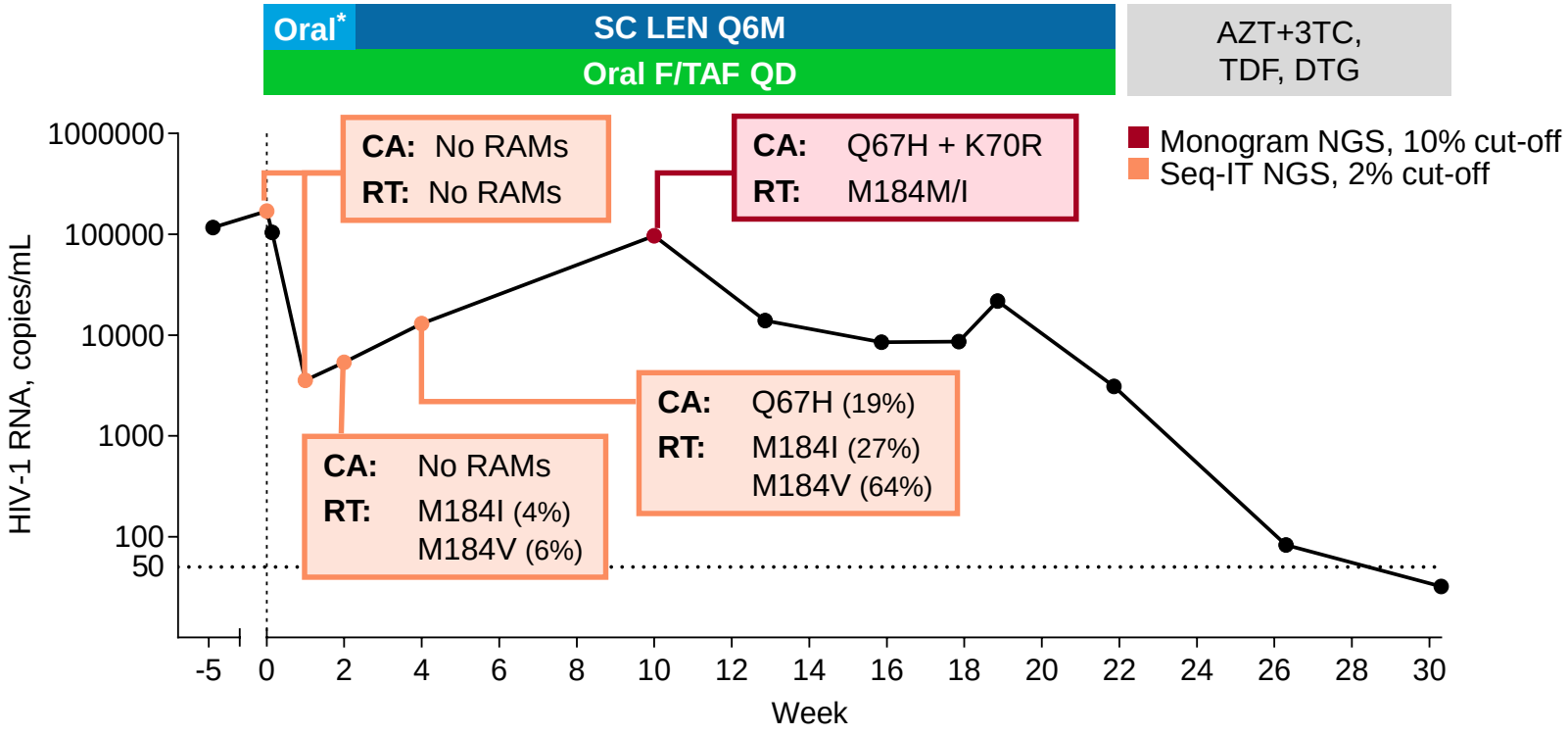


LEN (SC and oral) in combination with F/TAF rapidly achieved high rates of virologic suppression

*1 participant discontinued due to not meeting the protocol criteria of having HIV-1 RNA <50 c/mL prior to W28; 1 participant discontinued on D2
c, copies; D, Day; ITT, intent-to-treat; LEN, lenacapavir; M=F, missing=failure; QD, once daily; SC, subcutaneously; W, Week

Gupta S, et al. vIAS 2021, OALB0302

Emergence of Resistance Mutations



3 participants met resistance analysis criteria

- 2 participants resuppressed at a later visit with no emergent resistance
- 1 participant developed CA and RT resistance by Week 10

Phenotypic Analysis

EC_{50} Fold Change from WT†	CA‡	RT‡	
	LEN	TFV	FTC
Baseline	1.2	ND	ND
Week 10	20	0.46	>58

In TN PLWH, there was one case of treatment-emergent capsid resistance (n=1/157)
The pattern of mutation emergence may suggest partial adherence to the oral components of the regimen

*LEN oral lead-in (600 mg on D1 and D2, 300mg on D8) dosing observed during oral lead-in period
†Ratio of Mutant//wild-type EC_{50}
‡ CA:PhenoSense Gag-Pro assay (Monogram Biosciences), RT: PhenoSense GT assay (Monogram Biosciences)
Screening CD4 levels: 233 cells/µL
ND, not determined; NGS, next generation sequencing; RAM, resistance-associated mutation

VanderVeen et al. IDWeek2021. Oral 73

Laboratory Abnormalities

≥3% Participants in LEN total, %	LEN Total TG 1+2+3 n=157	B/F/TAF TG 4 n=25
Any Grade 3 or 4 lab abnormality	17	12
Low creatinine clearance/eGFR	4	8
High creatine kinase	5	0
Nonfasting/fasting hyperglycemia*	3	0

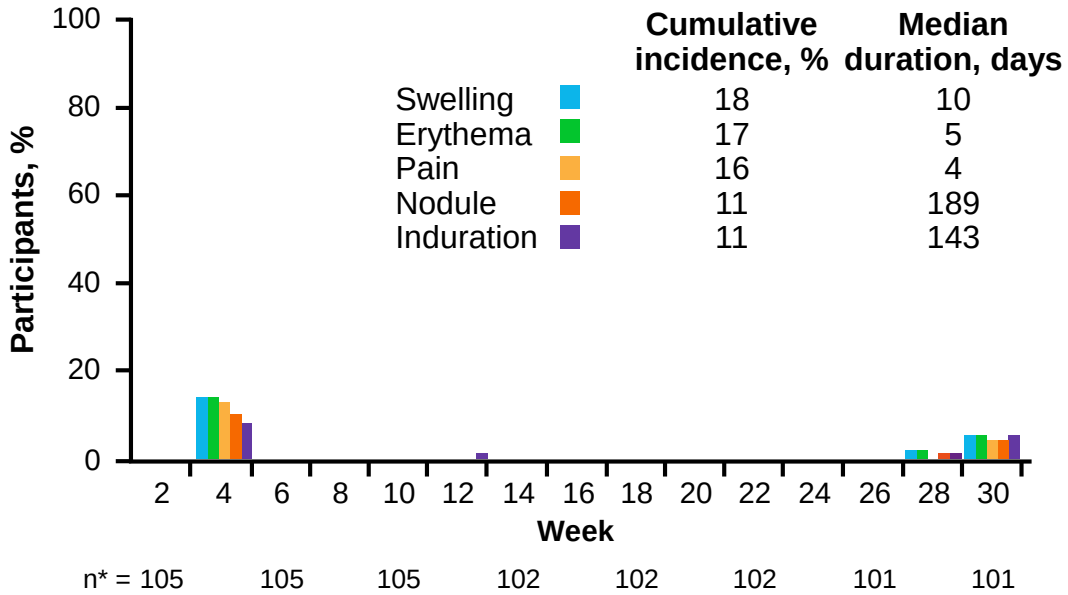
- No Grade 3 or 4 lab abnormalities were clinically relevant
  - No discontinuations associated with Grade 3 or 4 lab abnormalities
  - Alternative explanation (e.g. creatine kinase elevation after strenuous activity)
  - One participant had Grade 4 ALT, which was associated with trimethoprim/sulfamethoxazole used to treat the SAE of *P. jirovecii* pneumonia

*All with medical history of diabetes. ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; TG, Treatment Group

Gupta S, et al. vIAS 2021, OALB0302

LEN Safety and Tolerability in Treatment-naïve PLWH

Injection site reactions



ISRs

- No ISRs: 61% (63/103)
- Most ISRs Grade 1 (83% [33/40])
  - Generally resolved within days
- One Grade 3 ISR (nodule), no Grade 4 ISRs
  - All nodules but 1 were Grade 1
- 2 participants discontinued due to AEs (both due to Grade 1 injection-site induration)

AEs

No study drug–related SAEs
No study drug–related Grade 4 AEs

Most common AEs

Headache and nausea (11%)

GI AEs: SC versus oral

Nausea: **12%** versus **8%**

Diarrhea: **6%** versus **8%**

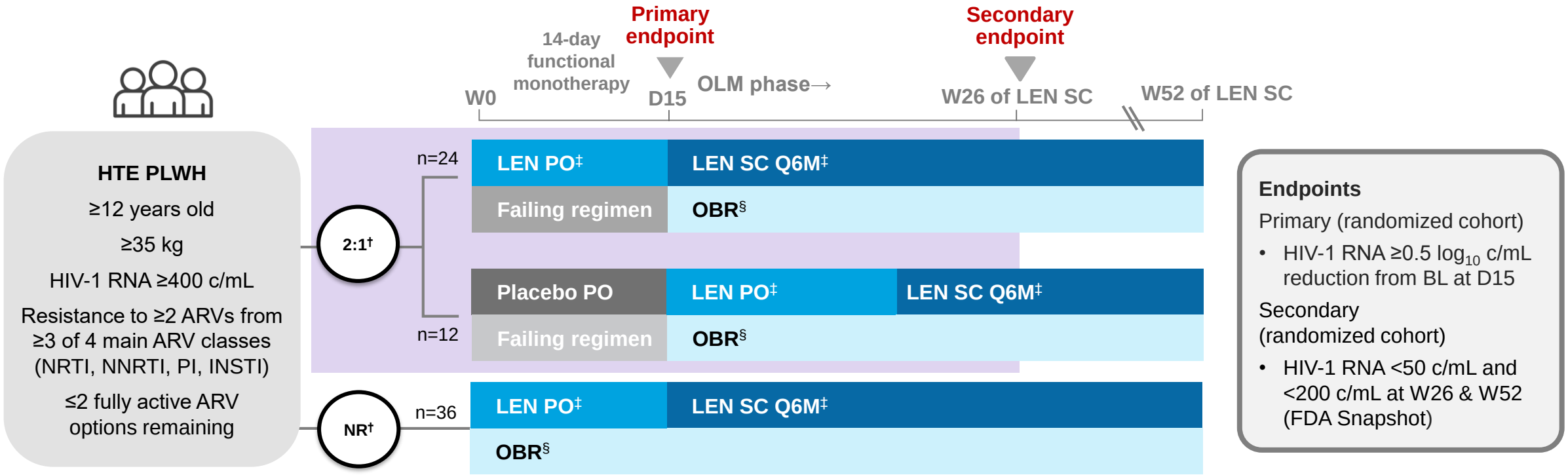
LEN demonstrated a favorable safety profile and was well tolerated with infrequent discontinuations due to AEs

*Total number of participants on study or last exposure date in 2-week interval
AE, adverse event; GI, gastrointestinal; ISR, injection site reaction; LEN, lenacapavir; SAE, serious adverse event; SC, subcutaneous

Gupta S, et al. vIAS 2021, OALB0302

LEN in Heavily Treatment-Experienced PLWH

Phase 2/3, blinded, placebo-controlled study to evaluate LEN as an add-on to a failing regimen in heavily treatment-experienced PLWH with MDR (N=72)



‡**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
§Investigational agents, such as fostemsavir, were allowed; atazanavir (ATV), ATV/cobicistat, ATV/ritonavir, efavirenz, entecavir, nevirapine, tipranavir were not allowed
‡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; SC, subcutaneous

1. Segal-Maurer S, et al. vCROI 2021. Oral #127 2. Molina JM, et al. vIAS 2021, OALX01LB02

Baseline Characteristics

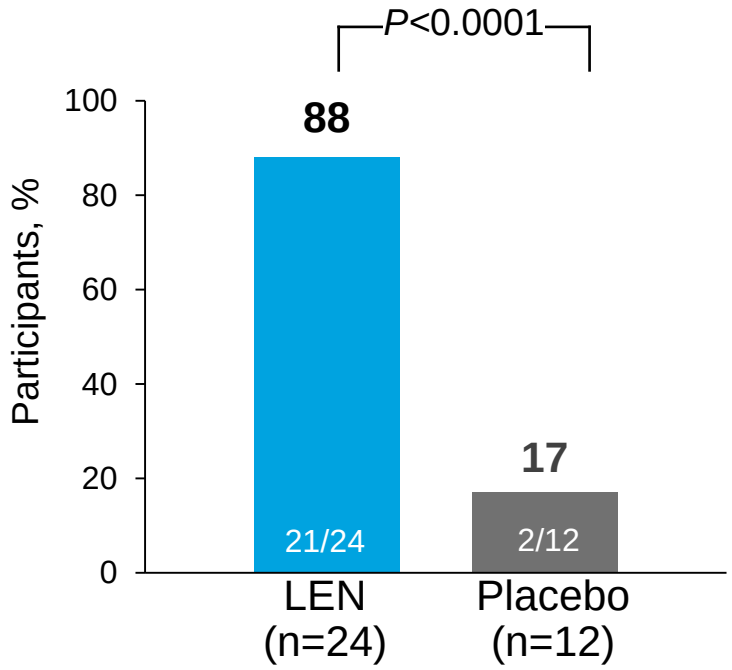
	Randomized		Nonrandomized	
	LEN n=24	Placebo n=12	LEN n=36	Total N=72
Age, median (range), years	55 (24 – 71)	54 (27 – 59)	49 (23 – 78)	52 (23 – 78)
Sex, % female at birth	29	25	22	25
Race, % Black	42	55	31	38
Ethnicity, % Hispanic/Latinx	25	36	14	21
HIV-1 RNA, median (range), log_{10}copies/mL	4.2 (2.3 – 5.4)	4.9 (4.3 – 5.3)	4.5 (1.3 – 5.7)	4.5 (1.3 – 5.7)
>75,000 copies/mL, %	17	50	28	28
CD4 count, median (range), cells/μL	172 (16 – 827)	85 (6 – 237)	195 (3 – 1296)	150 (3 – 1296)
≤200 cells/μL, %	67	92	53	64
Years since HIV diagnosis, median (range)	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

1. Segal-Maurer S, et al. vCROI 2021. Oral #127 2. Molina JM, et al. vIAS 2021. Oral #OALX01LB02

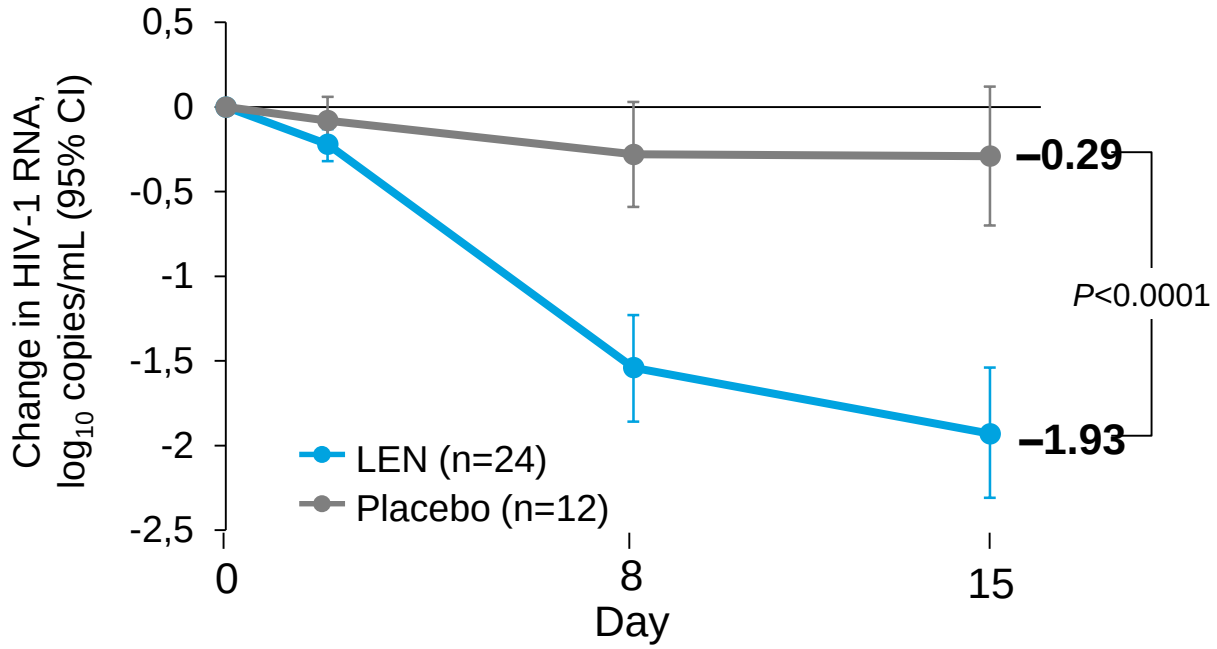
Antiviral Activity During Functional Monotherapy, Randomized Cohort

Primary Endpoint

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



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

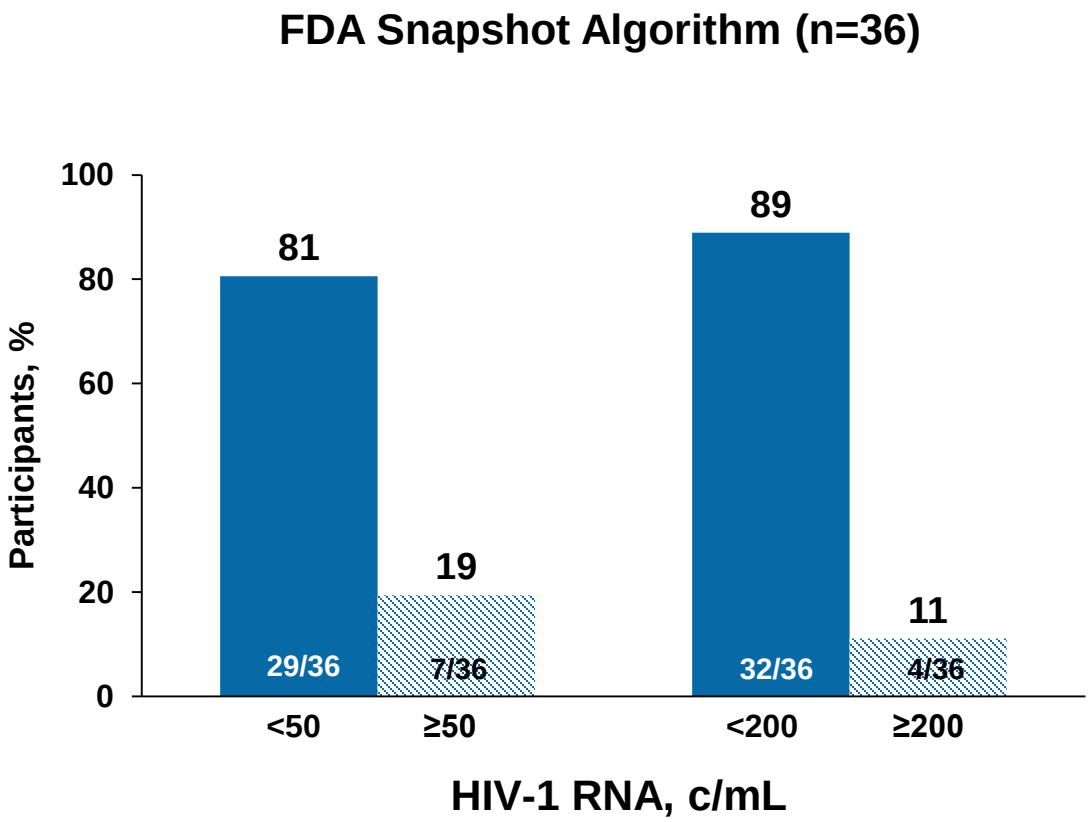


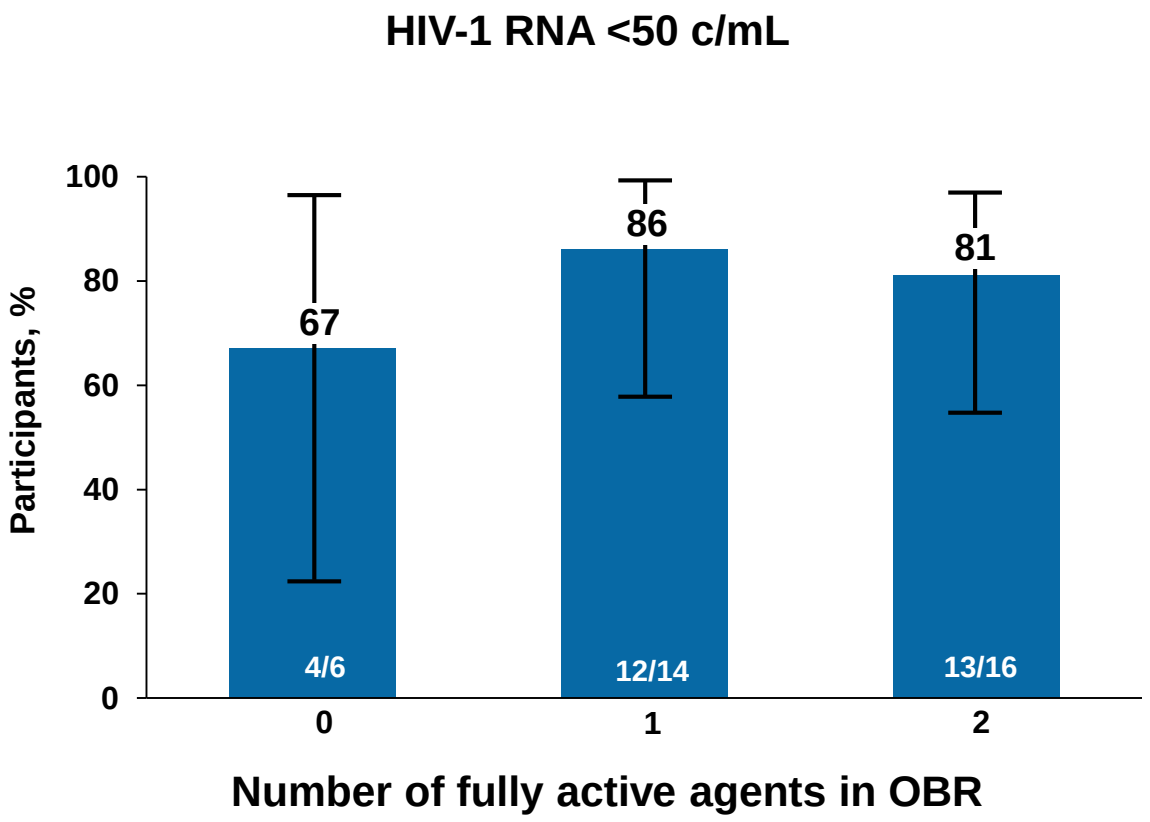
LEN showed potent antiviral activity when added to a failing regimen

HTE, heavily treatment-experienced

Segal-Maurer S, et al. vCROI 2021. Oral #127

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



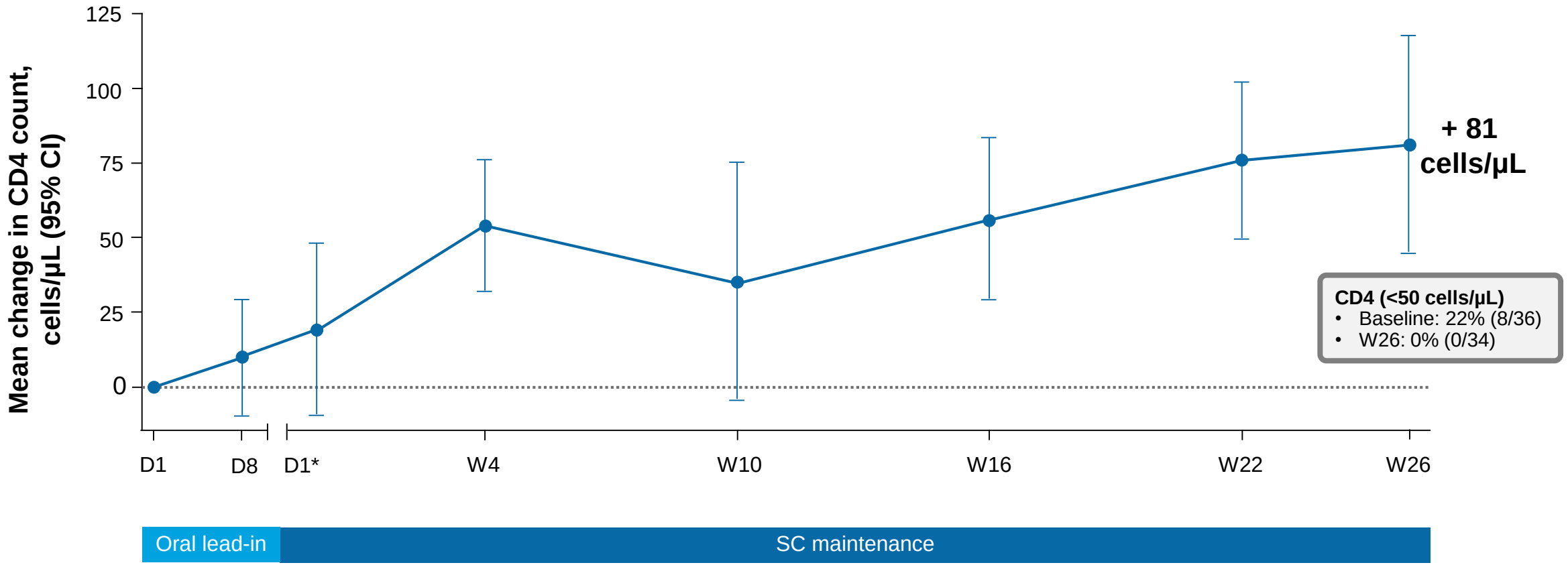


LEN in combination with OBR led to high rates of virologic suppression in HTE PLWH

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

Molina JM, et al. vIAS 2021, OALX01LB02

Changes in CD4 Count at W26, Randomized Cohort (n=36)



LEN in combination with OBR led to an improvement in CD4 count

*First day of LEN SC administration
D, day; 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

NOTE. 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. HIV-1, protease, reverse-transcriptase, and integrase genotypic and phenotypic testing were performed if the rebound or suboptimal virologic response were confirmed
HTE, heavily treatment-experienced; OBR, optimized background regimen
Molina JM, et al. vIAS 2021, OALX01LB02

CAPELLA Resistance Analysis: Summary of Patients With Emergent Capsid Resistance

Patient	First Visit With CA Resistance	CA RAMs	LEN Fold Change vs Wild Type	Fully Active Drugs, n	Comments
1	Wk 26	M66I	138	3	Effective LEN monotherapy; OBR nonadherence
2	Wk 10	M66I, N74D, A105T	>1445	0	Effective LEN monotherapy; no active ARVs in OBR
3	Wk 4	M66M/I	46	0	Effective LEN monotherapy; no active ARVs in OBR
4	Wk 4	M66M/I, K70K/S	ND	2	Effective LEN monotherapy; OBR nonadherence

- M66I emerged in 4 of 4 patients with CA resistance
  - Resulting in 46 to >1445-fold change in LEN susceptibility vs wild type
- All 4 patients with CA resistance were receiving effective LEN monotherapy at time of emergent resistance due to inadequate OBR potency or nonadherence

Margot. EACS 2021. Abstr OS11.

Slide credit: clinicaloptions.com

Grade 3 or 4 Laboratory Abnormalities

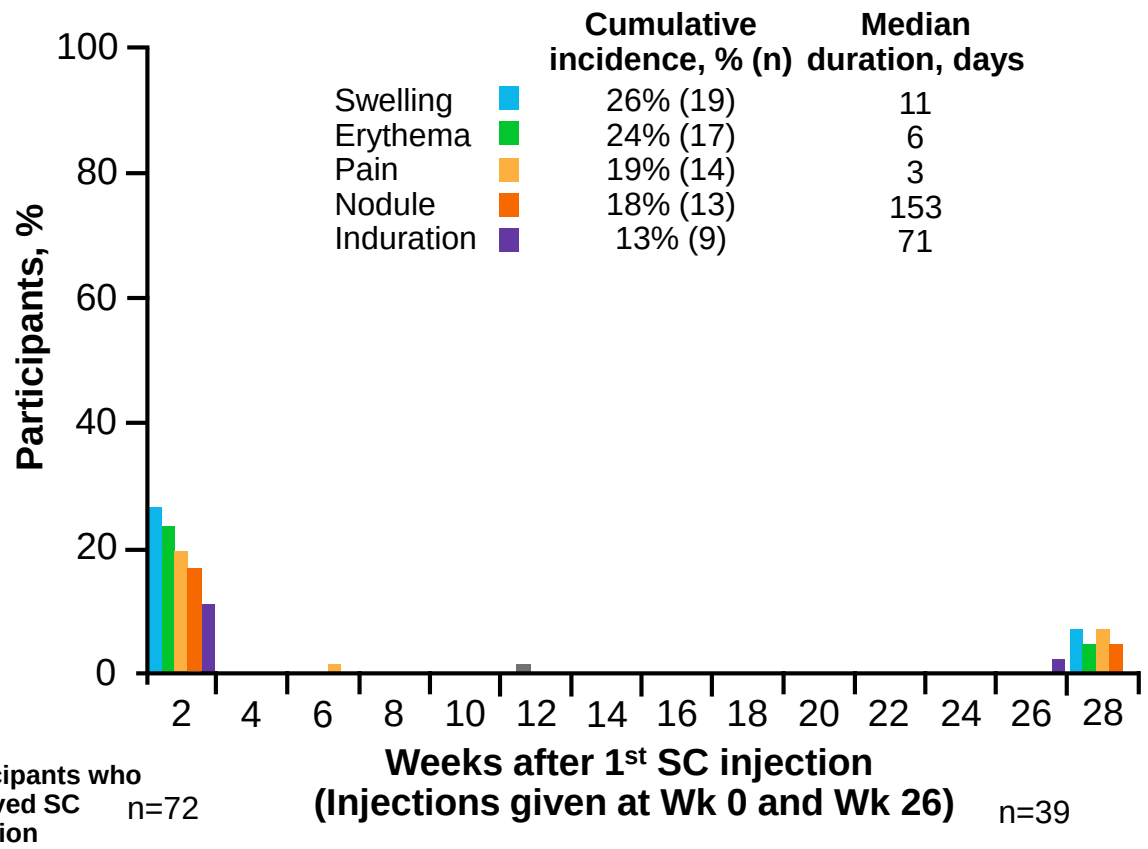
≥5% in total, (n)	Total (N=72)
Any Grade 3 or 4 lab abnormality	26% (19)
Low creatinine clearance (eGFR)/high creatinine*	11% (8)
Glycosuria	6% (4)
Nonfasting/fasting hyperglycemia	6% (4)

- None of the Grade 3 or 4 lab abnormalities were considered clinically relevant
- Low creatinine clearance/eGFR and/or high creatinine were transient or unconfirmed abnormalities
- Hyperglycemia/glycosuria were transient, unconfirmed, or related to underlying diabetes

*Per DAIDS scale, Grade 3 creatinine clearance is <60–30 mL/min or 30–<50% decrease from baseline;
Grade 3 creatinine is >1.8–<3.5 x upper limit of normal or increase to 1.5–<2.0 x baseline. eGFR, estimated glomerular filtration rate.

LEN Safety and Tolerability in HTE PLWH, Total LEN (N=72)

Injection Site Reactions



- 44% (32/72) of participants reported no ISRs
- 56% (40/72) of participants had ≥1 ISR related to LEN
  - Most ISRs were Grade 1 (70% [28/40]) and generally resolved within days
  - 2 participants had Grade 3 ISRs*
  - No Grade 4 ISRs occurred
- All nodules were Grade 1
- No discontinuations due to ISRs

LEN was well tolerated with no AEs that led to discontinuation in HTE PLWH

- No SAEs related to study drug†
- No AEs leading to study drug discontinuation

*One with swelling and erythema that resolved in 4 and 8 days, respectively; and one with pain that resolved in 1 day
†SAEs not related to study drug: 1) neoplasm malignant with fatal outcome, dizziness; 2) abdominal pain, pancreatic mass, *Clostridium difficile* infection; 3) proctalgia; 4) femoral neck fracture
AE, adverse event; HTE, heavily treatment-experienced; ISR, injection site reaction; SAE, serious AE

Molina JM, et al. vIAS 2021, OALX01LB02

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 LAO (QW) and LAI (Q1-3M) complete regimens **QW LAO** **Q1-3M LAI**	**Ultimate Transformative Therapy** Launch best in class LEN-containing LAI therapies to optimize frequency, formulation and dosing (aspirationally, a Q6M complete regimen) **Q6M LAI**

30 * 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

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 LAO (QW) and LAI (Q1-3M) complete regimens **QW LAO** **Q1-3M LAI**	**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 **Q6M LAI**	

31 * 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

Monoclonal Antibody Ibalizumab

- Ibalizumab binds to the T-cell CD4 receptor and prevents conformational changes in CD4-gp120 complex, thereby blocking viral entry[1]
- Approved in combination with other ARVs for heavily treatment–experienced adults with multidrug-resistant HIV infection who are experiencing failure of current regimen[2]
  - May be used for patients without sufficient treatment options

1. Emu. NEJM. 2018;379:645. 2. Ibalizumab-uiyk PI.

Ibalizumab: humanized monoclonal antibody

Ibalizumab (IBA) is a humanized monoclonal antibody with a molecular weight of ~150 kDa targeting CD4

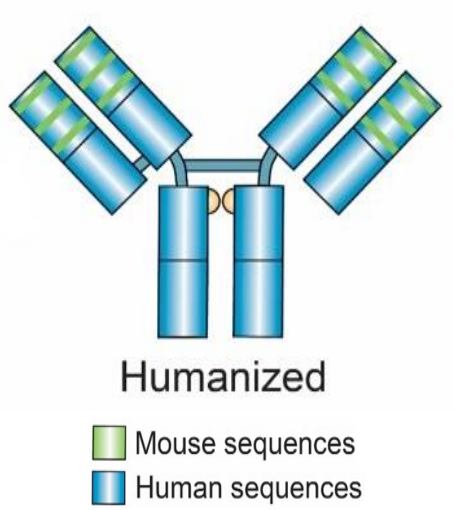
Engineered from its murine progenitor (mu5A8)

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



Ibalizumab: humanized monoclonal antibody

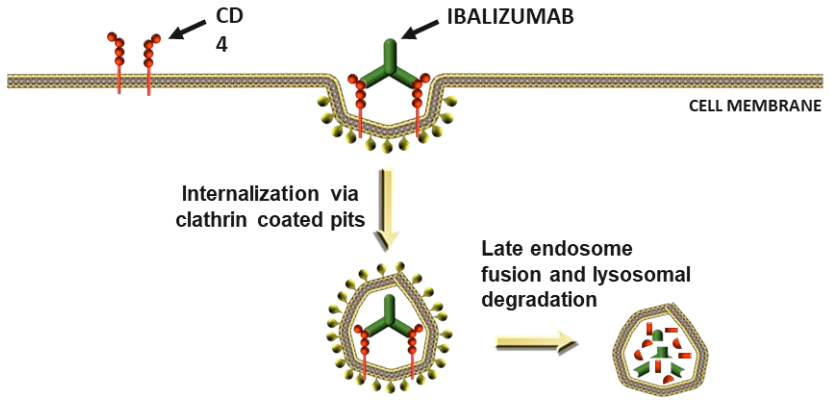
Metabolized by CD4 receptor internalization

The Ibalizumab-CD4 complex is removed by internalization into lysosomes (which are degraded).

In free form, Ibalizumab is cleared in the same way as circulating endogenous IgG4 antibodies, through pinocytosis in the vascular endothelium and degradation in lysosomes

No drug-drug interactions (DDI) with approved ARVs

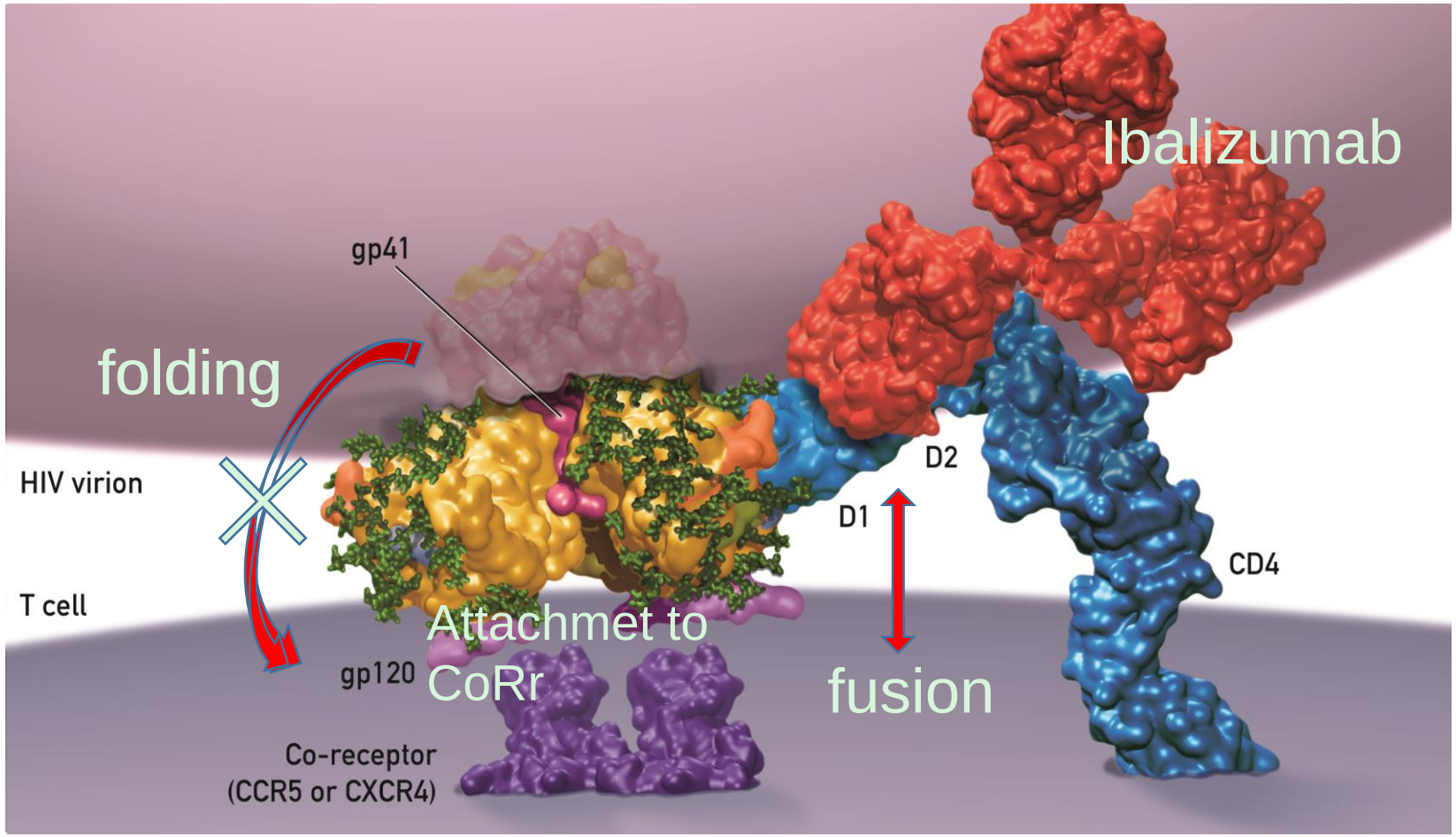
No other significant DDI identified in clinical trials



Ibalizumab

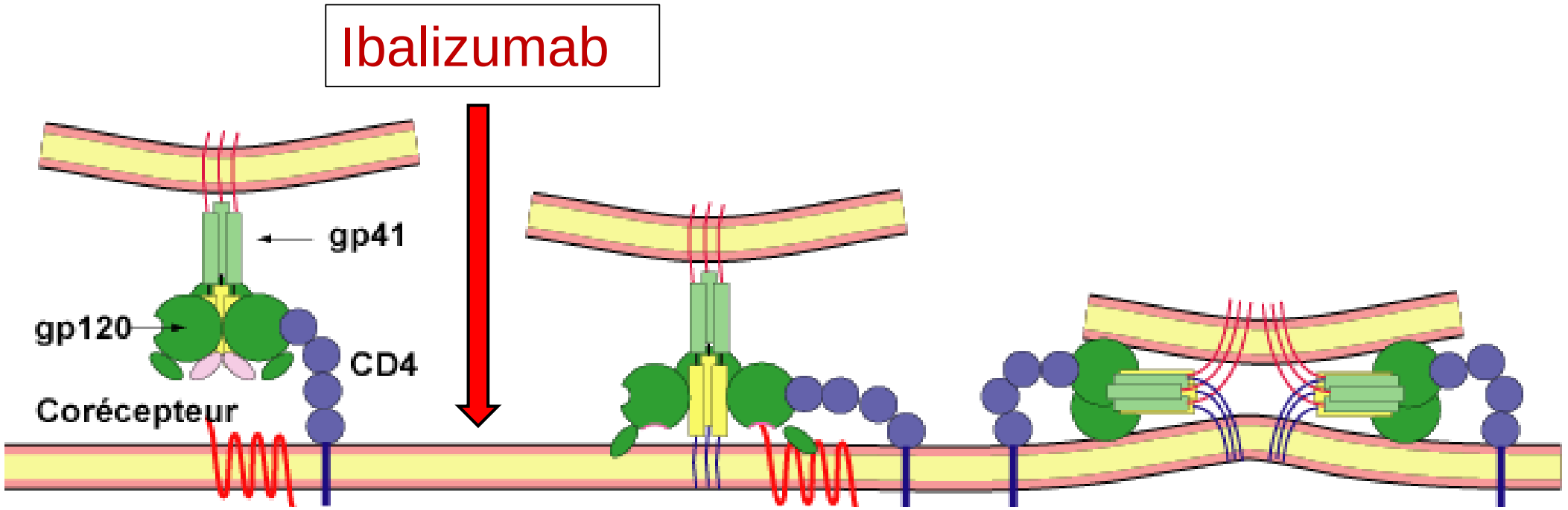
Mechanism of Action: CD4-directed antibody:“post attachment Inhibitor”

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



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

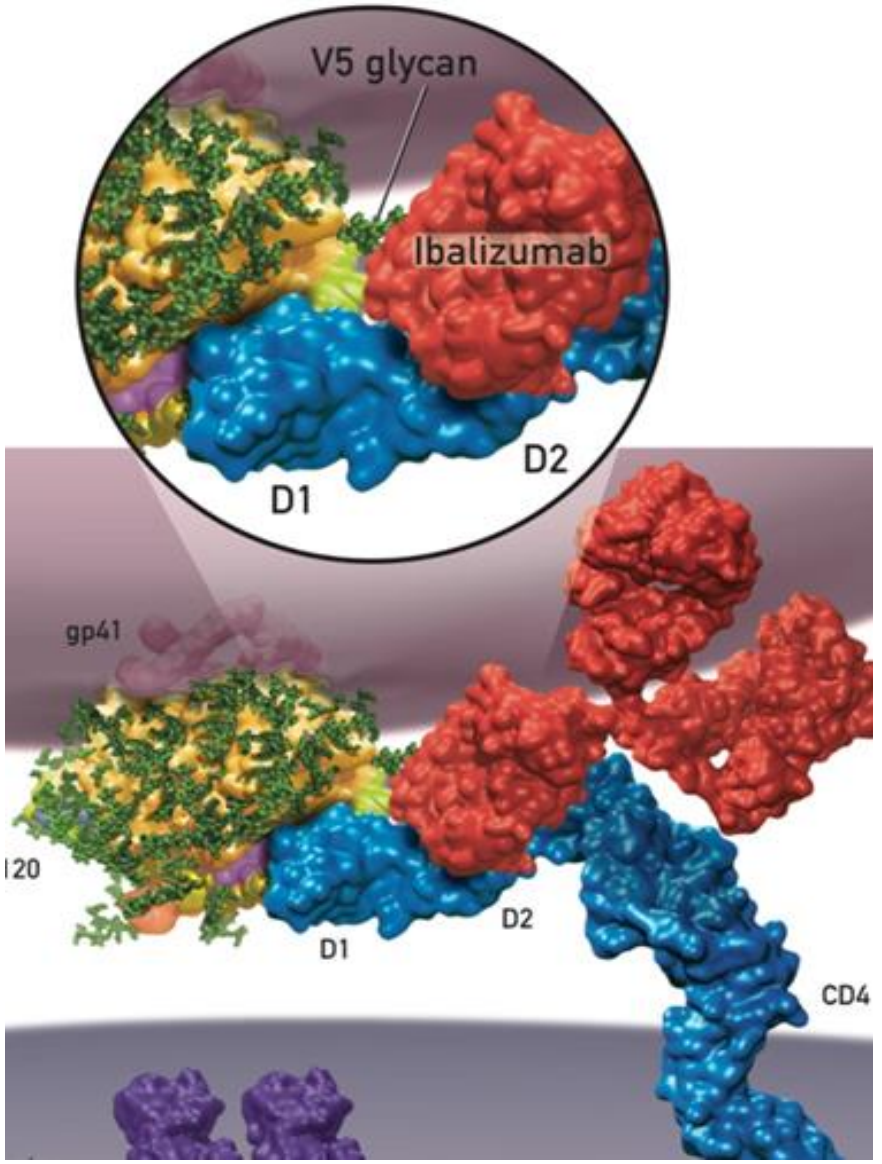
binds GP41

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]

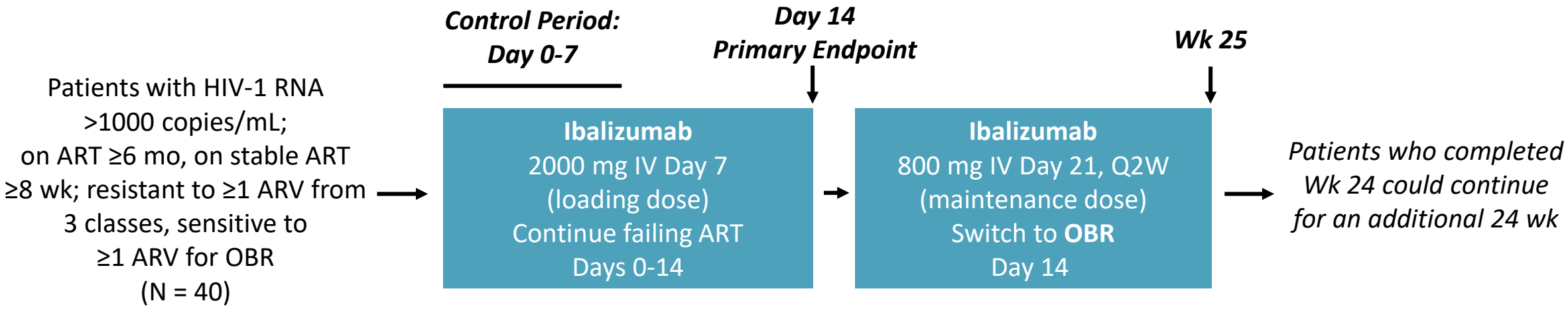
Decrease in susceptibility to ibalizumab has been associated to Loss of Potential N-linked Glycosylation Sites (=PNGS) in the V5 loop of HIV-1 gp120.[2,3]



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.

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

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

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 Wk

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 wk
  - 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.

Ibalizumab in Italy

- Approved by EMA on July 2019:

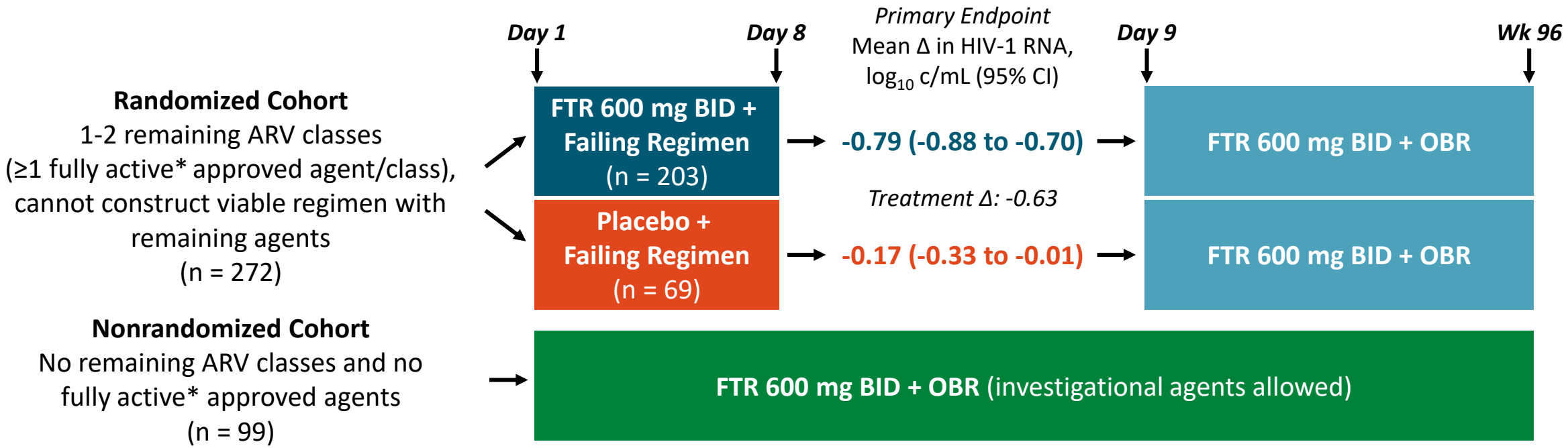
Trogarzo, in associazione a uno o ad altri antiretrovirali, è indicato per il trattamento di adulti con infezione da virus dell'immunodeficienza umana (HIV-1) resistente ai medicinali per i quali non sarebbe altrimenti possibile predisporre un regime antivirale soppressivo

Fostemsavir

- Temsavir—active metabolite of fostemsavir—binds to HIV-1 envelope glycoprotein 120 and prevents conformational changes needed for viral interaction with CD4, thereby blocking viral attachment and subsequent entry[1]
- Approved in combination with other ARVs for heavily treatment–experienced adults with multidrug-resistant HIV infection who are experiencing failure of current regimen due to resistance, intolerance, or safety considerations[2]
- IAS-USA: *"…fostemsavir can be used when creating a salvage regimen* ***for individuals with extremely limited treatment options"***[3]
- DHHS: *"Patients with* ***ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen*** *may be candidates for … the gp-120-directed attachment inhibitor FTR"*[4]

1. Kozal. NEJM. 2020;382:1232. 2. Fostemsavir PI. 3. Saag. JAMA. 2020;324:1651.
4. DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV.

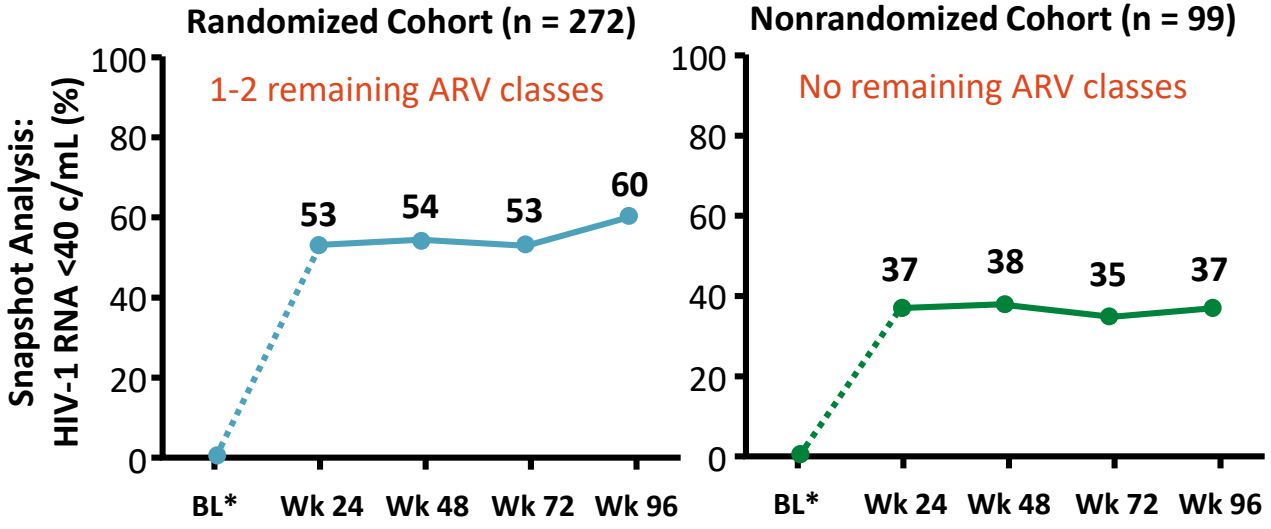
BRIGHTE: Fostemsavir in Heavily Treatment–Experienced Adults With Multidrug-Resistant HIV



*No evidence of resistance; patient eligible for, tolerant of, willing to receive the ARV.

Kozal. NEJM. 2020;382:1232. Pialoux. AIDS 2018. Abstr THPEB045.

BRIGHTE: Virologic and Safety Outcomes Through 96 Wk



Outcome at Wk 96, n (%)	Randomized (n = 272)	Nonrandomized (n = 99)
HIV-1 RNA <40 c/mL	163 (60)	37 (37)
HIV-1 RNA ≥40 c/mL	81 (30)	43 (43)
No virologic data	28 (10)	19 (19)
▪ D/c due to AE or death	15 (6)	14 (14)

*Snapshot analysis excluded BL data; 1 patient had BL HIV-1 RNA <40 c/mL.

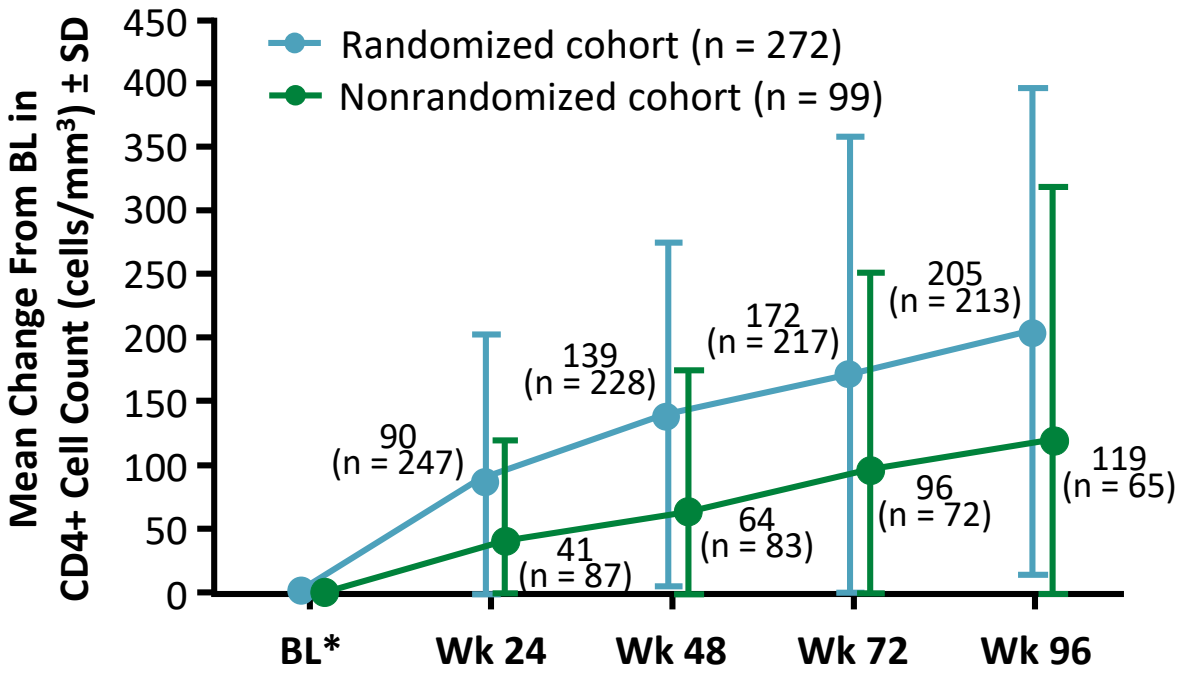
- Cumulative safety outcomes through Wk 96 for all treated patients
  - Drug-related AEs: grade 2-4, 21%; serious, 3%
  - AEs leading to d/c: 7%
  - Death: 8%; most due to AIDS-related events or acute infections, 1 deemed treatment-related (IRIS)

1. Lataillade. IAS 2019. Abstr MOAB0102. 2. Lataillade. Lancet HIV. 2020;7:e740

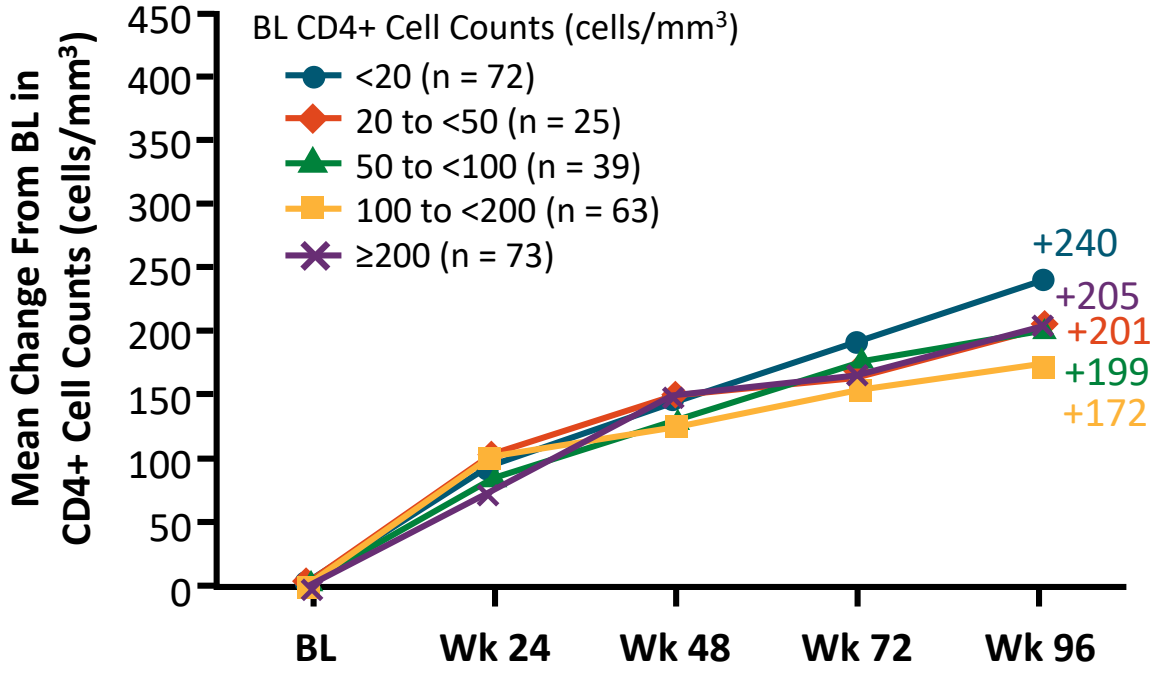
BRIGHTE: CD4+ Cell Counts Through Wk 96

- Among randomized patients with BL CD4+ cell count <50 cells/mm^3, 56% had a CD4+ cell count ≥200 cells/mm^3 at Wk 96

By Cohort



By BL CD4+ Cell Count (Randomized Cohort)

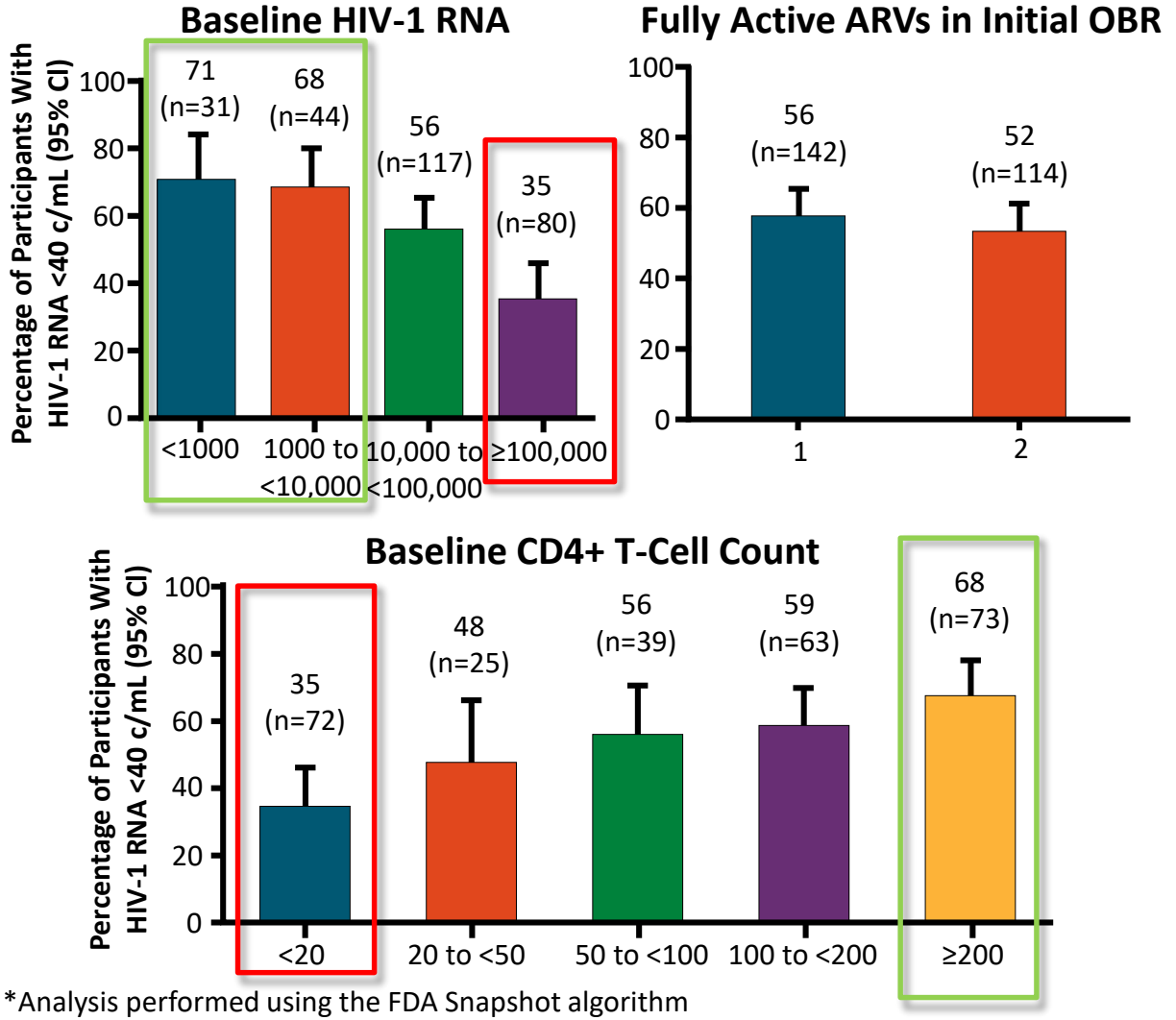


*BL mean CD4+ cell count, cells/mm^3: randomized cohort, 153; nonrandomized cohort, 99.

1. Lataillade. IAS 2019. Abstr MOAB0102. 2. Lataillade. Lancet HIV. 2020;7:e740

BRIGHTE: Subgroup Analysis of Fostemsavir Efficacy by Disease Characteristics at 48 Wk

- Randomized cohort (n = 272)[1,2]
- Similar efficacy with sex, age (older adults), geographic region or race
- Data suggest earlier use of FTV in salvage



*Analysis performed using the FDA Snapshot algorithm

1. Molina. HIV Glasgow 2018. Abstr O334B. 2. Kozal. NEJM. 2020;382:1232.

Challenges with Defining the HTE Population

- FDA defines HTE PLWH as individuals with resistance to multiple drugs and drug classes and unable to construct a regimen that suppresses HIV-RNA to below assay quantification limits[1]

Literature
Triple-class virologic failure[2,3]
Patients with MDR virus after failure of an INSTI-based regimen[4]
≤2 available classes with limited number of active drugs in each class[5]
Have ≤ 2 fully active ARVs remaining from the 4 main classes that can be effectively combined to form a viable regimen[6]

Treatment Guidelines
DHHS: multiple or extensive drug resistance with few treatment options
EACS: limited options
IAS-USA: triple-class resistance

FDA Product Labels
MDR HIV-1 infection failing their current antiretroviral regimen +/-due to resistance, intolerance, or safety considerations[7,8]

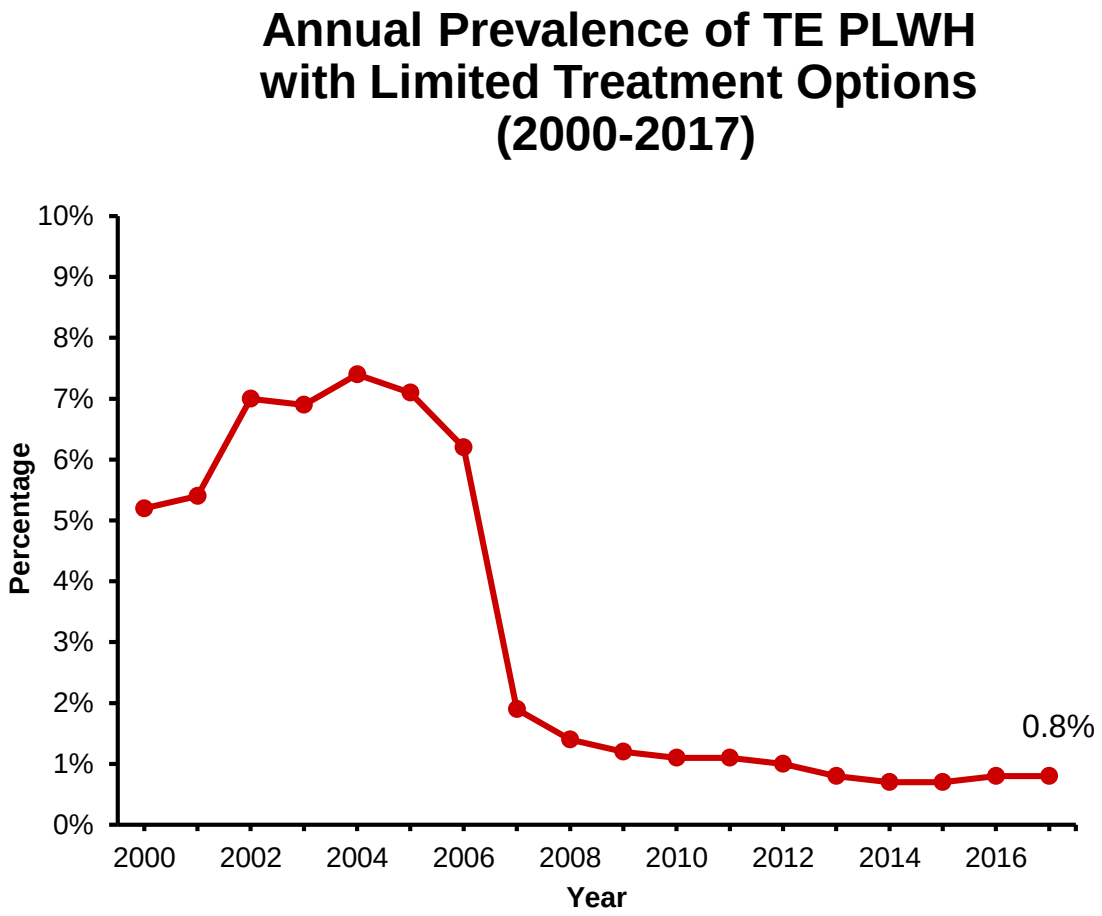
EMA Product Labels
Treatment of adults with MDR HIV-1 infection, for whom it is otherwise not possible to construct a suppressive antiviral regimen[9,10]

HTE, heavily treatment-experienced; MDR, Multi-drug resistant

1.Guidance for Industry: HIV-1 Infection: Developing ARV Drugs for Treatment. US DHHS, FDA, CDER. Revision 1. November 2015 2.Costagliola D et al. Lancet Infec Dis 2012;12:119-127
3.Lohse N et al.. AIDS 2005;19:815-822
4. Santoro M et al. IJAA 2020;56(1):106027
5. Bajema. K et al. AIDS 2020;34:2051-59
6. Segal-Maurer S, et al. vCROI 2021. Oral #127
7. VIIV Healthcare, Inc. Rukobia US Prescribing Information. July 2020
8.Theratechnologies. Trogarzo US Prescribing Information. April 2020.
9. VIIV Healthcare, Inc. Rukobia. SmPC. Feb 2021.
10. Theratechnologies. Trogarzo SmPC. March 2018

Prevalence of HTE PLWH in the United States

- HTE with limited treatment options (LTO) defined as:
  - ≤ 1 ARV class available
  - Only two active ARV classes available in which there are a limited number of active drugs
    - NRTIs and PIs are considered limited if there are ≤ 2 active drugs
    - NNRTIs and INSTIs are considered limited if there are ≤1 active drug
- Overall prevalence rate of HTE individuals has decreased due to availability of improved antiretroviral regimens

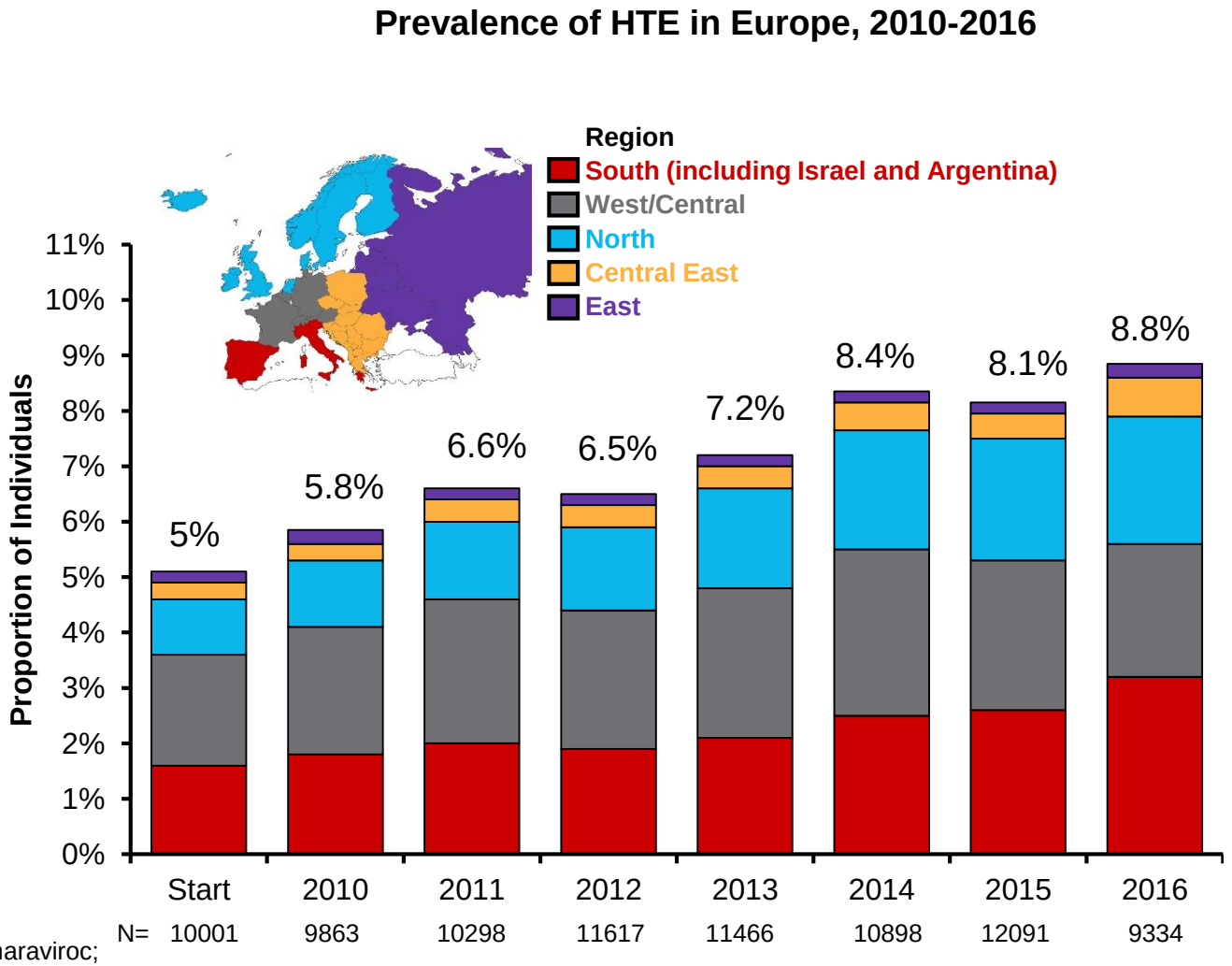


CFAR, Center for AIDS Research; HTE, heavily treatment-experienced; TE, Treatment experienced
*Data is from 7 CFAR Network of Integrated Clinical Systems (CNICS)

Bajema K, et al. AIDS 2020;34:2051-59

Prevalence of HTE PLWH in Europe

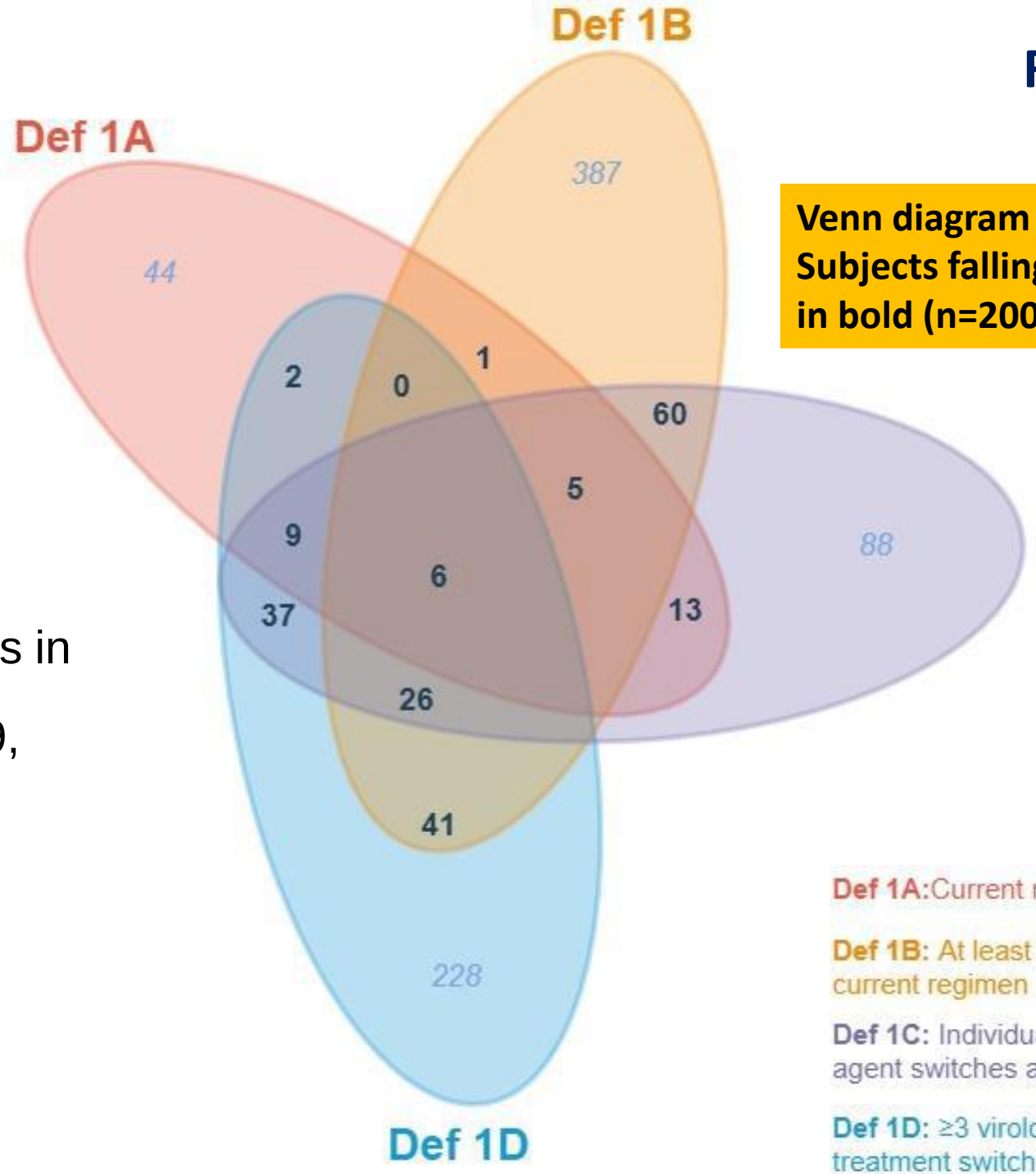
- HTE composite definition includes resistance to NRTIs, NNRTIs, and PIs or they met at least two of the following:
  - *Definition 1*: ≤ 2 drug classes available
  - *Definition 2*: ≥ 4 anchor agent switches and the 4th anchor agent was ENF, DRV, ETR, MVC, TPV, DTG or RAL
  - *Definition 3*: use of ≥ 4 of the following ARVs (DTG, DRV, ETR, RAL) together with a PI, MVC or ENF
- HTE 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.

Results



Venn diagram of the 4 used definition for HTE. Subjects falling within at least 2 of the definitions are in bold (n=200)

Prevalence 1,5%

- 13,285 subjects in care between 2009 and 2019,

Def 1A: Current regimen indicative of HTE

Def 1B: At least 3 core ARV classes prior to current regimen

Def 1C: Individuals who had at least 4 anchor agent switches at any previous time

Def 1D: ≥3 virologic failure followed by treatment switch

Conceived by Professor Mauro Moroni
Fondazione Icona

HTE Studies: Design

	CAPELLA (Lenacapavir)[1]	BRIGHTE (Fostemsavir)[2]	TMB-301 (Ibalizumab)[3]
Administration	SC every 6 months	Oral tablets twice daily	IV every 2 weeks
Trial inclusion criteria	• ≥ 12 yrs; ≥ 35 kg • HIV-1 RNA > 400 copies/mL • Resistance to ≥ 2 ARVs from each of ≥ 3 of 4 main ARV classes • ≤ 2 fully active ARV options remaining	• ≥ 18 yrs • HIV-1 RNA ≥ 400 copies/mL • ≤ 2 classes of ARV medications remaining at baseline due to resistance, intolerability, contraindication, or other safety considerations.	• ≥ 18 yrs • HIV-1 RNA > 1,000 copies/mL • Resistance to ≥ 1 ARV from each of 3 classes of ARV medications (NRTI, NNRTI, and PI)
Study design	• Placebo controlled study • 2 cohorts • Screening period • Randomized <0.5 log VL decline • Non-randomized ≥0.5 log VL decline	• Placebo controlled study • 2 cohorts • Randomized 1 or 2 fully active ARV options • Non-randomized 0 fully active ARV option	• Single arm (no placebo group) • 1 cohort • Control period for 7 days
Primary endpoint	Day 14: Proportion achieving ≥ 0.5 log_{10} c/ml reduction from BL in VL by end of monotherapy	Day 8: VL log_{10} change from day 1 to day 8	Day 14 (control period + 7 days of IBA): Proportion of patients who had a VL decrease of at least 0.5 log_{10} c/ml from baseline

1. Internal data. Oral #OALX01LB02 2. Kozal. M et al. NEJM 2020;382:1232-43 3. Emu. B et al. NEJM 2018;379:645-54

HTE Studies: Baseline Characteristics

	CAPELLA (Lenacapavir)[1]		BRIGHTE (Fostemsavir)[2]		TMB-301 (Ibalizumab)[3]
	Randomized n=36	Non-randomized n=36	Randomized n=272	Non-randomized n=99	Single cohort n=40
Age, years (median)	54	49	48	50	53
Female sex at birth	28%	22%	26%	10%	15%
Race (Black)	46%	31%	22%	23%	33%
VL log_{10} c/ml (median)	4.5	4.5	4.7	4.3	4.6
VL of >100,000 c/ml	19.4%	9.4%	29%	15%	18%
CD4 cells/µL (median)	127	195	99	41	73
<50	19%	25%	35%	54%	43%
≥50 -200	56%	28%	37%	25%	25%
≥200	25%	47%	27%	20%	33%

1. Internal data 2. Kozal. M et al. NEJM 2020;382:1232-43 3. Emu. B et al. NEJM 2018;379:645-54

‡

HTE Studies: Results

	CAPELLA (Lenacapavir)[1]	BRIGHTE (Fostemsavir)[2]	TMB-301 (Ibalizumab)[3]
> 0.5 log_{10} decline in HIV RNA during monotherapy	LEN 88% *vs* placebo 17%	FTR 68% *vs* placebo 19%	IBA 83% *vs* control 3%
Mean reduction in HIV RNA level during monotherapy	LEN vs Placebo 1.93 *vs* 0.29 log_{10} c/ml	FTR vs Placebo 0.79 ± 0.5 *vs* 0.17 ± 0.08 log_{10} c/ml	IBA vs Control 1.1 *vs* 0 log_{10} c/ml
Virologic suppression	81% of subjects achieved virologic suppression at week 26 (<50 copies/mL)	53% of subjects achieved virologic suppression at week 24 (<40 copies/mL)	43% of the subjects achieved virologic suppression at week 25 (<50 copies/mL)
Resistance	4/36 (11%) developed LEN resistance in randomized cohort	69/272 (25%) developed FTR resistance in randomized cohort	10/40 (25%) participants developed resistance
Most common AE	ISR (46%), diarrhea (6%), nausea (6%), Headache (5%)	Diarrhea (2%), nausea (4%), HA (2%)	Diarrhea (20%), dizziness (13%), fatigue (13%), nausea (13%), rash (13%)
Discontinuation due to AE	No discontinuations due to AE as of July 2021	26 (7%)	5 (13%)

Differences in study designs, populations and outcomes should be considered when interpreting study results

ISR, injection site reactions

1. Internal data. Oral #OALX01LB02 2. Kozal. M et al. NEJM 2020;382:1232-43 3. Emu. B et al. NEJM 2018;379:645-54

Heavily Treatment–Experienced People With HIV: 2 Primary Populations

- **Older people** with HIV treated in the early yr of ART
- MDR HIV emerged as a result of **sequential, partially suppressive ARV regimens**
  - Mono/dual NRTI ART regimens (decades ago)
  - Failure of first-generation NNRTIs or unboosted first-generation PIs (yr ago)
  - Sequential functional monotherapy with new ARV drugs (yr ago) or more recent regimens based on EVG/COBI, RAL, RPV
  - Partial adherence to non-coformulated regimens

- **Younger people** with congenital HIV infection who are now adults

Common Background

- Initially treated with **less potent regimens** that had **low resistance barriers**
- **Adherence issues:** severe social problems, mental health issues, addictions
- **Complex cases:** usually with complicated lives

Weinstock. J Infect Dis. 2004;189:2174. Yazdanpanah. Clin Infect Dis. 2009;49:1441. Tassiopoulos. Clin Infect Dis. 2020;71:133.

Predictors of Virologic Failure in Individuals on ART

Patient Adherence Factors	HIV-Related Factors	ARV Regimen-Related Factors
Comorbidities (eg. substance abuse, mental health disorders)	Transmitted or acquired drug resistance	Suboptimal pharmacokinetics
Psychosocial factors (eg. unstable housing)	Prior treatment failure	Suboptimal virologic potency
Missed clinic appointments	Innate resistance to ARV drugs	Low genetic barrier to resistance
Interruption/intermittent access to ART	Higher pretreatment HIV RNA level	Prior suboptimal therapy (eg. monotherapy etc.)
Cost and affordability of ART		Food requirements
Adverse drug effects		Drug interactions
High pill burden/dosing frequency		Prescription errors

DHHS. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, 2021. Accessed June 2021.

Guideline Based Definitions and Management: HTE PLWH

EACS[1]	IAS-USA[2]
If limited options, consider experimental and new drugs, favoring clinical trials (but avoid functional monotherapy). New drugs with promising results include humanized CD4+-binding antibody ibalizumab and attachment inhibitor fostemsavir.	In the setting of **multiclass resistance (3-class resistance)**, the next regimen should be constructed using drugs from new classes if available (evidence rating: BIII); eg, fostemsavir (Alb) or ibalizumab (BII) with at least 1 additional active drug in an optimized ART regimen.

DHHS[3]

Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
Drug resistance **with fully active treatment** options	Use past and current genotypic +/- phenotypic resistance testing and ART history when designing new regimen.	• Two fully active agents, at least one of which has a high barrier to resistance; otherwise three fully active agents are preferred • Partially active drugs may be used when no other options are available. • Consider using an ARV drug with a different mechanism of action.	Resuppression
Multiple or extensive drug resistance **with few treatment** options	• Use past and current genotypic and phenotypic resistance testing to guide ART • Consider viral tropism assay when use of MVC is considered • Consult an expert in drug resistance, if needed.	• Identify as many active or partially active drugs as possible based on resistance test results. • Consider using an ARV drug with a different mechanism of action (ie. ibalizumab, fostemsavir). • Consider enrollment into clinical trials or expanded access programs for investigational agents, if available (ie. lenacapavir, leronimab, islatravir). • Discontinuation of ARV drugs **is not recommended.**	Resuppression, if possible; otherwise, keeping viral load as low as possible and CD4 count as high as possible.

1. EACS Guidelines version 10.1. October 2020. Accessed February 2021. 2. Saag MS, et al. JAMA . October 2020. Accessed February 2021
3. DHHS. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, 2021. Accessed June 2021.

How to Treat Multidrug Resistant HIV With LTO and Virologic Failure?

- **Construct an ART regimen with ≥2, preferably 3, active drugs or sum up equivalent with partially active drugs[1]**
  - Precise estimation of residual activity can be challenging (phenotype)
  - Choose best OBR (often among DRV/RTV BID + DTG BID + ETR BID ± TAF/FTC)
    - Avoid using a drug if full resistance: >60 points in HIVDB Stanford or history of treatment-limiting toxicity

- **Choose ≥1 active drug with new MoA and no cross resistance based on OBR:**
  - Ibalizumab: 800 mg IV every 14 days[2]
  - Fostemsavir: 600 mg BID PO[3]
  - Lenacapavir*: 600 mg PO Days 1 and 2, 300 mg Days 8, then 927 mg SC Day 15 and every 6 mo[4]
  - Islatravir,[5] bNAbs[6]: investigational
  - Do not forget[1]: enfuvirtide (if no previous failure) and maraviroc (CCR5 tropic)
- Limited information (usually) in salvage ART trials due to limited number of subjects and study design (ethics)

*Submitted for FDA approval June 28, 2021.

1. DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2. Ibalizumab PI. 3. Fostemsavir PI. 4. NCT04150068. 5. clinicalinfo.hiv.gov/en/drugs/islatravir/health-professional. 6. Hsu. Front Immuno. 2021;12:2771.