Terapia dei pazienti multifalliti

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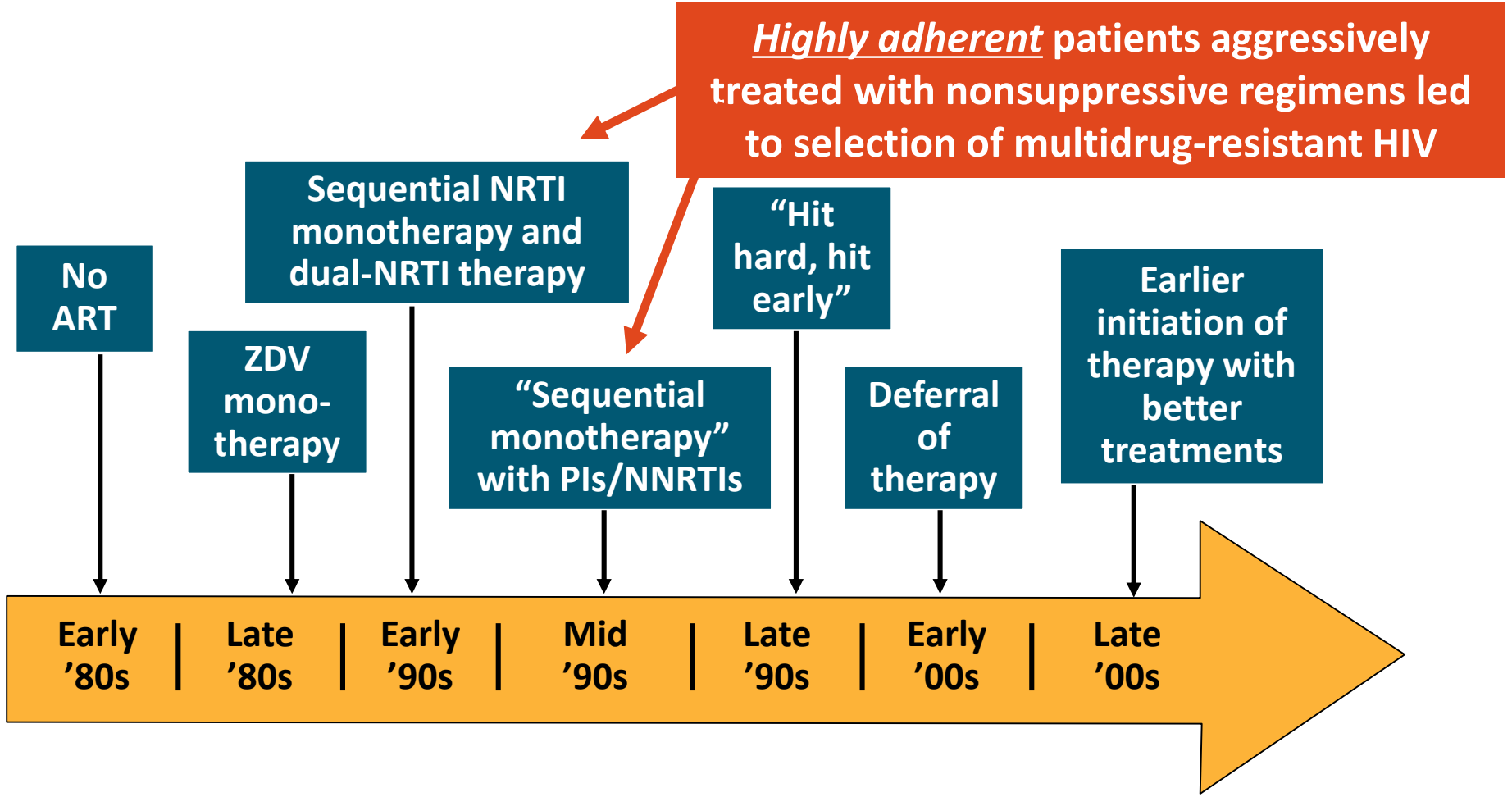
COIs

GSK, Gilead, Janssen-Cilag, MSD, ViiV Healthcare, Theratechnologies

MEDICI CON L'AFRICA CUAMM

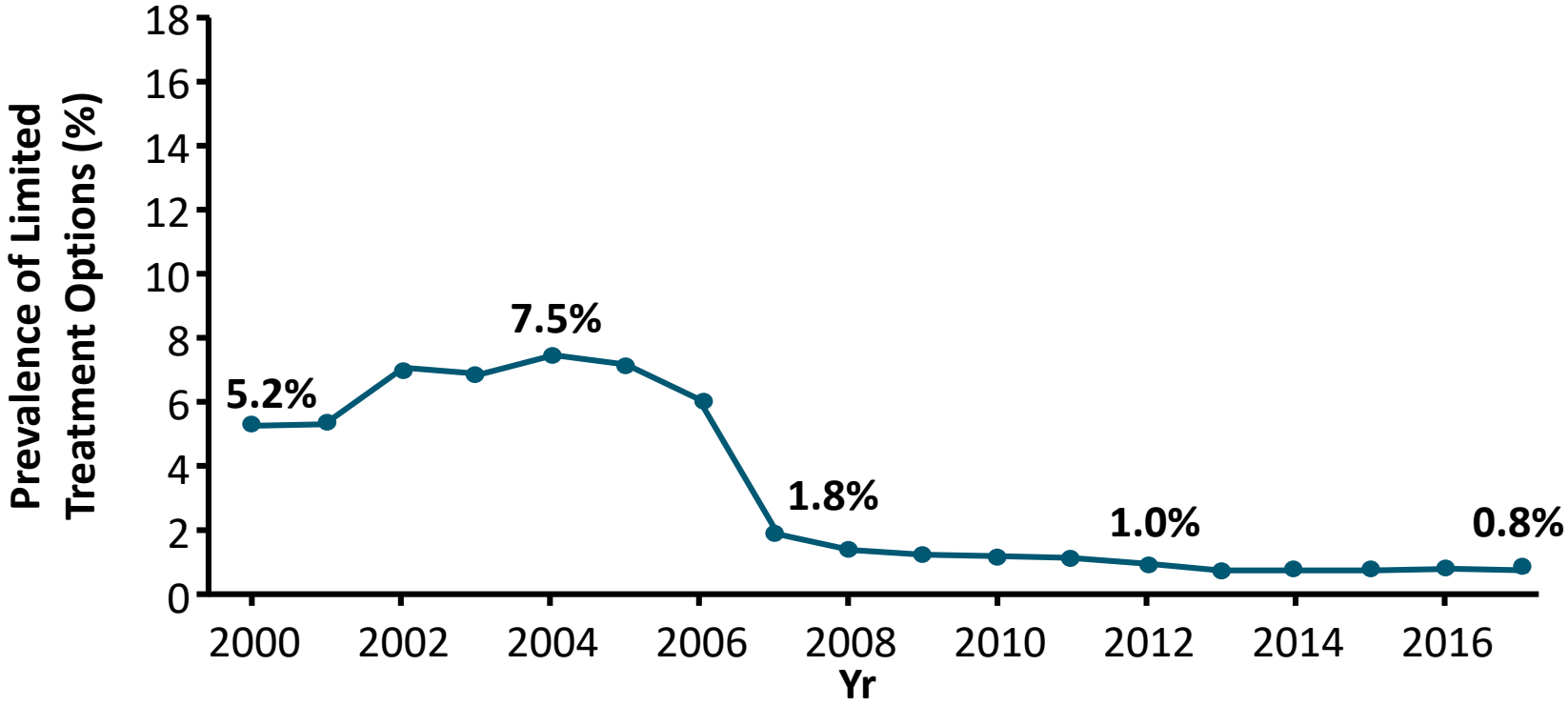
Who Are the People With Multidrug Resistant HIV?



Slide credit: clinicaloptions.com

Prevalence of Heavily Treatment–Experienced Patients With Multiclass Resistance/Limited Treatment Options

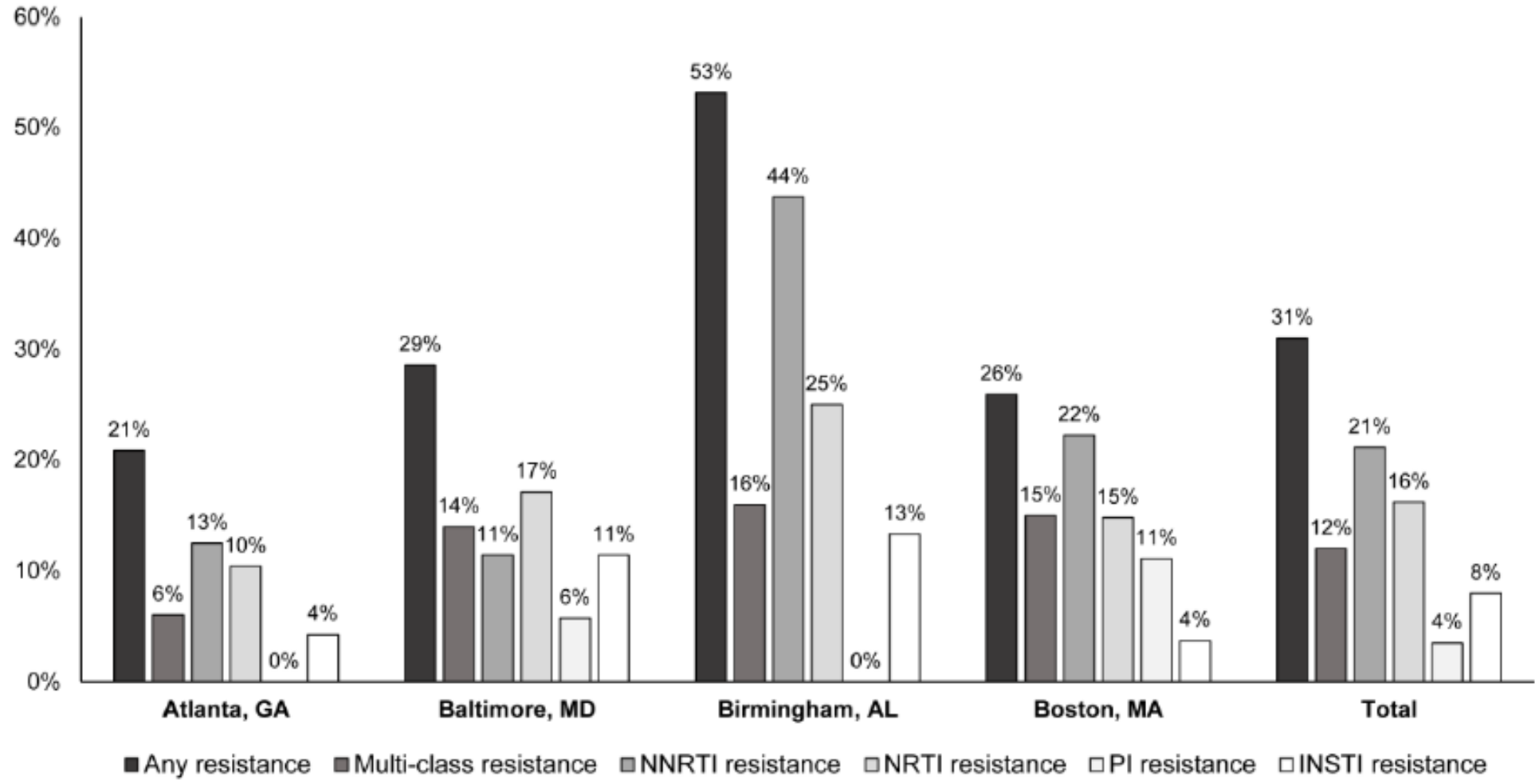
- CNICS cohort of > 26,000 ART-experienced people with HIV receiving care in the US
- Limited treatment options defined as ≤ 2 available classes with ≤ 2 active drugs per class by resistance testing



Bajema. AIDS. 2020;34:2051.

Slide credit: clinicaloptions.com

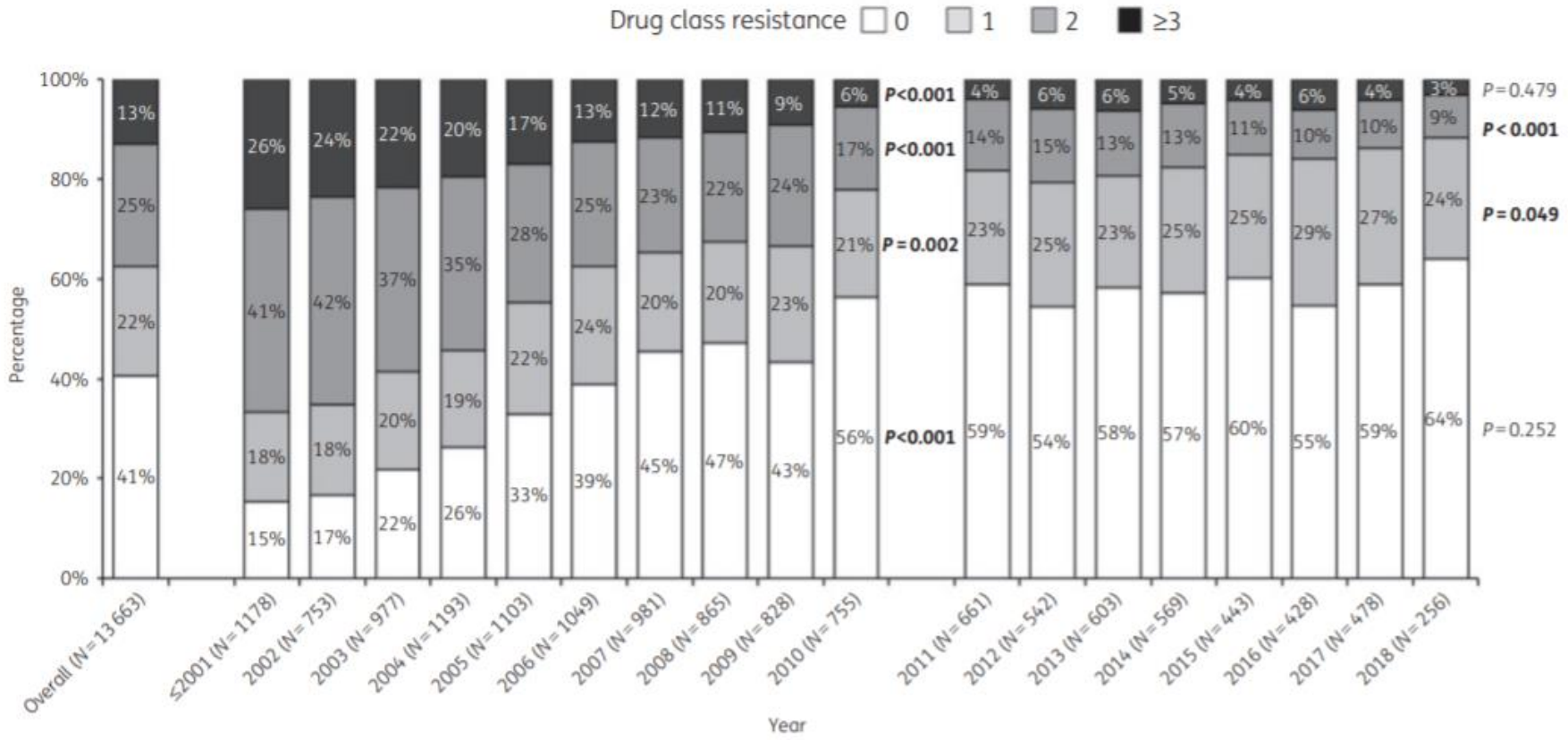
HIV drug resistance in a cohort of HIV-infected MSM in the United States



Jessica M. Fogel et al. AIDS 2020, 34:91–101

Heavily Treatment-Experienced (HTE) patients

HIV MDR is still a relevant issue despite its dramatic drop over the years

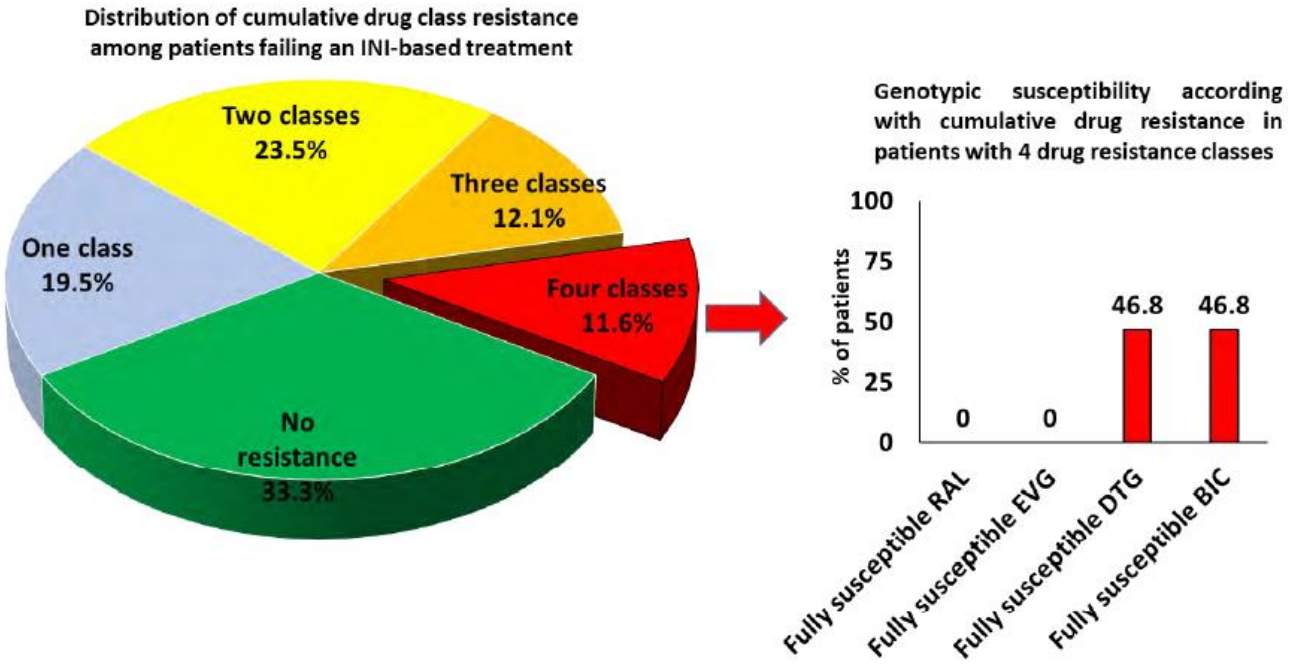


Armenia D, J Antimicrob Chemother 2020; 75: 1301–1310

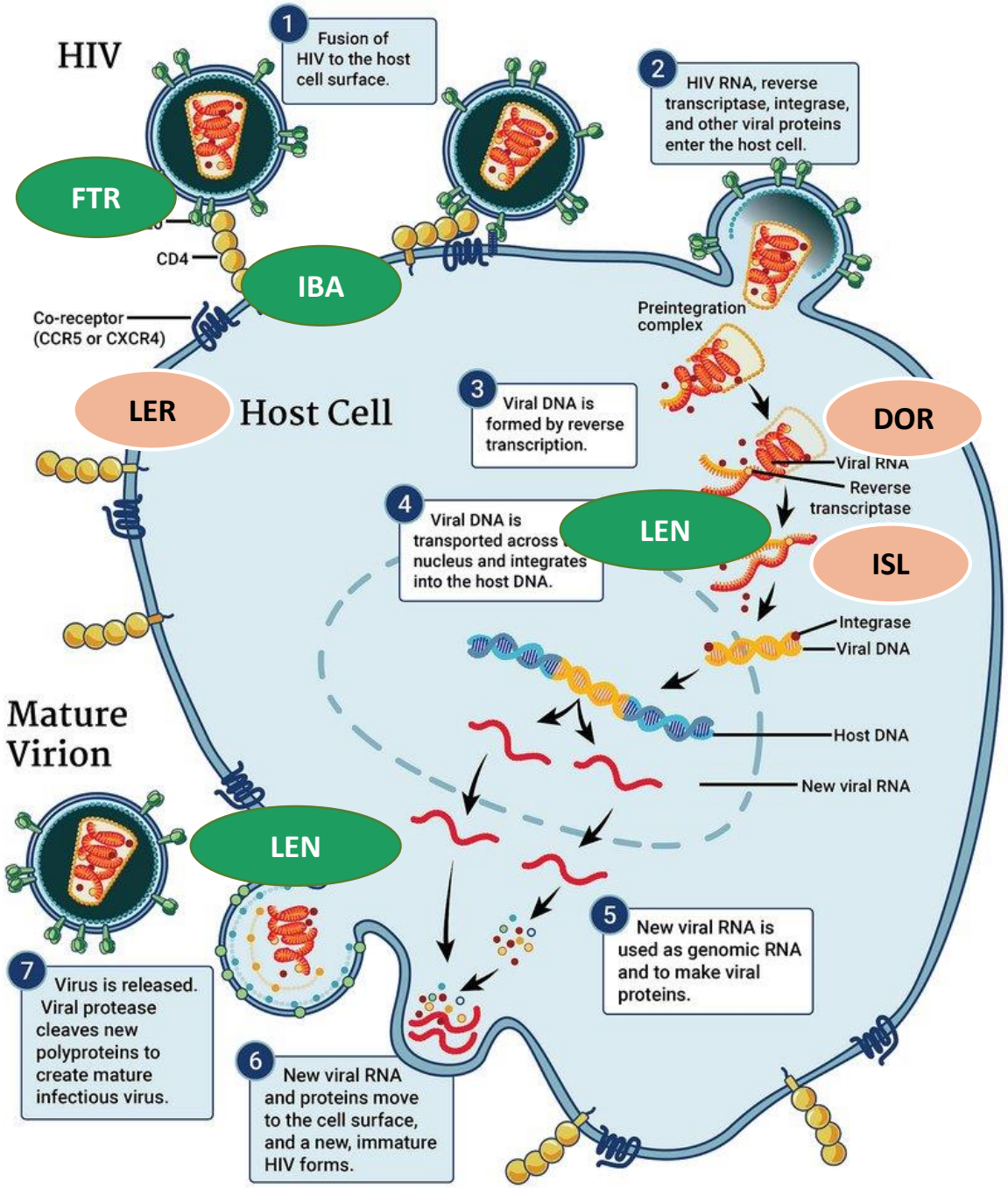
Heavily Treatment-Experienced (HTE) patients

INTEGRASE INHIBITOR RESISTANCE DYNAMICS FROM 2007 TO 2017 IN ITALIAN CLINICAL ISOLATES

Among 405 INI-failing patients, 47 (11.9%) patients showed cumulative four-drug class resistance. Of them, only 22 (46.8%) showed full GS to DTG or BIC.



Armenia D, CROI 2021, PO 535



HIV life cycle and upcoming drugs for MDR HIV

- Novel drugs
  - NNRTI: Doravirine* (DOR)
  - NRTI: Islatravir (ISL)
  - Anti-CCR5: Leronlimab (LER)
- Novel classes
  - Anti-CD4: Ibalizumab* (IBA)
  - Anti-gp120: Fostemsavir* (FTR)
  - Capsid inhibitors: Lenacapavir (LEN)

*FDA approved

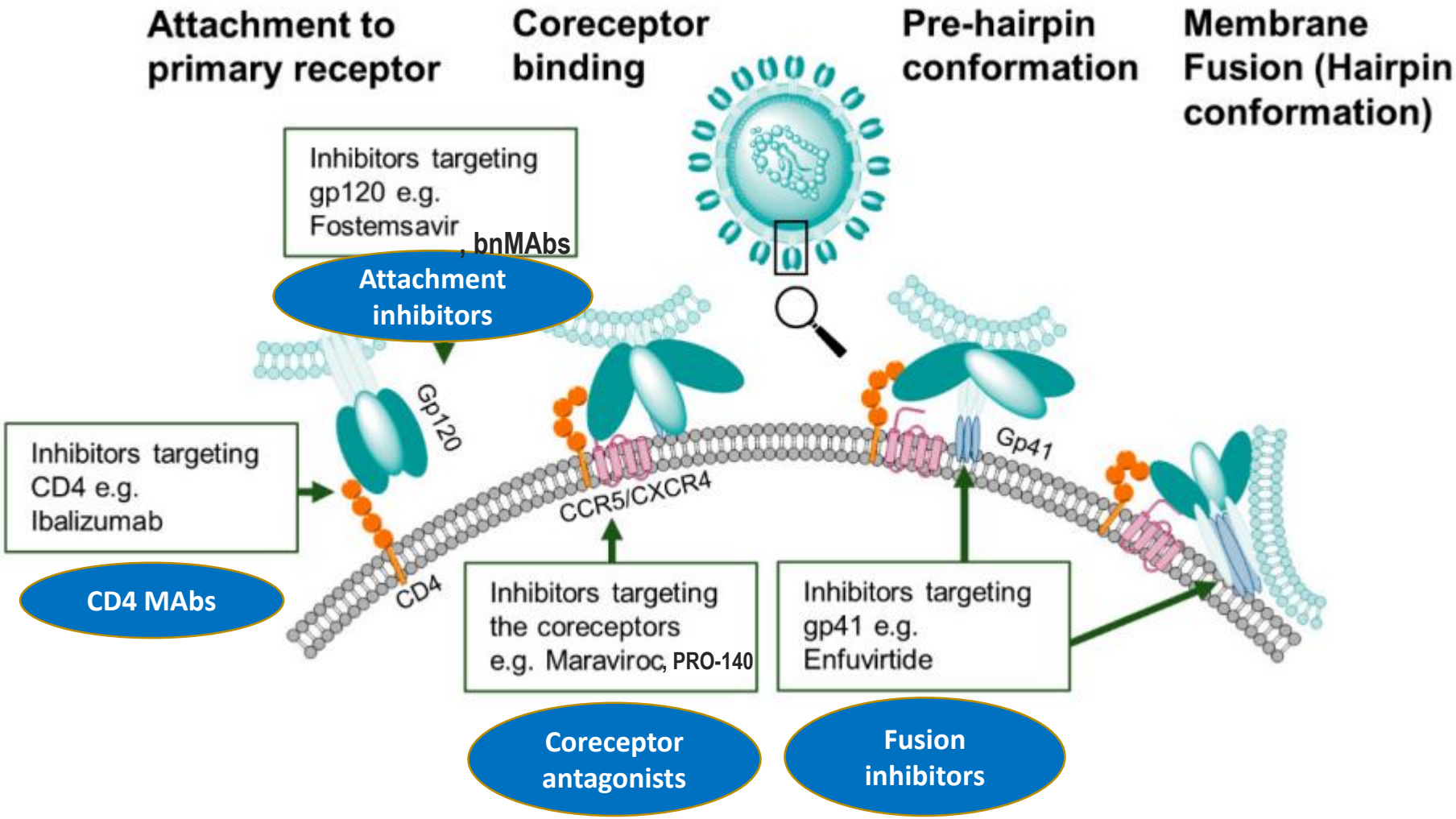
New options for MDR HIV
Genotypic interpretation

Drug	Target	Genotypic interpretation	Comments
Doravirine*	RT	Available	Role of minor RAMs possibly underestimated
Islatravir	RT	Not available	Signature RAMs and cross-resistance to be further defined
Leronlimab	CCR5 (host)	Available (geno2pheno)	Resistance through use of Leronlimab-bound CCR5, similar to MVC, not defined
Ibalizumab*	CD4 (host)	Not available	Most resistant strain occur through use of ibalizumab-bound CD4 following loss of N-glycosylation site(s) in gp120 V5 domain
Fostemsavir*	Gp120	Not available	Signature RAMs to be further defined, genotype and phenotype poorly predictive of treatment response
bnMAbs	Gp120	Not available	Resistance hardly predictable by genotype
Lenacapavir	Capsid	Not available	Signature RAMs to be further defined

Courtesy of M. Zazzi

*FDA approved

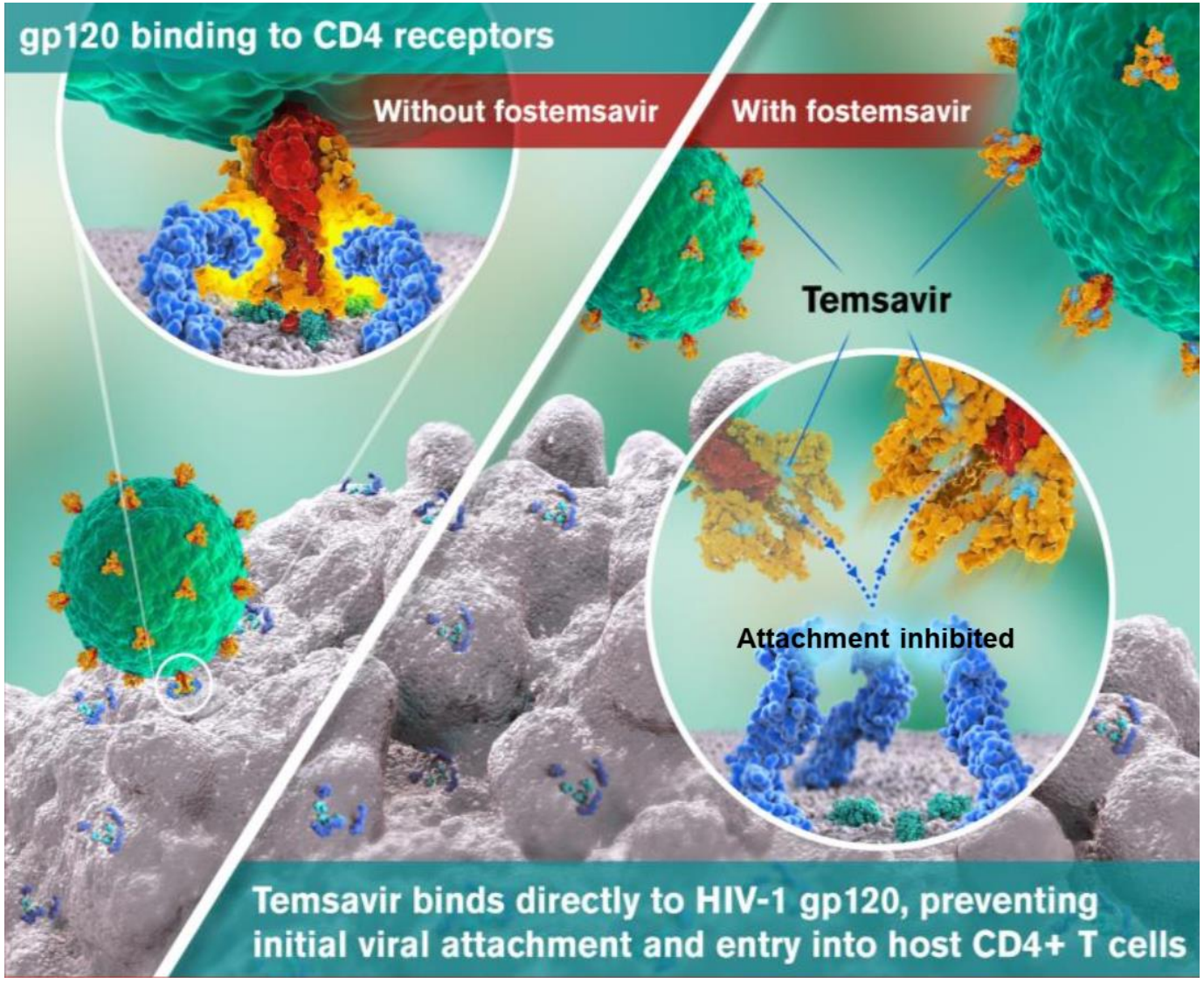
HIV entry steps and entry inhibitors



Bruxelle, Microorganisms 2021

New options for MDR HIV

Fostemsavir → targets HIV gp120



Susceptibility of global HIV-1 clinical isolates to fostemsavir using the PhenoSense Entry assay

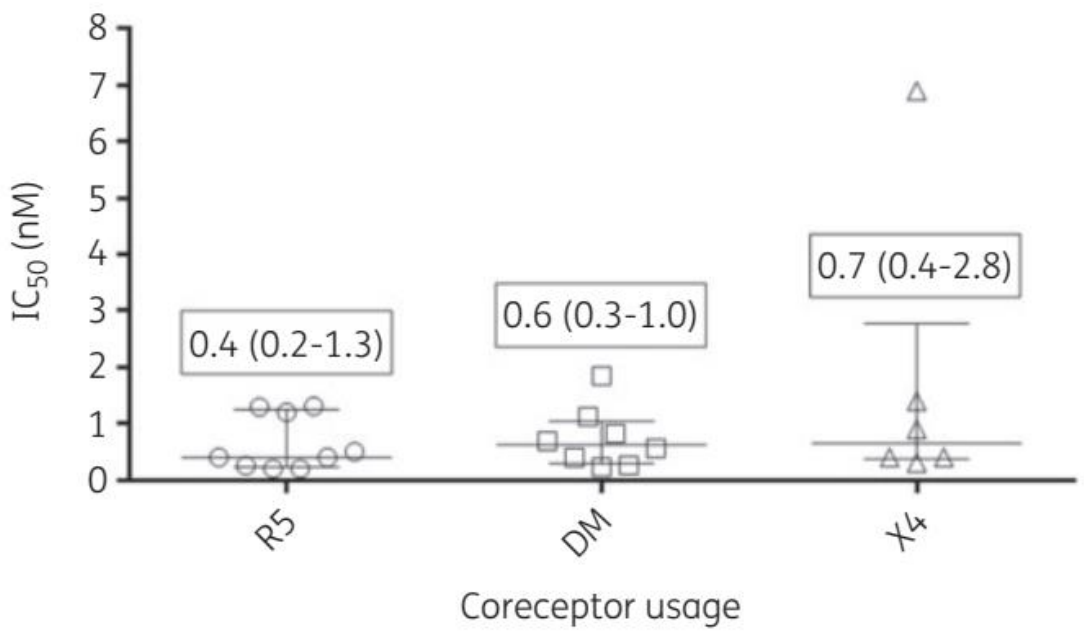
Subtype	#	IC_{50} <1 nM (%)	IC_{50} >1 to <10 nM (%)	IC_{50} >10 to <100 nM (%)	IC_{50} >100 nM (%)
All	1337	719 (53.8)	352 (26.3)	146 (10.9)	120 (9.0)
B	881	544 (61.7)	196 (22.2)	85 (9.6)	56 (6.4)
C	156	78 (50.0)	56 (35.9)	15 (9.6)	7 (4.5)
A1	17	5 (29.4)	11 (64.7)	0 (0)	1 (5.9)
A	43	10 (23.3)	21 (48.8)	8 (18.6)	4 (9.3)
BF	19	5 (26.3)	8 (42.1)	2 (10.5)	4 (21.1)
F1	48	8 (16.7)	15 (31.3)	13 (27.1)	12 (25.0)
B, F1	29	4 (13.8)	9 (31.0)	5 (17.2)	11 (37.9)
CRF01_AE	5	0 (0)	0 (0)	0 (0)	5 (100)

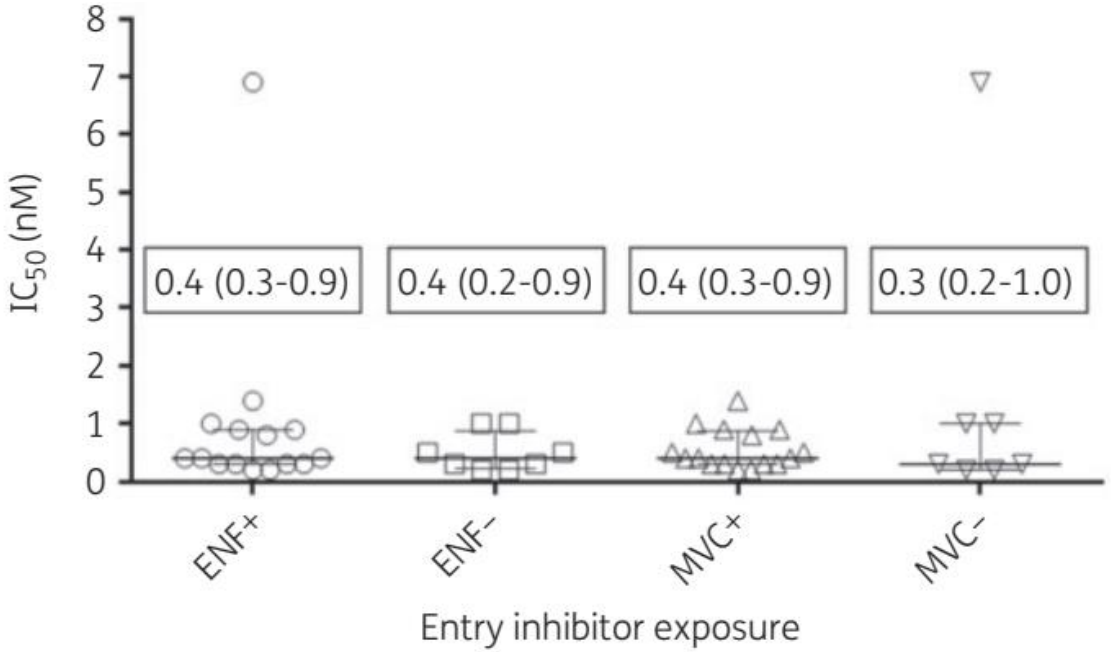
CRF01_AE is the least susceptible variant, however variable proportions of strains with reduced susceptibility may be present also within other subtypes or recombinants (mainly F-related)

Gartland, J Antimicrob Chemother 2020

Susceptibility to the novel attachment inhibitor Fostemsavir in patients harboring 4-class resistant HIV

Phenotypic analysis of 24 patients harboring MDR HIV from the PRESTIGIO registry





Susceptibility to Fostemsavir is comparable for viruses using different coreceptors

Susceptibility to Fostemsavir is not affected by past exposure to enfuvirtide or maraviroc

Saladini, J Antimicrob Chemother 2020

CCR5-Tropic MVC Resistance Was Not Predictive of Reduced Susceptibility to TMR in MOTIVATE-1 and -2

- No clinical samples from MOTIVATE were available, although gp120 sequences were accessible
- Sequences of envelopes from 5 participants who exhibited CCR5-tropic MVC resistance were used to regenerate functional envelopes
- All 5 exhibited resistance to MVC (and were CCR5-tropic), while 4/5 were fully susceptible to TMR
- The 1 envelope with reduced susceptibility to TMR contained an M426L polymorphism
- Site-directed mutagenesis reverting the virus back to M426 resulted in full sensitivity to TMR while MVC resistance remained

Envelope	TMR EC_{50} (nM)	MVC EC_{50} (nM)
MP5.7	1.00	>5000
MP35.2	1.00	>5000
MP49.20	1.56	>5000
MP53.36	0.51	>5000
MP11.38 (M426L)	412.7	>5000
MP11.38 (M426M; SDM)	0.98	>5000

EC_{50}, half-maximal effective concentration; SDM, site-directed mutagenesis.

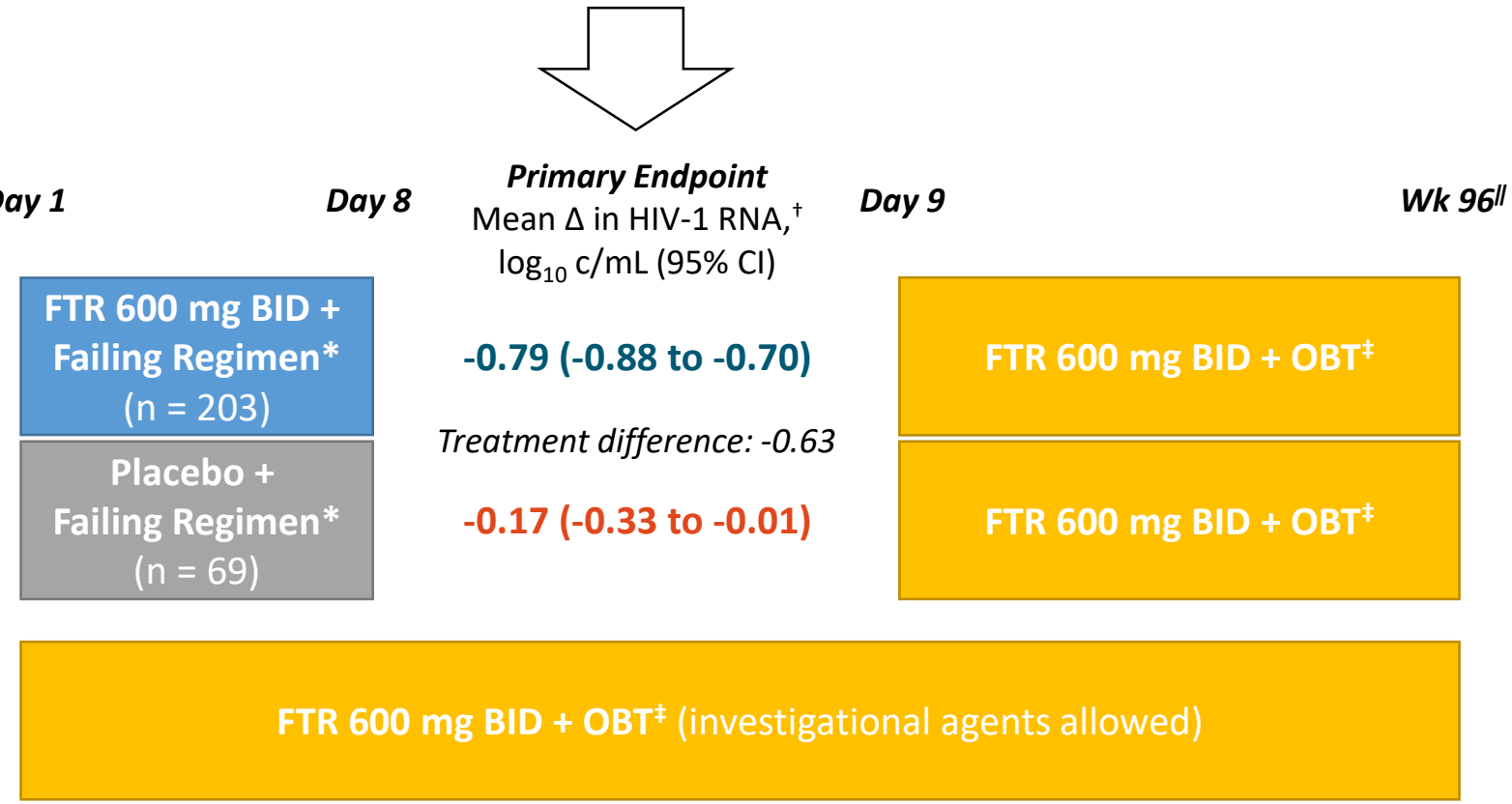
Rose, CROI 2021; AIDS 2022, 36:11-18

Fostemsavir in HTE individuals: the BRIGHTE study

Study design and primary endpoint

Randomized Cohort
1-2 remaining ARV classes
(≥ 1 fully active [§] approved agent/class), cannot construct viable regimen with remaining agents
(n = 272)

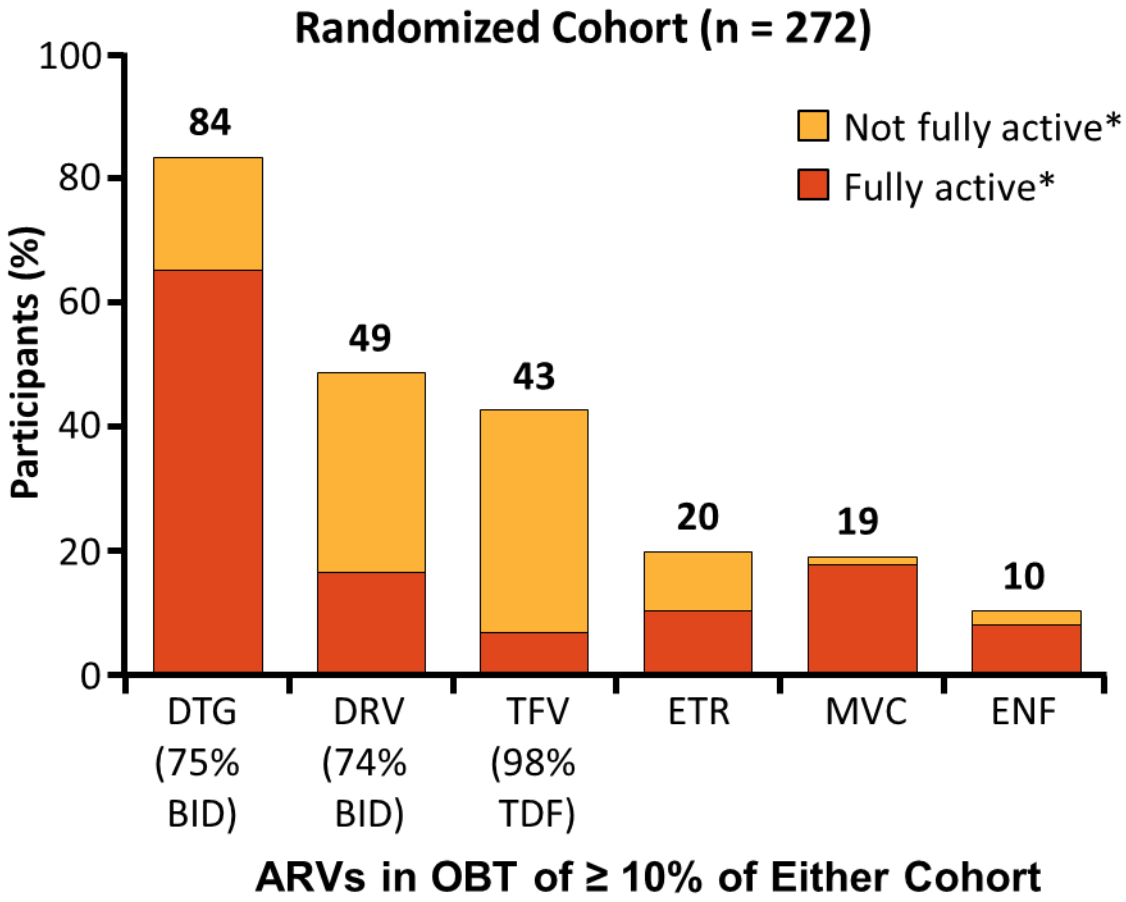
Nonrandomized Cohort
No remaining ARV classes and no fully active [§] approved agents
(n = 99)

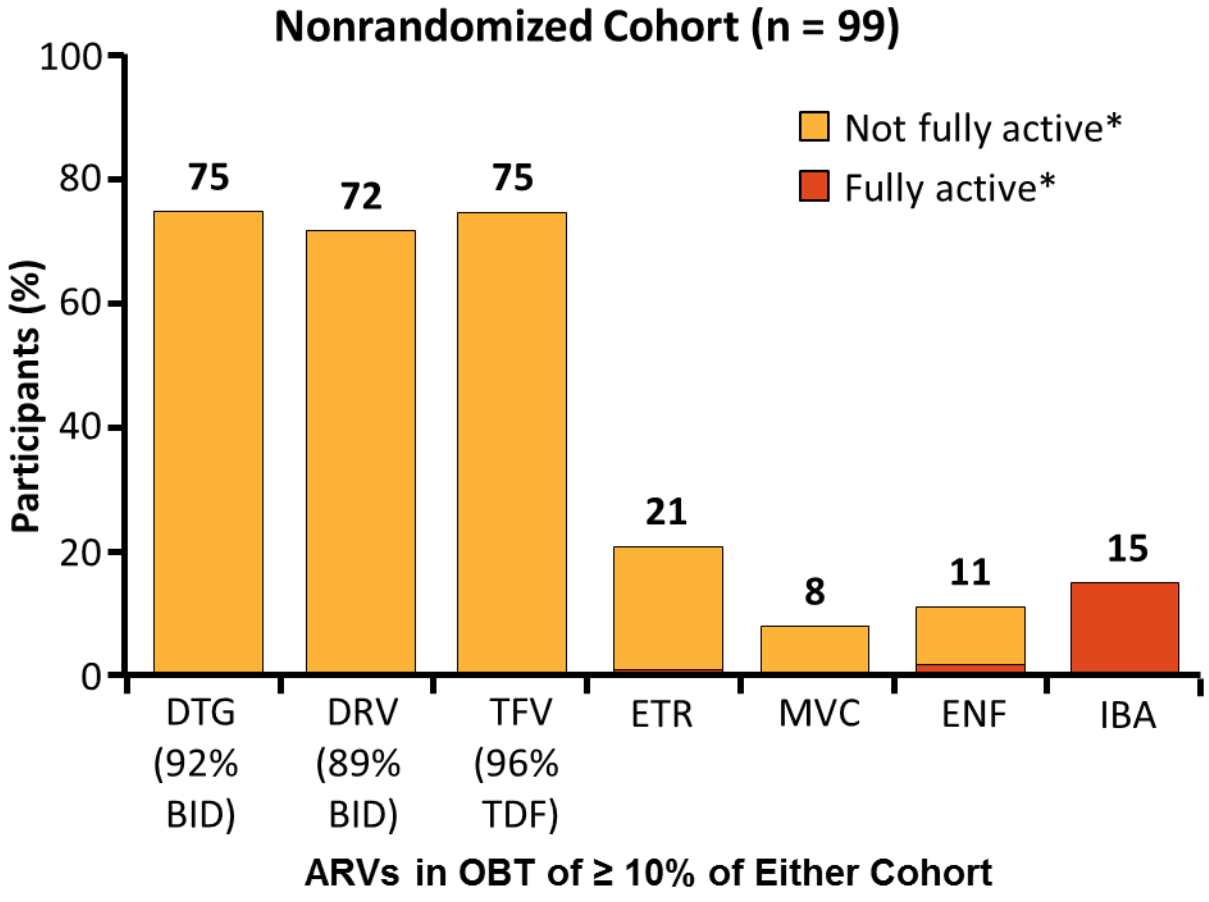


*Blinded. †Day 8 adjusted by Day 1. ‡Open label. § No evidence of resistance; patient eligible for, tolerant of, willing to receive the ARV. ‖Measured from start of open-label treatment. Study conducted until another option, rollover study, or approved ARV available.

Lataillade, IAS 2019

Fostemsavir in HTE individuals: the BRIGHTE study

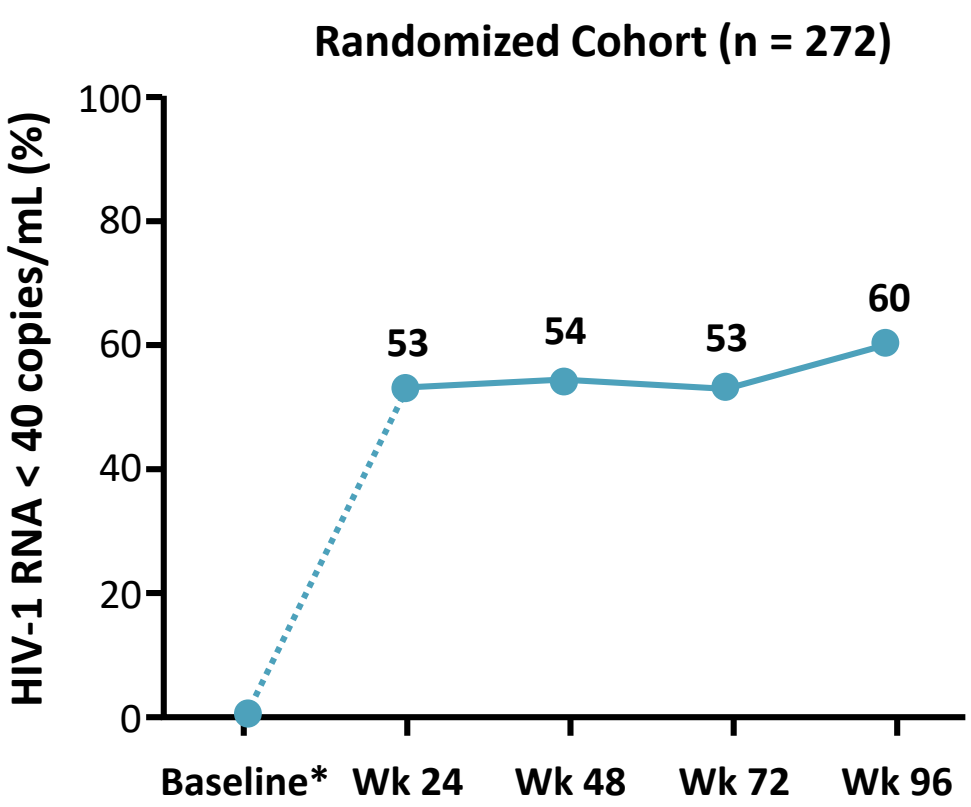


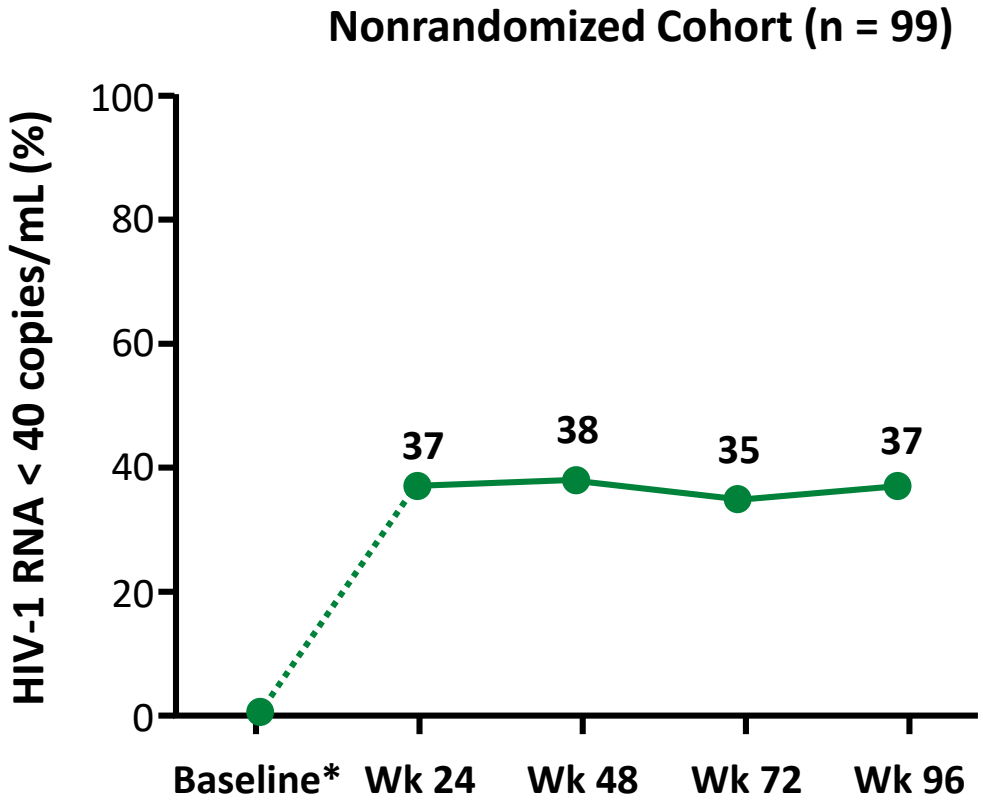


*Determined by commercial phenotype assays, historical resistance, eligibility, and tolerability.

Lataillade, IAS 2019

Fostemsavir in HTE individuals: the BRIGHTE study

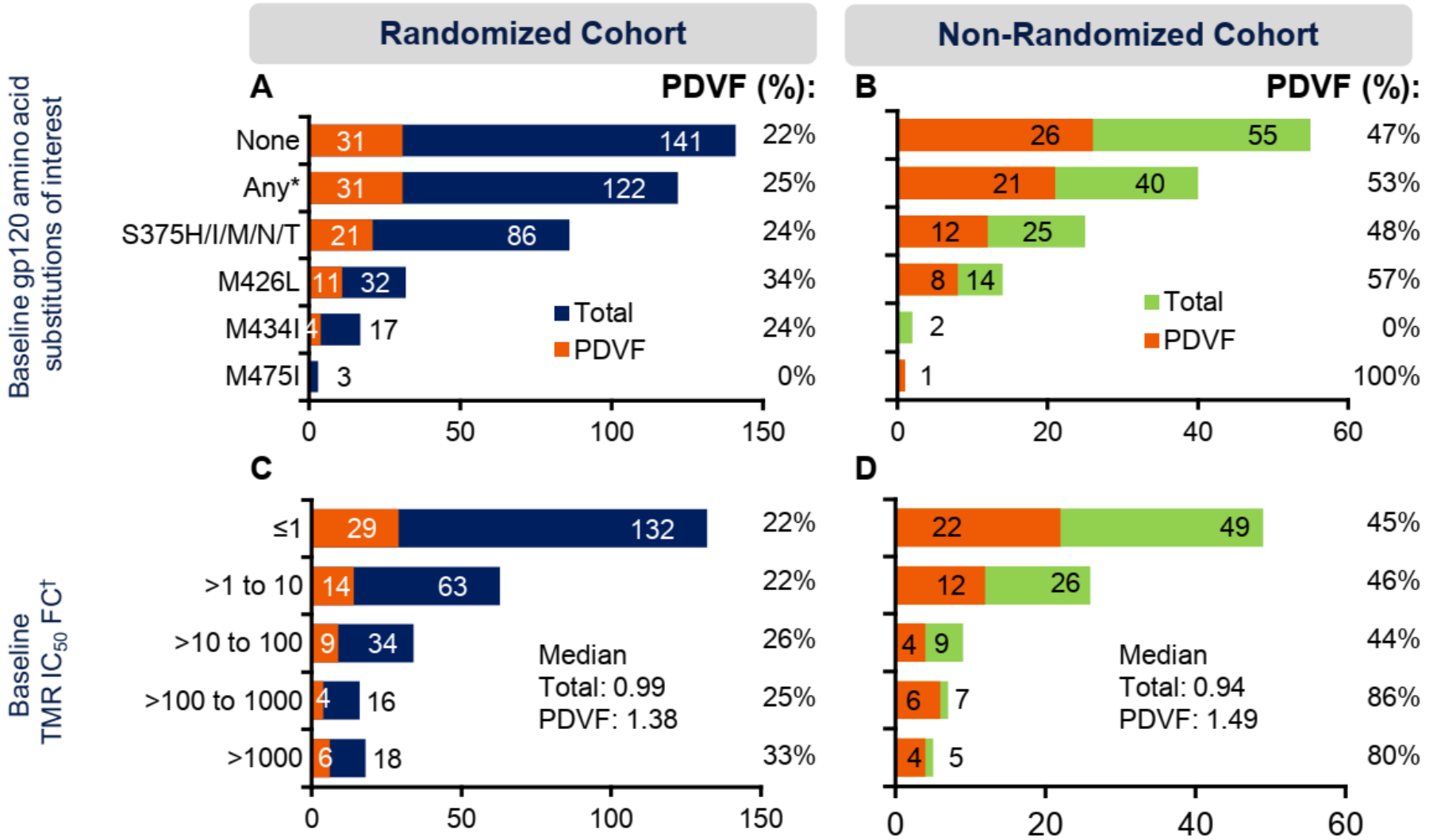




*Snapshot analysis excluded baseline data. 1 patient had BL HIV-1 RNA < 40 copies/mL.

Lataillade, IAS 2019

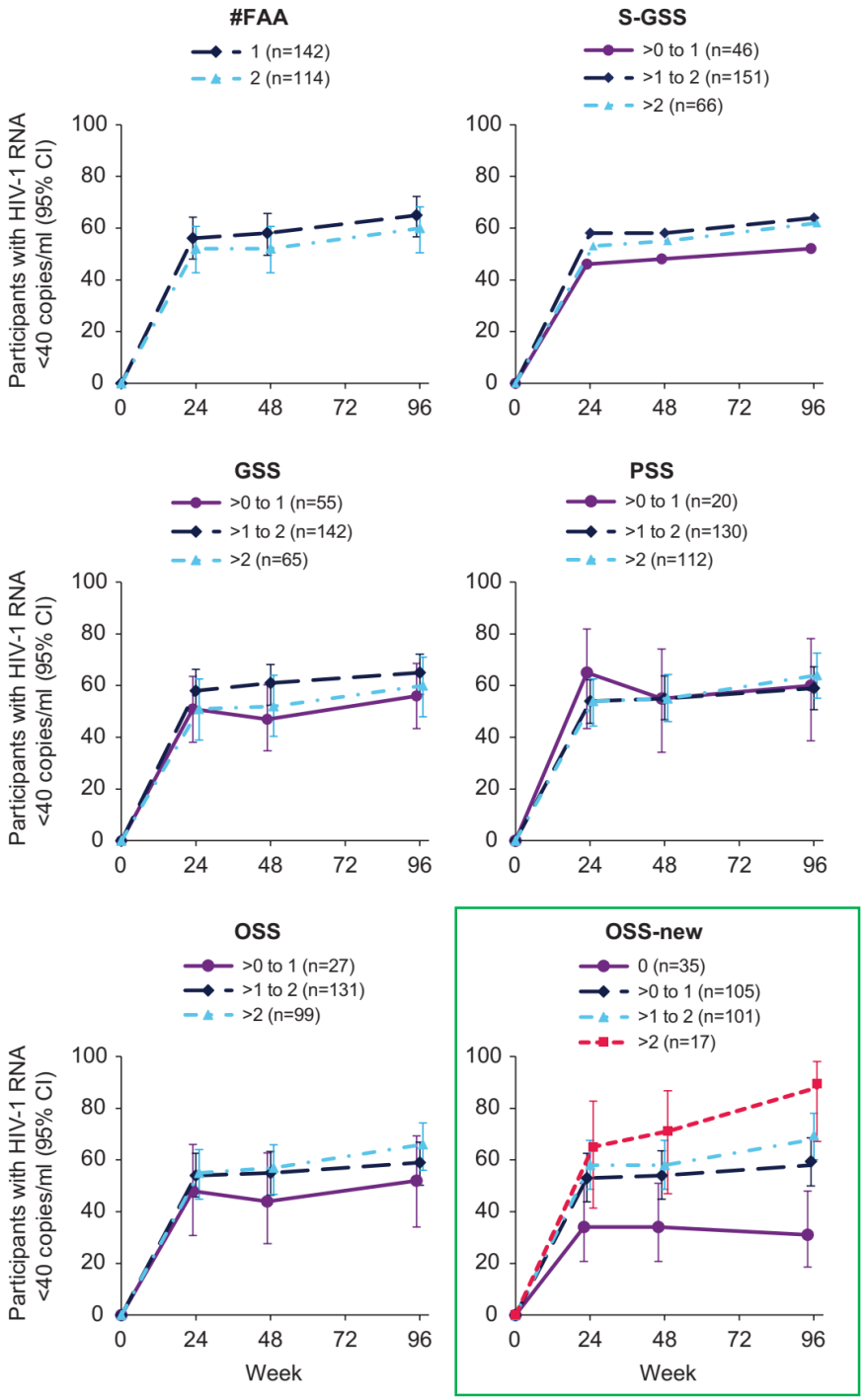
Fostemsavir in HTE individuals: the BRIGHTE study



PDVF Through Week 96 for Randomized and Non-Randomized Cohorts by **Baseline gp120 Substitutions of Interest** (A and B) and **TMR IC50 FC** (C and D)

- No correlation between baseline **genotypic** resistance and response
- Correlation between baseline **phenotypic** resistance (>100 FC IC50) and response limited to the non-randomized cohort

Ackerman, EACS 2019

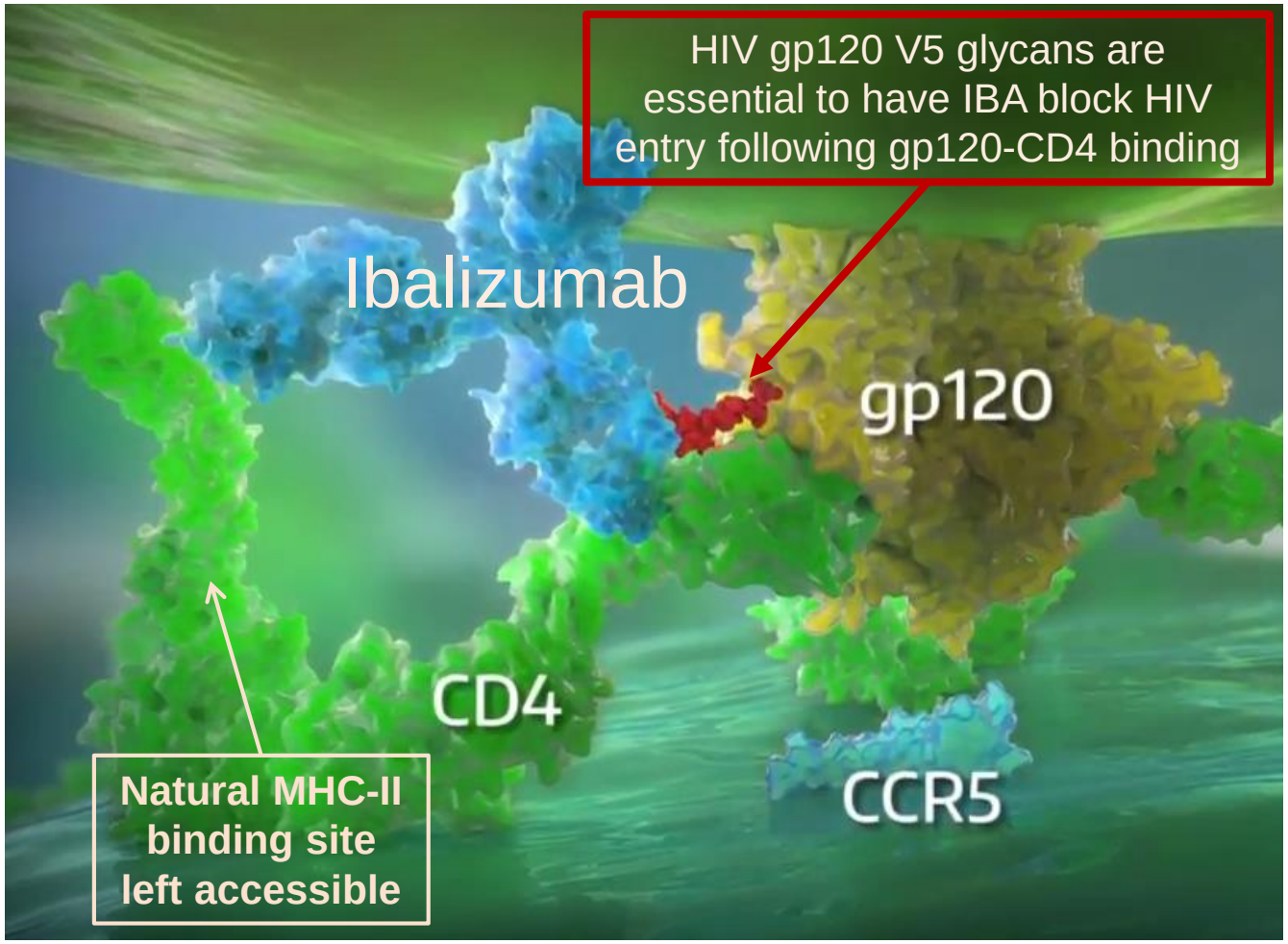


Fostemsavir in HTE individuals: the BRIGHTE study

- VL <40 cp/mL by initial optimized background susceptibility scores
  - **FAA**, fully active agents
  - **S-GSS**, Stanford HIVdb genotypic susceptibility
  - **GSS**, Monogram genotypic susceptibility
  - **PSS**, Monogram phenotypic susceptibility
  - **OSS**, overall susceptibility (combined GSS & PSS)
  - **OSS-new**, OSS only for newly used drugs

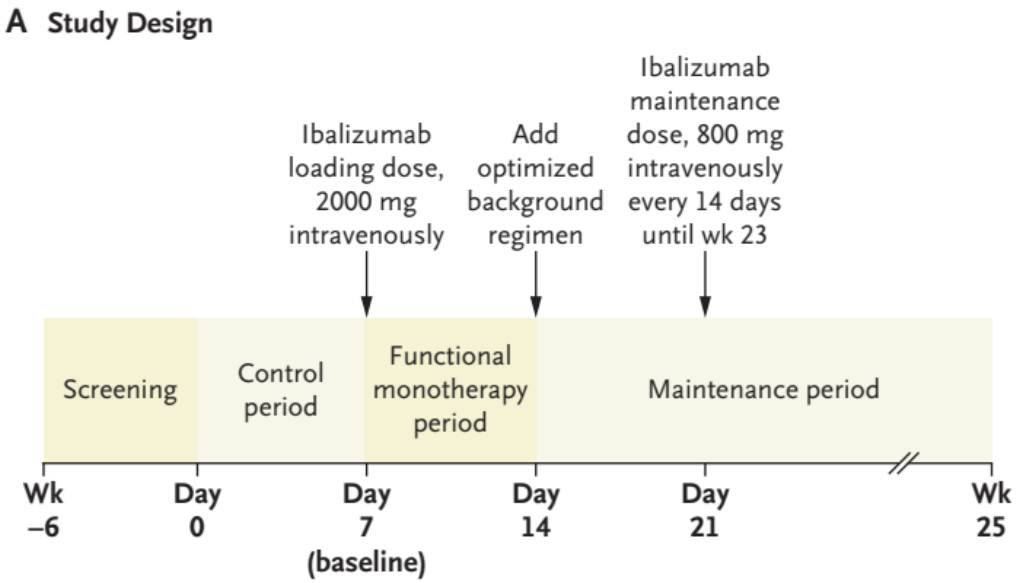
Ackerman, AIDS 2021

New options for MDR HIV
Ibalizumab → targets CD4



New options for MDR HIV
Ibalizumab → targets CD4

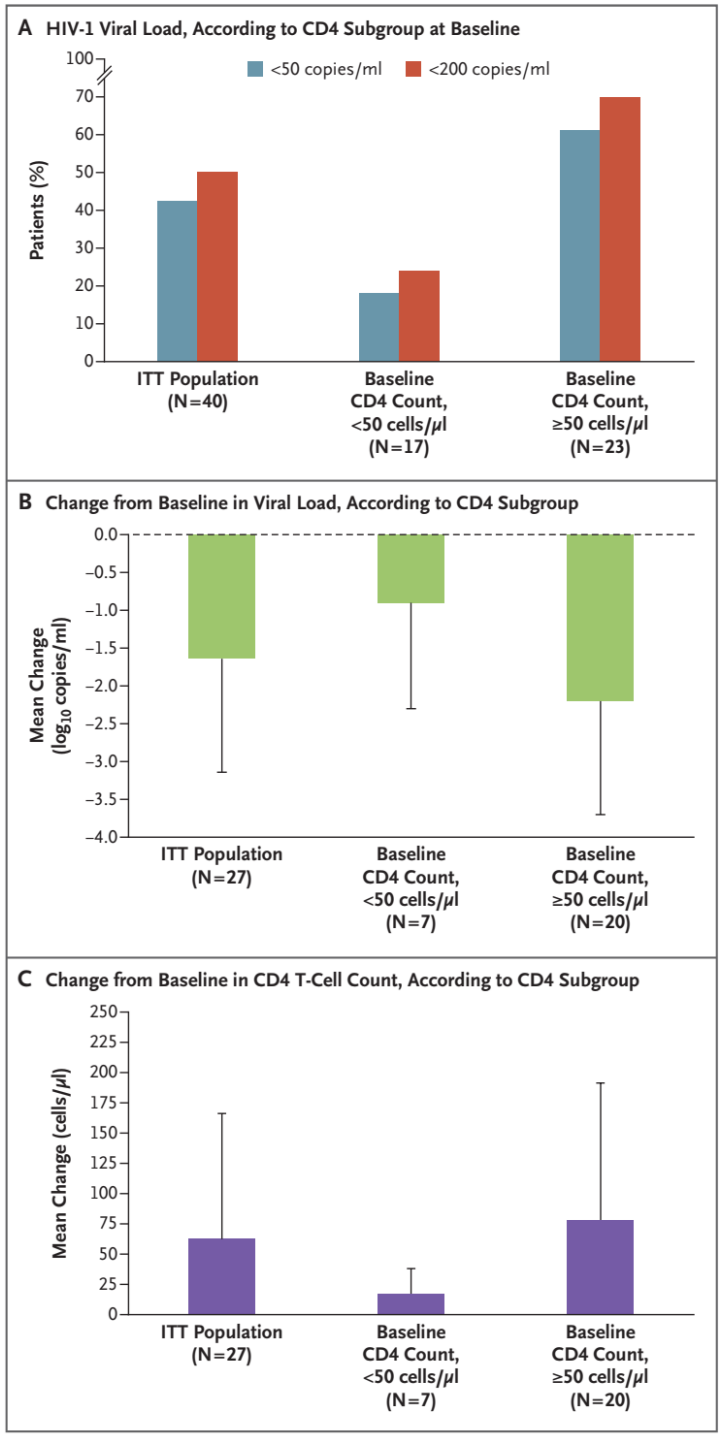
Known resistance to ≥1 drug in class — no. (%)	
Nucleoside reverse-transcriptase inhibitor	37 (93)
Non-nucleoside reverse-transcriptase inhibitor	37 (93)
Protease inhibitor	36 (90)
Integrase inhibitor	27 (68)
Coreceptor antagonist‡	33 (87)
Fusion inhibitor‡	9 (24)
Known resistance to all drugs in class — no. (%)	
Nucleoside reverse-transcriptase inhibitor	26 (65)
Non-nucleoside reverse-transcriptase inhibitor	26 (65)
Protease inhibitor	25 (63)
Integrase inhibitor	19 (48)
Coreceptor antagonist‡	33 (87)
Fusion inhibitor‡	9 (24)



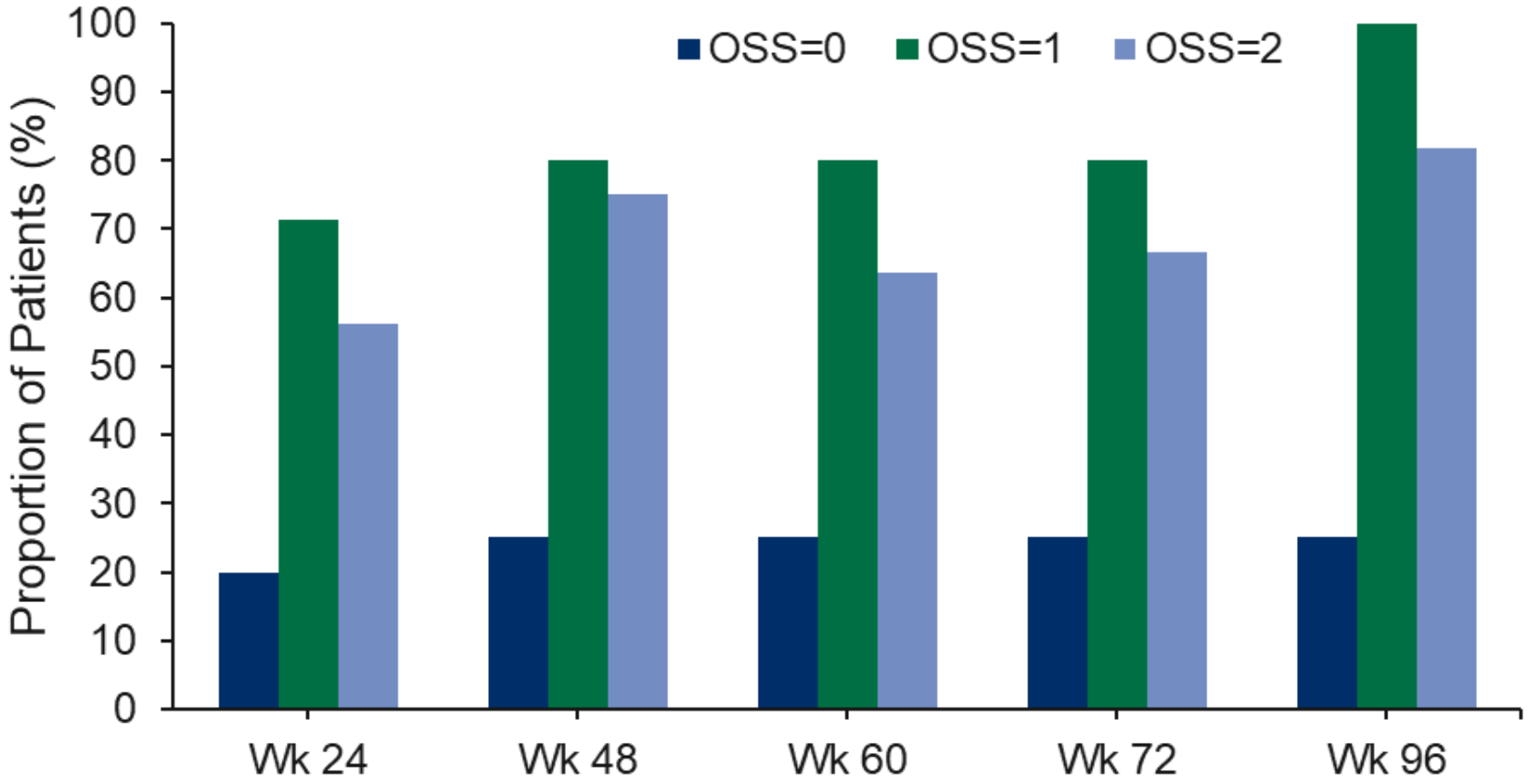
- TMB-301 study: 40 PLWH with extensively drug resistant HIV and VL >3 log (mean 4.5±0.8 log)
- Primary end point: % patients with a decrease in VL ≥0.5 log from baseline (day 7) to day 14

- **On day 14, 33 (83%) had a decrease in VL ≥0.5 log10 copies/ml from baseline**
  - **Mean VL decrease: 1.1 log10 copies/ml**
- At week 25:
  - Mean decrease of 1.6 log10 copies/ml from baseline
  - 43% VL <50 copies/ml; 50% VL <200 copies/ml
  - **10 patients had virologic failure or rebound**
    - **9 had a lower degree of susceptibility to ibalizumab than at baseline**

Emu, NEJM 2018



TMB-311: Proportion of patients with viral loads <50 cp/mL stratified by OSS (OT Population)



Overall susceptibility score (**OSS**) was calculated for each patient as the number of fully active ARVs (Stanford levels 1 and 2) in the OBR at baseline determined by viral genotype and phenotype (Monogram, San Francisco, CA) and historical results

Kumar, IDWeek 2020

Long-term Efficacy, Safety, and Durability of Ibalizumab-based Regimens in Subgroup of TMB-202 Participants

William Towner[1], MD, FACP, FIDSA, Edwin DeJesus[2], MD, FIDSA, Shannon Schrader[3], MD, Jerome de Vente[4], MD, Colleen McGary[5], PhD, Mohammed Zogheib[5], PharmD, MPH, Steven Weinheimer[6], PhD, Pedro Mesquita[7], PhD

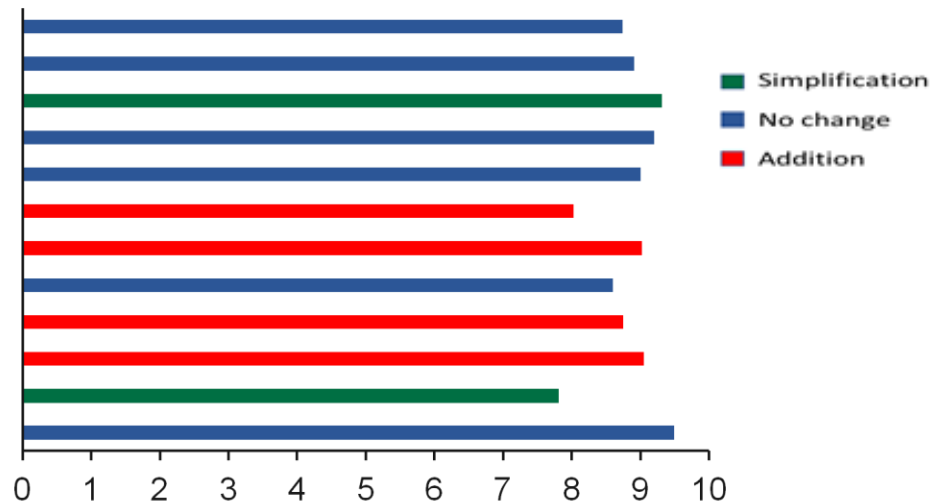
[1]Kaiser Permanente Southern California; Pasadena, CA; [2]Orlando Immunology Center, University of Central Florida College of Medicine; Orlando, FL; [3]Research Access Network; Houston, Texas; [4]Long Beach Education and Research Consultants; Long Beach, California; [5]Syneos Health, Somerset, NJ; [6]Taimed Biologics; Irvine, California; [7]Theratechnologies Inc., Montreal, QC, Canada;

THERA technologies

Results (cont'd)

Durability of Response

- Overall, the 12 patients remained on IBA for an average of 8.9 years (range 7.8-9.5)
- During this period, 8/12 did not require addition of new ARVs to their OBR to maintain suppression.



IV PUSH ADMINISTRATION OF IBALIZUMAB: PHARMACOKINETICS, SAFETY, AND EFFICACY

429

Edwin Dolezal[1], Gary Richmond[2], Margalie Berrie[3], Anthony Mills[4], Tanya Schreiberman[5], Charlotte-Paige Roller[1], Kuei-Ling Kuo[6], Mohammed Zaghwi[7], Olivia G. Soto[1], R. Brandon Cash[8], Yinglin Lu[9], Martin Markowitz[10], Pedro M. Mesquita[6]

THERA technologies

Background

- Long-acting injectable antiretrovirals (LAIs) are becoming increasingly available for the treatment of HIV due to perceived reduction in pill burden, improved compliance through directly observed therapy, and patient preference.
- Ibalizumab (IBA) is a long-acting post-attachment inhibitor approved for the treatment of multidrug resistant HIV-1 infection in heavily treatment experienced (HTE) adults failing their current antiretroviral (ARV) regimen.[1]
- IBA is diluted in 250 mL of saline and administered via intravenous infusion (IVI) as a loading dose of 2000 mg over 30 minutes followed by 800 mg maintenance doses over 15 minutes every 2 weeks.[1]
- In TMB-302, we sought to evaluate the pharmacokinetics (PK), safety, and efficacy of administering IBA maintenance doses as undiluted IV push (IVP) or as intramuscular (IM) injections to improve convenience and offer patients more options. Here we present the IVP analysis.

OBJECTIVES

- **Primary: A)** Evaluate the safety of administering IBA maintenance doses as an undiluted intravenous push (IVP) over 30 seconds, compared to 15-minute IVI. **B)** Compare the area under the curve (AUC) and trough serum drug concentrations (C_{trough}) after IVP vs. IVI.
- **Secondary: A)** Assess efficacy of IVP IBA in people with HIV (PWH). **B)** Determine arising antibodies (ADA).

Methods

- In TMB-302, an open-label non-randomized phase 3 study, clinically stable PWH with viral load (VL) < 1000 c/mL while on IBA-containing ARV regimens for at least 3 months, and HIV-uninfected individuals (UI) were administered IBA as shown in Study Design.
- **Sentinel Group** participants (n=5 PWH) received IBA at progressively increasing concentrations over shortening intervals prior to IVP dosing. Following Data Monitoring Committee (DMC) review, **Core Group** (n=4 PWH and n=2 UI) participants were enrolled and administered IBA as shown.

Methods (cont'd)

- Blood samples were taken at various times pre- and post-administration to measure PK and viral load.
- Treatment-emergent adverse events (TEAEs) were recorded throughout, and the development of ADA was monitored.

STUDY DESIGN

Results

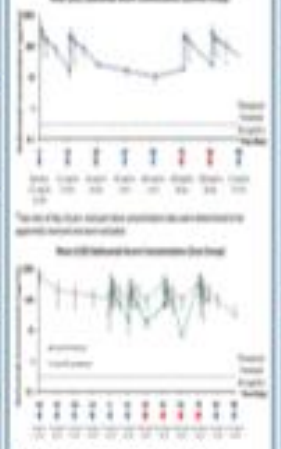
- A total of 22 subjects were enrolled including 9 PWH.
- All PWH and 10 out of 13 UI completed the study.
- Reasons for treatment discontinuation included adverse events (AEs: 2 mild nausea and tremors, and moderate headache, unrelated to study drug), consent withdrawn, and noncompliance with study schedule in 1 UI each.

BASELINE CHARACTERISTICS

Results (cont'd)

PHARMACOKINETICS

- Serum concentrations of IBA remained >1 µg/mL at all timepoints, which suggests that IVP administration is effective at maintaining drug concentrations above therapeutic levels (0.1 µg/mL).



PK bridge between IVI and IVP was established:

- Proportion of subjects with average C_{trough} ≥0.5 µg/mL was 18/19 (94.7%) for both IVI and IVP.
- 95% CI of the AUC ratio of IVP to IVI was within the target value of 0.80-1.25 (0.94 [90 % CI 0.88, 1.00]).

SAFETY

- Overall, 11 subjects (39.3%) reported TEAEs during the study, including 1 of 5 subjects (20.0%) in the Sentinel Group, 3 of 9 subjects (33.3%) in the HIV-infected Core Group, and 10 of 13 subjects (76.9%) in the HIV-uninfected Core Group.
- The most frequently reported TEAEs were nausea (3 mild AEs; 9.3%) and headache (3 mild, 1 moderate AE; 9.3%).
- There were no clinically significant differences in the occurrence of AEs during IVI or IVP. Importantly, infusion reactions and rashes were not observed when IBA was administered as IVP.
- No deaths or serious TEAEs were reported, and no subjects developed ADA.

Results (cont'd)

EFFICACY

- Among PWH, there were no virologic failures. Mean [SD] VL (copies/mL) at baseline (BL) and end of study (EOS) were:
  - Sentinel Group: 0.4 [0.8] BL and 76 [151] EOS
  - Core Group: 0 [0.0] BL and 34 [76.0] EOS
- One Sentinel PWH experienced virologic rebound following the last IVP dose, which was linked to nonadherence to the oral ARV regimen.
- Median VL at BL and EOS was <20 copies/mL for both groups.

Conclusions & Future Perspective

- Administration of IBA as an **undiluted IVP over 30 seconds was safe and well tolerated** in all participants and remained effective among PWH.
- **Bioequivalence between IVI and IVP administration** was demonstrated and supports IVP as a potential alternative for delivery of IBA.
- Reducing the time required for IBA administration may **improve patient acceptability** for increasing convenience.
- Assessment IM injection as an additional delivery option for HTE patients is ongoing in this study.

References:
1. Trogarzo® Prescribing Information. Theratechnologies Inc; 2022.

HIV-1 NON-GROUP M PHENOTYPIC SUSCEPTIBILITY TO IBALIZUMAB

00501

L. Poisson-Arnaud[1], Quentin le Hingrat[2], JC Plantier[1] and E Alessandri-Gradt[1]

[1] Normandie Univ, UNIROUEN, GRAM2.0, Rouen University Hospital F-76000 France ; [2]Université de Paris, IAME, UMR 1137, Sorbonne Paris Cité, Paris, France

BACKGROUND

While HIV-1 group M is responsible for the large majority of HIV infections worldwide, 3 other groups named O, N and P (HIV-1 non-M) are more genetically divergent and endemic in West-central Africa, mainly in Cameroon.

Due to the natural genetic polymorphisms associated with HIV-1 non-M, fully-active antiretrovirals are more restricted than for HIV-1/M.[1] Therefore, novel drugs such as Ibalizumab (IBA), the first-in-class long-acting CD4-directed post-attachment inhibitor, could provide important alternatives for treatment regimens.[2]

OBJECTIVES

→ **To determine the phenotypic susceptibility of HIV-1/non-M clinical isolates to IBA**

METHODS

7 clinical isolates of HIV-1/non-M were tested
- 5 HIV-1/O (4 subgroup H and 1 subgroup T)
- 1 HIV-1/N
- 1 HIV-1/P

and BRU-HXB2 HIV-1 reference strain.

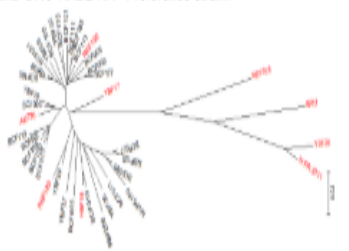


Figure 1 : Phylogenetic tree representing the diversity of the studied strains (in red) analysis made with Mega7.Evolutionary history was inferred using the Neighbor-Joining method and evolutionary distances using Kimura 2-parameter method)

For the phenotypic assay PHA stimulated-PBMC from healthy donors were preincubated with IBA for 1h. Then, $2.5x10^5$ PBMC previously infected for 2h with 100 $TCID_{50}$ of each viral supernatants, were incubated (37°C, 5% CO_2) in quadruplicate in a 96-wells plate with 5 increasing concentrations of Ibalizumab (from 1 to 10 000 ng/ml) for 3 days.

Viral RNA was extracted from 200µl of supernatant by EZ1 advanced XI Qiagen® and quantified by various methods described as following[3]: Integrase-based specific in house qRT-PCR (HIV-1/O), LTR-M Biocentric® (HIV-1/M and N) and Aptima HIV-1 Quant Dx Hologic®, for the calculation of inhibitory concentrations 50% (IC_{50}), maximum percent inhibition (MPI) and fold-change (FC) calculated from BRU-HXB2 IC_{50}.

The highest IC_{50}values were controlled for reproducibility.

IBA demonstrated *in vitro* susceptibility of HIV-1/O while phenotypic results with HIV-1/P suggest potential resistance

RESULTS

Five clinical isolates (4 HIV-1/O and 1 HIV-/N) had a **mean IC_{50} (min; max) of 0.119 ($6x10^{-11}$; 0.227) ng/ml** and median **MPI of 96.9%,** comparable to those of the HIV-1/M reference (IC_{50} and MPI of 0.186 ng/ml and 90.9% respectively).

In contrast with these results, the RBF168 clinical **isolate of HIV-1/P was naturally resistant** (IC_{50}>10 000 ng/ml and MPI<25%), in two independent experiments.

Finally, YBF17, a divergent clinical isolate of HIV-1/O subgroup H, had a FC of 824 (IC_{50} of 153 ng/ml) with intermediate MPI (75.9%) but within the susceptibility range defined in the literature for HIV-1/M (max at 600 ng/ml). This strain also showed high intra-group O genetic diversity (Fig1).

Table 1 : Phenotypic results of the 7 HIV-1/non-M strains and BRU.HXB2

Group	Strain	IC_{50} (ng/mL)	MPI	FC
M	**BRU.HXB2**	0.186	90.9	-
N	**YBF30**	0.216	98.1	1.16
O	**RBF189**	$6.19x10^{-11}$	93.6	< 0.01
O	**RBF130**	0.0644	94.0	0.35
O	**ANT70**	0.0089	96.9	0.48
O	**YBF16**	0.227	98.5	1.22
O	**YBF17**	153	75.9	824
P	**RBF168**	> 10 000	< 25	-

CONCLUSION

Our results demonstrate the susceptibility of HIV-1 non-M to Ibalizumab with **100% of HIV-1/O and N isolates tested being susceptible, while IBA had no activity against the single HIV-1/P isolate tested**.

These results should now be confirmed in a larger panel and potential N-linked glycosylation sites (PNGS) should be assessed to determine their potential role in resistance of HIV-1/non-M to IBA.

REFERENCES & FUNDINGS

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[2] Theratechnologies. Monograph - Trogarzo. Approved by the U.S. FDA; 2020
[3] Alessandri-Gradt, *J. Antimicrob. Chemother.* 2017 72(9):2431-2437

This study was supported by Santé publique France and ANRS MIE
IBA was kindly provided by Mr Henri Jullien from Theratechnologies

CROI 2022

Clinical Characteristics and Outcomes of Coronavirus Disease 2019 Patients Who Received Compassionate-Use Leronlimab

Bryant Yang,[1] Jennifer A. Fulcher,[1,2] Jenny Ahn,[3] Marlene Berro,[3] David Goodman-Meza,[1] Kush Dhody,[4] Jonah B. Sacha,[5] Arash Naeim,[3] and Otto O. Yang[1,6]

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Background. Leronlimab, a monoclonal antibody blocker of C-C chemokine receptor type 5 originally developed to treat human immunodeficiency virus infection, was administered as an open-label compassionate-use therapeutic for coronavirus disease 2019 (COVID-19).

Methods. Twenty-three hospitalized severe/critical COVID-19 patients received 700 mg leronlimab subcutaneously, repeated after 7 days in 17 of 23 patients still hospitalized. Eighteen of 23 received other experimental treatments, including convalescent plasma, hydroxychloroquine, steroids, and/or tocilizumab. Five of 23 received leronlimab after blinded, placebo-controlled trials of remdesivir, sarilumab, selinexor, or tocilizumab. Outcomes and results were extracted from medical records.

Results. Mean age was 69.5 ± 14.9 years; 20 had significant comorbidities. At baseline, 22 were receiving supplemental oxygen (3 high flow, 7 mechanical ventilation). Blood showed markedly elevated inflammatory markers (ferritin, D-dimer, C-reactive protein) and an elevated neutrophil-to-lymphocyte ratio. By day 30 after initial dosing, 17 were recovered, 2 were still hospitalized, and 4 had died. Of the 7 intubated at baseline, 4 were fully recovered off oxygen, 2 were still hospitalized, and 1 had died.

Conclusions. Leronlimab appeared safe and well tolerated. The high recovery rate suggested benefit, and those with lower inflammatory markers had better outcomes. Some, but not all, patients appeared to have dramatic clinical responses, indicating that unknown factors may determine responsiveness to leronlimab. Routine inflammatory and cell prognostic markers did not markedly change immediately after treatment, although interleukin-6 tended to fall. In some persons, C-reactive protein clearly dropped only after the second leronlimab dose, suggesting that a higher loading dose might be more effective. Future controlled trials will be informative.

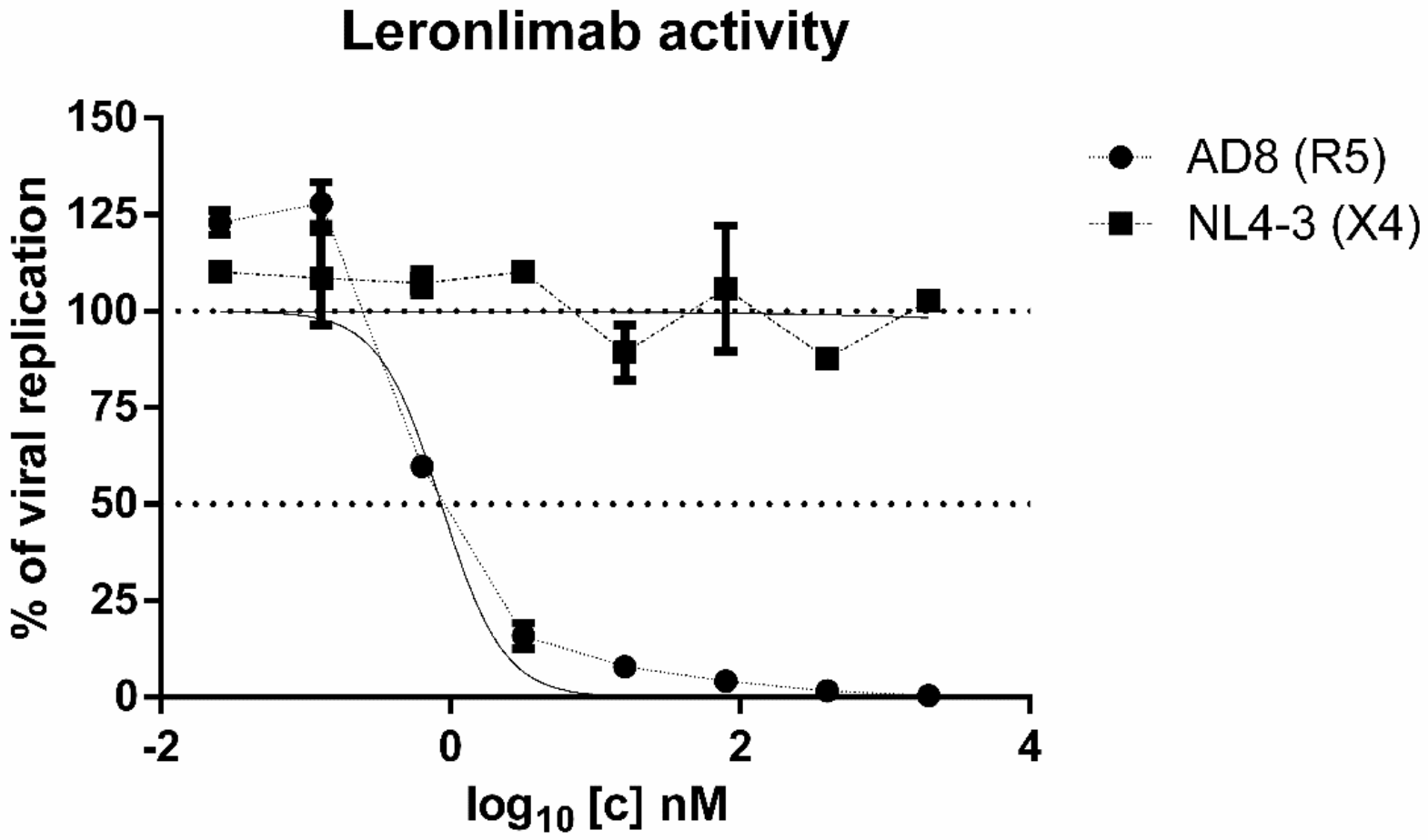
CID 2021

Leronlimab (PRO 140) *in vitro* activity against 4-class drug resistant HIV-1 from heavily treatment experienced subjects

Variable	Patient population (n=24)
Age (years), median (IQR)	48.0 (39.1 – 52.7)
Male gender, N (%)	19 (79%)
Calendar year of first HIV positive test, median (IQR)	1992 (1988 – 1993)
Years since first HIV positive test, median (IQR)	22.3 (19.3 – 25.2)
Calendar year of ART start, median (IQR)	1993 (1992 - 1997)
Years since ART start, median (IQR)	19.7 (15.6 – 22.9)
Months to ART start since first HIV positive test, median (IQR)	11.1 (1.2 – 48.7)
Previous diagnosis of AIDS, N (%)	14 (58%)
Nadir $CD4^+$ T-cells (N/µL), median (IQR)	52 (9 - 184)
Zenith HIV-1 RNA (log_{10} copies/mL), median (IQR)	5.06 (4.36 – 5.60)
Duration (months) with detectable plasma HIV-1 RNA (>50 copies/mL) at the time of current analysis, median (IQR)	20.1 (4.4 – 55.8)
HIV-1 RNA (log_{10} copies/mL), median (IQR)	4.69 (4.11 – 5.20)
$CD4^+$ T-cells (N/µL), median (IQR)	192 (65.5 - 252)
$CD8^+$ T-cells (N/µL), median (IQR)	950 (656 - 1728)
$CD4^+/CD8^+$ ratio, median (IQR)	0.14 (0.09 – 0.26)

S. Rusconi, Pharmacological Research 2022

Leronlimab (PRO 140) *in vitro* activity against 4-class drug resistant HIV-1 from heavily treatment experienced subjects



S. Rusconi, Pharmacological Research 2022

Leronlimab (PRO 140) *in vitro* activity against 4-class drug resistant HIV-1 from heavily treatment experienced subjects

Table 1. Baseline HIV-1 RNA, $CD4^+$ T cell counts Genotypic coreceptor tropism results obtained by Sanger and NGS and leronlimab in vitro susceptibility for the 9 phenotypically R5 pseudoviruses.

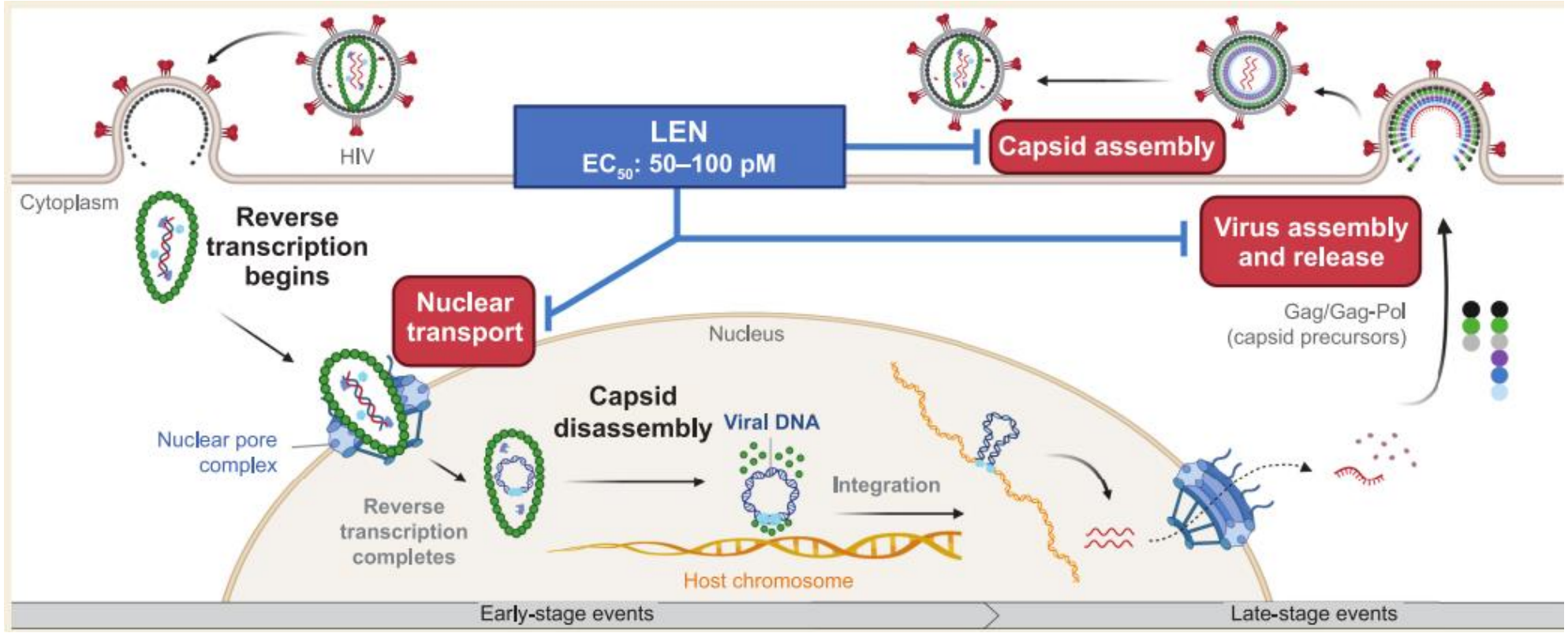
Patient ID	HIV-1 RNA (copies/mL)	$CD4^+$ T-cells/µL	Percentage of non-R5 variants by NGS (FPR ≤3.5%)	FPR by Sanger (%)	IC_{50} (mean±SD) PRO 140	Previous maraviroc exposure	Exposure to maraviroc at current analysis
25	1,104	240	32.7	4.4	0.3±0.2	Yes	No
27	13,835	168	0.1	not done	1.2±0.3	No	No
37	12,580	207	0.1	69.8	0.4±0.3	Yes	Yes
55	17,888	326	0.0	54.7	0.7±0.2	No	No
58	2,986	518	0.0	51.3	0.5±0.3	No	No
82	373,713	942	83.8	54.7	0.4±0.3	No	No
90	84,534	201	0.6	16.4	0.8±0.6	No	No
117	6,718,473	34	0.1	51.2	0.3±0.1	Yes	Yes

NGS, Next Generation Sequencing. FPR, False Positive Rate. IC_{50}, Half-maximal inhibitory concentration. SD, standard deviation.

S. Rusconi, Pharmacological Research 2022

New options for MDR HIV

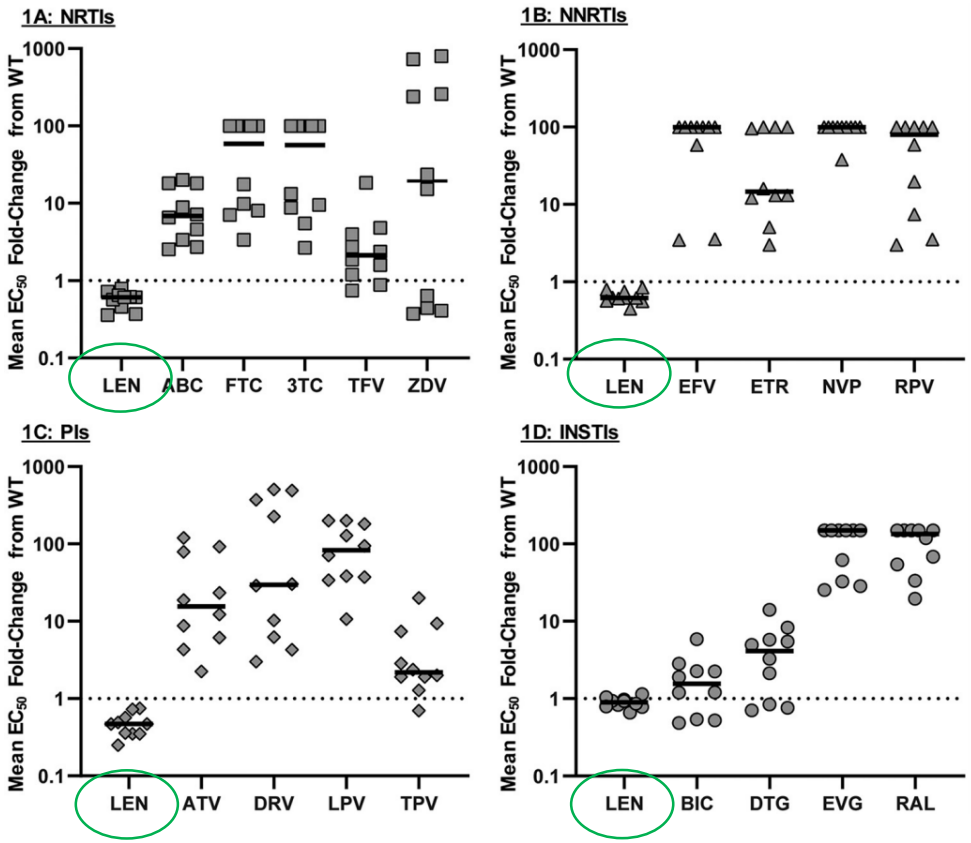
Lenacapavir → targets HIV capsid



- First-in-class capsid (CA) inhibitor
- Picomolar potency (EC50 = 50-100 pM)
- LEN inhibits CA-mediated nuclear entry of HIV DNA, HIV assembly and proper capsid formation

Stellbrink, EACS 2021

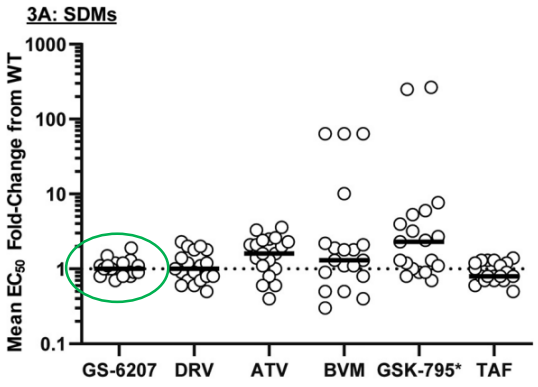
Lenacapavir



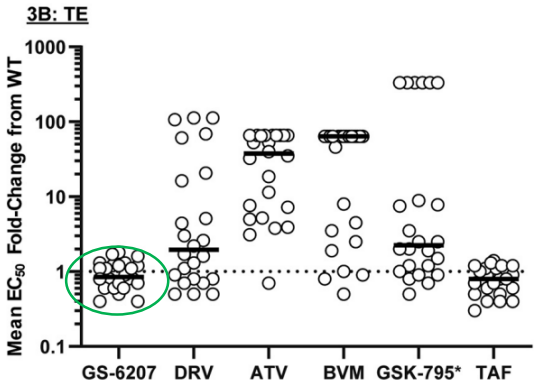
- Activity of LEN in **mutants resistant to other drug classes**
- HIV mutations were inserted into the pXXLAI clone, and the resulting mutants (*n* = 40) were evaluated using a 5-day antiviral assay

N Margot, Antimicrobial Agents Chemother 2021

Lenacapavir



Site-directed mutants



Clinical isolates from treatment experienced subjects

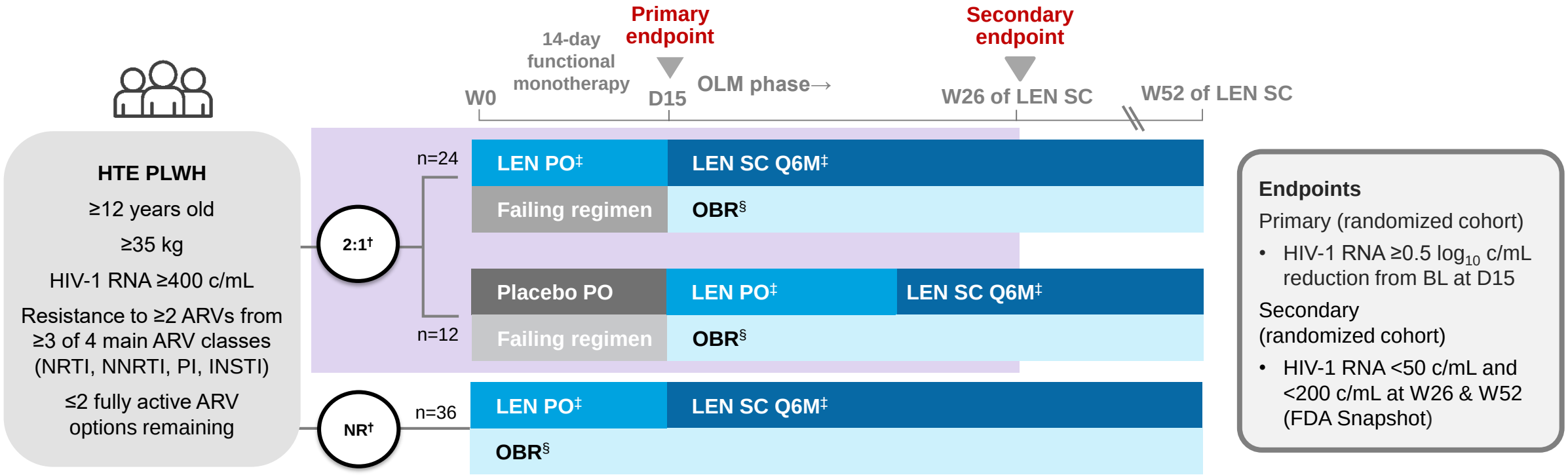
*The maturation inhibitor GSK3532795 was discontinued

- Activity of LEN in mutants with **Gag cleavage site mutations**
- HIV mutations were inserted into the pXXLAI clone, and the resulting mutants (*n* = 43) were evaluated using a 5-day antiviral assay

N Margot, Antimicrobial Agents Chemother 2021

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)**

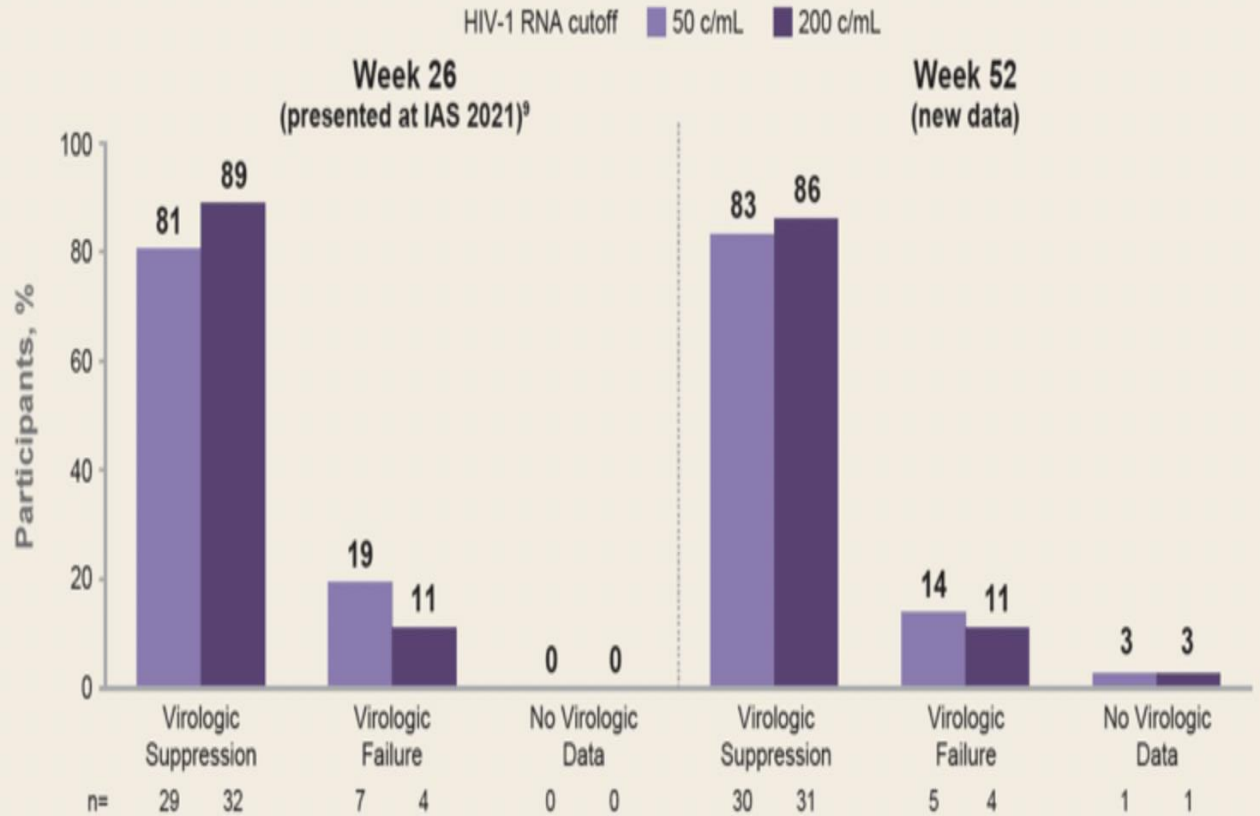
†Participants with <0.5 $\log_{10}$ decline in HIV-1 RNA during screening entered the randomized cohort; participants with ≥0.5 $\log_{10}$ decline in HIV-1 RNA during screening entered the non-randomized cohort
§Investigational agents, such as fostemsavir, were allowed; atazanavir (ATV), ATV/cobicistat, 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

Long-Acting Lenacapavir in People With Multidrug-Resistant HIV-1: Week 52 Results

Onyema Ogbuagu,[1] Sonam Segal-Maurer,[2] Cynthia Brinson,[3] Ploenchan Chetchotisakd,[4] Kenneth Lichtenstein,[5] Joseph McGowan,[6] Andrew A. Wiviott,[7] Kimberly Workowski,[8] Hui Wang,[9] Nicolas Margot,[9] Hadas Dvory-Sobol,[9] Martin S. Rhee,[9] Jared M. Baxton,[9] Jean-Michel Molina[10]

Efficacy in Randomized Cohort (n=36)



Efficacy by No. of Fully Active Agents in OBR at Week 52 in Randomized Cohort (n=36)

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Long-Acting Lenacapavir in People With Multidrug-Resistant HIV-1: Week 52 Results

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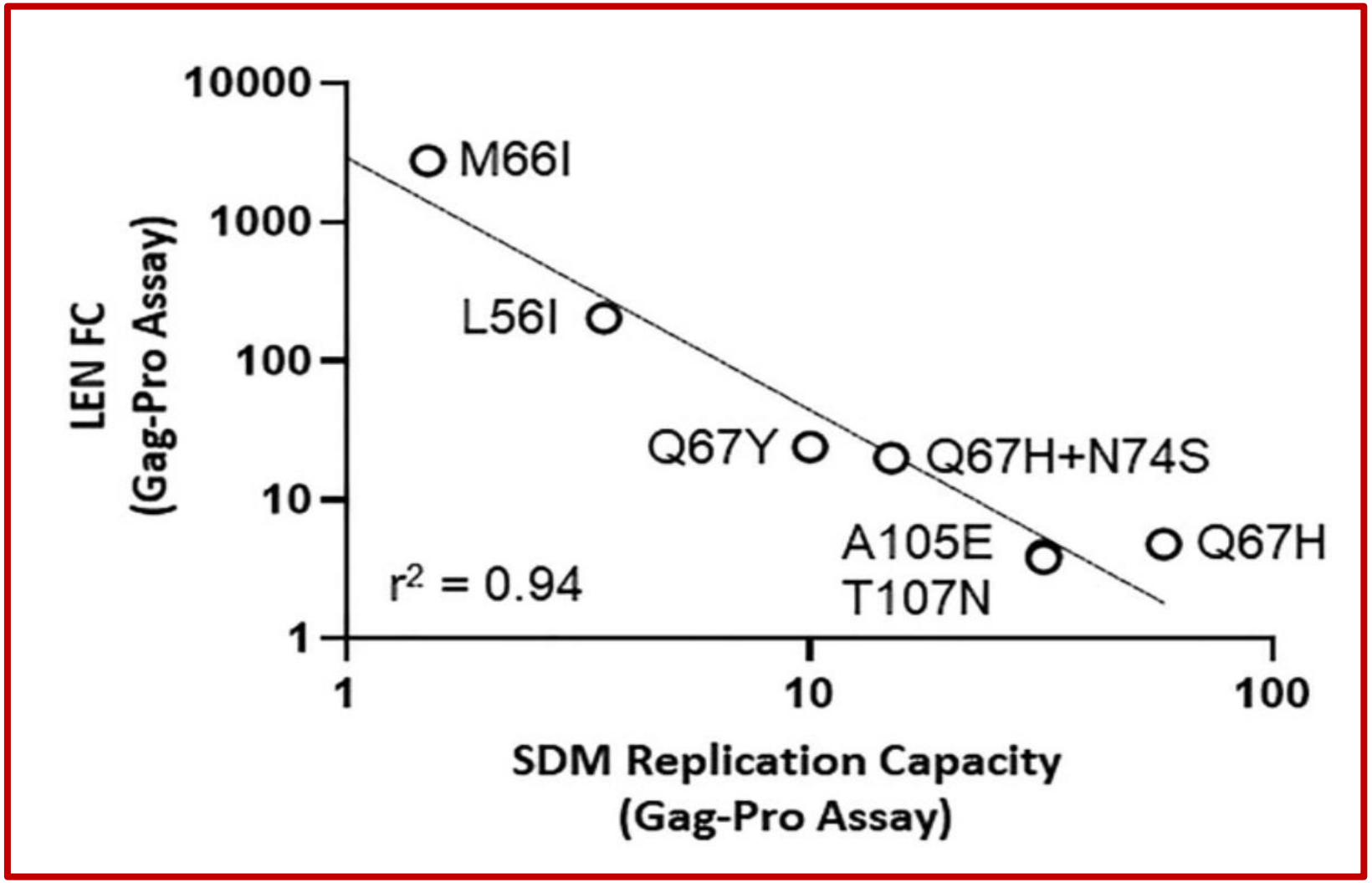
[1]Yale University, New Haven, CT; [2]New York Presbyterian Queens, NY; [3]Central Texas Clinical Research, Austin, TX; [4]Srinagarind Hospital, Khon Kaen, Thailand; [5]Eisenhower Health Center, Palm Springs, CA; [6]Northwell Health, Manhasset, NY; [7]Jacobi Medical Center, Bronx, NY; [8]Emory University, Atlanta, GA; [9]Gilead Sciences, Inc., Foster City, CA; [10]Hôpital Saint Louis, Paris, France

Emergent LEN Resistance*

n (%)	Randomized Cohort: n=36 (presented at IAS 2021, EACS 2021)[5,10]	Nonrandomized Cohort: n=36
Participants meeting criteria for resistance testing	11 (31)	10 (28)
Emergent LEN resistance†	4 (11)	4 (11)
M66I	4	2
Q67H/K/N	1	2
K70H/N/R/S	1	3
N74D/H/S	3	0
A105S/T	3	1
T107A/C/N	1	3

*Capsid genotypic and phenotypic resistance testing performed on any participants with confirmed HIV-1 RNA ≥50 c/mL and <1 $\log_{10}$ HIV-1 RNA reduction from Day 1 at Week 4 visit, at any visit after achieving HIV-1 RNA <50 c/mL and rebound to ≥50 c/mL, and at any visit with >1 $\log_{10}$ increase from nadir; HIV-1, protease, reverse-transcriptase, and integrase genotypic and phenotypic testing were performed if rebound or suboptimal virologic response were confirmed; †Developed during maintenance period (Week 4 [n=5], Week 10 [n=2], and Week 26 [n=1]).

Correlation between replication capacity and fold change in lenacapavir susceptibility in the Gag-Pro assay.



N. Margot, JAC 2021

Long-Acting Lenacapavir in People With Multidrug-Resistant HIV-1: Week 52 Results

Onyema Ogbuagu,[1] Soriana Segal-Maurer,[2] Cynthia Brinson,[3] Phoenchan Chetchotisakd,[4] Kenneth Lichtenstein,[5] Joseph McGowan,[6] Andrew A. Wiavia,[7] Kimberly Workowski,[8] Hui Wang,[9] Nicolas Margot,[9] Hadas Dvory-Sobol,[9] Martin S. Rhee,[9] Jared M. Baeten,[9] Jean-Michel Molina[10]

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Adverse Events (excluding ISRs)*

≥10% Total in Any Grade, % (n)	Total LEN: N=72
Diarrhea	13 (9)
Nausea	13 (9)
COVID-19	11 (8)

*Serious adverse events (AEs) not related to study drug: malignant neoplasm and dizziness (n=1); abdominal pain, pancreatic mass, *Clostridium difficile* colitis, and angina pectoris (n=1); anal squamous cell carcinoma, proctalgia, impaired healing, and anal cancer (n=1); femoral neck fracture (n=1); COVID-19 (n=2); pneumonia (n=1); and septic shock, renal impairment, and shock (n=1). ISRs, injection-site reactions.

Incidence of ISRs Related to SC LEN*

ISR Types, %	After 1st SC Dose at Week 1 N=72	After 2nd SC Dose at Week 26 n=70	Median Duration, d
Swelling	26	13	12
Erythema	24	11	6
Pain	22	21	3
Nodule	22	11	180
Induration	11	10	118

*Only includes AEs related to LEN and excludes those not related to it.

Long-Acting Lenacapavir in People With Multidrug-Resistant HIV-1: Week 52 Results

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Grade 3 or 4 Laboratory Abnormalities

Laboratory Abnormality, % (n)	Total: N=72
Any Grade 3 or 4	29 (21)
≥5% in total	
Low creatinine clearance (eGFR)*	14 (10)
Elevated creatinine†	13 (9)
Glycosuria	6 (4)
Nonfasting/fasting hyperglycemia	6 (3)

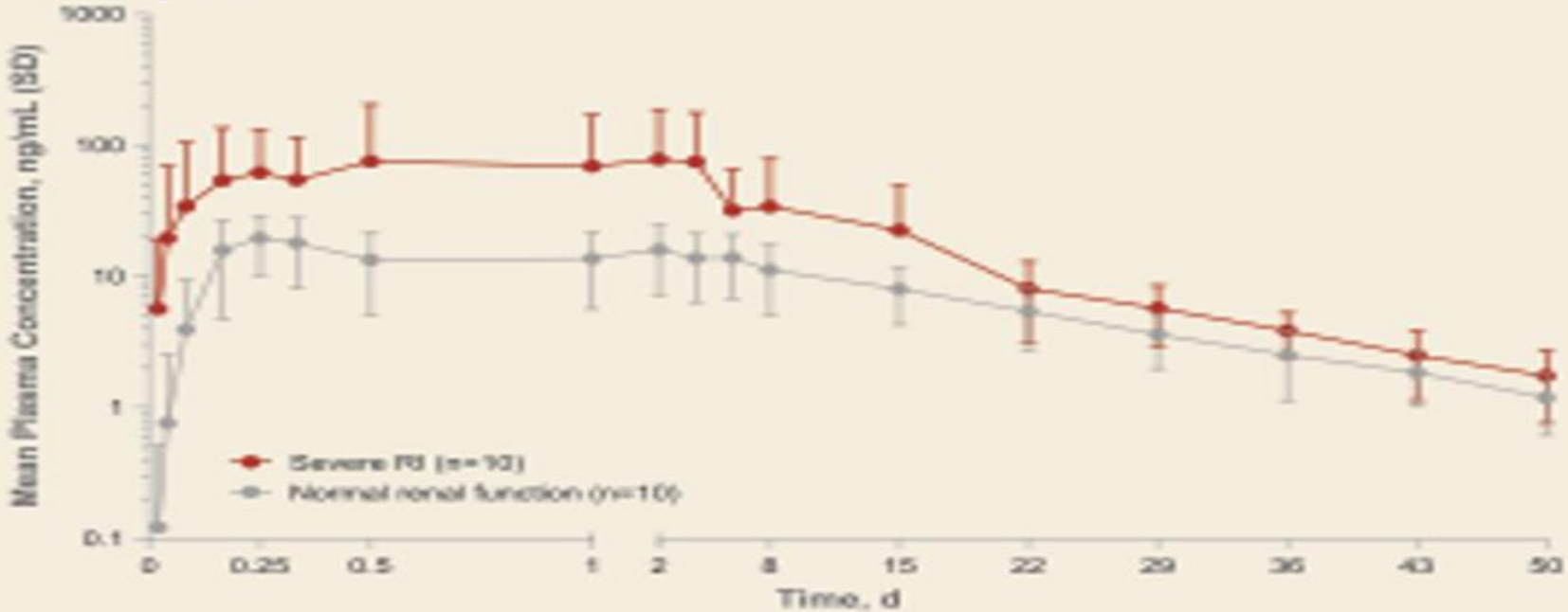
*Per Division of AIDS scale, Grade 3 creatinine clearance is <60–30 mL/min or 30–<50% decrease from baseline; †Grade 3 creatinine is >1.8–<3.5 x upper limit of normal or increase to 1.5–<2.0 x baseline. eGFR, estimated glomerular filtration rate.

CROI 2022

Pharmacokinetics of Lenacapavir in Participants With Severe Renal Impairment

Elijah J. Weber, Hiba Graham, Steve K. West, John Ling, Martin Rhee, Ramesh Palaparthy — Gilead Sciences, Inc., Foster City, CA

LEN PK in Participants With Severe RI and Matched Healthy Controls



PK Parameter*	Severe RI (n=10)	Normal Renal Function (n=10)	%GLSMR [90% CI]
AUC_{∞}, h·ng/mL	19,000 [35]	7400 [45]	184 [93.6, 360]
AUC_{tau}, h·ng/mL	18,300 [101]	6640 [45]	189 [95.2, 377]
C_{max}, ng/mL	118 [129]	22.1 [44]	262 [112, 614]
T_{max}, h	8.00 [8.00, 24.0] [0.33 d]	8.00 [8.00, 8.00] [0.25 d]	—
$t_{1/2}$, h	234 [176, 354] [9.75 d]	318 [270, 357] [13.3 d]	—

*AUC from time-0 to ∞ (AUC$_{\infty}$), AUC from time-0 to last measured concentration (AUC$_{tau}$), and C_{max} presented as mean (% coefficient of variation); and time to C_{max} (T_{max}) and half-life ($t_{1/2}$) presented as median (quartiles 1, 3).

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-/.

Islatravir development : Current Status

Full hold
Long-Acting Oral
islatravir + lenacapavir

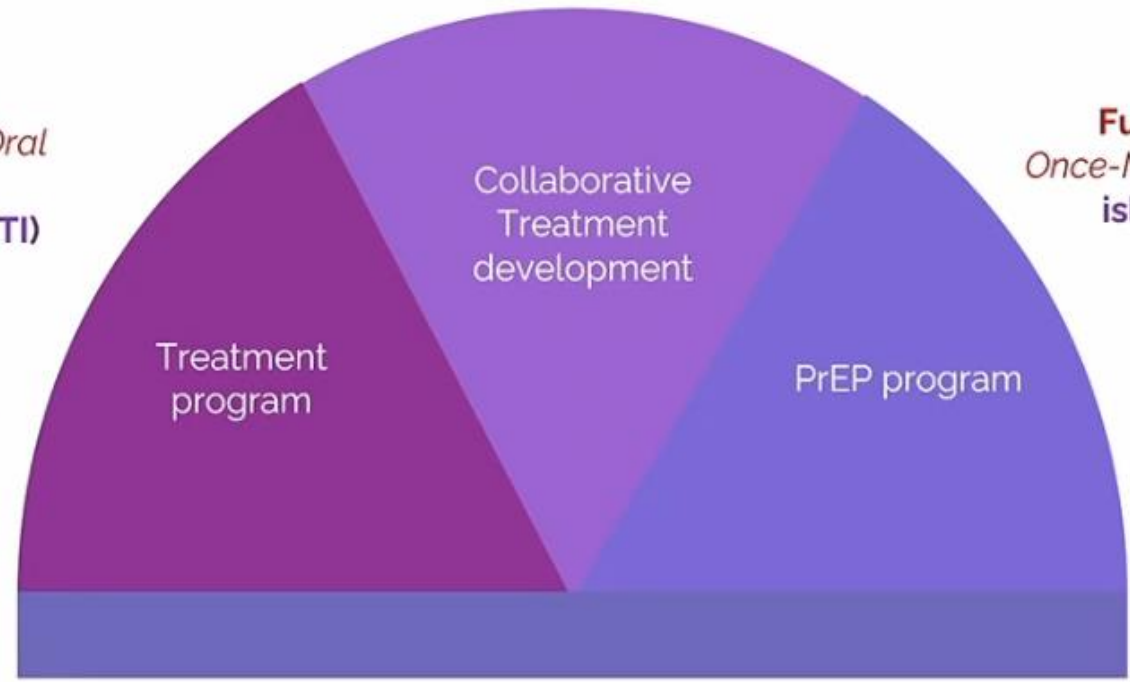
Not starting
Long-Acting Injectable
islatravir + lenacapavir

Full hold
Once-Weekly Oral
Islatravir
MK8507 (NNRTI)

Full Hold
Once-Monthly Oral
islatravir

Partial hold
Once-Daily Oral
islatravir + doravirine

Not starting
Once-Yearly Implant
islatravir



C. Orkin, CROI 2022

A RANDOMIZED TRIAL OF DTG PLUS DRV/c AS A SWITCH STRATEGY IN SUBJECTS WITH MDR HIV-1 Poster-I02

José R. Santos,[1] Pere Domingo,[2] Joaquín Portilla,[3] Félix Gutiérrez,[4] Arkaitz Imaz,[5] Helem Vilchez,[6] Adrià Curran,[7] Nieves Valcarce-Pardeiro,[8] Antoni Payeras,[9] Enrique Bernal,[10] Marta Montero-Alonso,[11] Miguel Yzuski,[12] and R. Paredes[13] on behalf of the 2D Study

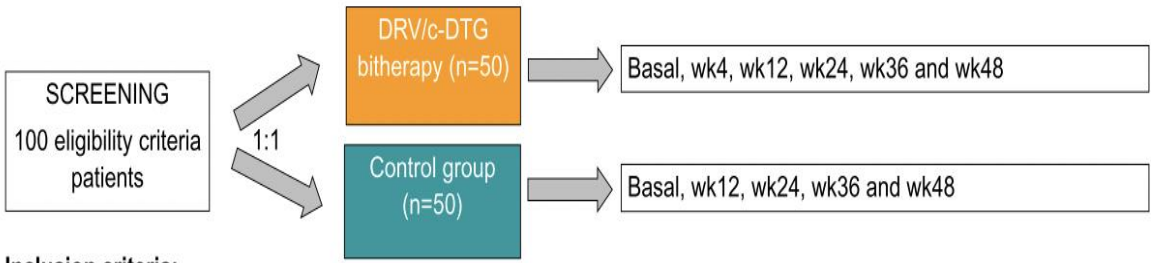
[1]Hospital Germans Trias i Pujol, [2]Hospital de la Santa Creu i Sant Pau, [3]Hospital General Universitario de Alicante, [4]Hospital G. U. de Elche, [5]Hospital Universitari de Bellvitge, [6]Hospital Universitario Son Espases, [7]Hospital Vall d'Hebron, [8]Hospital Arquitecto Marcide, [9]Hospital Son Llàtzer, [10]Hospital General Universitario Reina Sofia de Murcia, [11]Hospital Universitario y Politécnico La Fe, [12]Hospital General Nuestra Señora del Prado

METHODS

Study design and patients

- Study design: This is an open label, multicenter, randomized pilot study to evaluate the efficacy and safety of switching to DTG+DRV/c as a 2-pill once-daily simplification strategy in well-suppressed and highly ART-experienced patients harboring archived DRM against at least 2 antiretroviral classes.

- Subjects who meet all eligibility criteria were randomly assigned to:
  - Experimental group: Bitherapy based on DTG (50 mg QD) plus DRV/c (800/150 mg QD).
  - Control group: Continuation of their current stable ART.

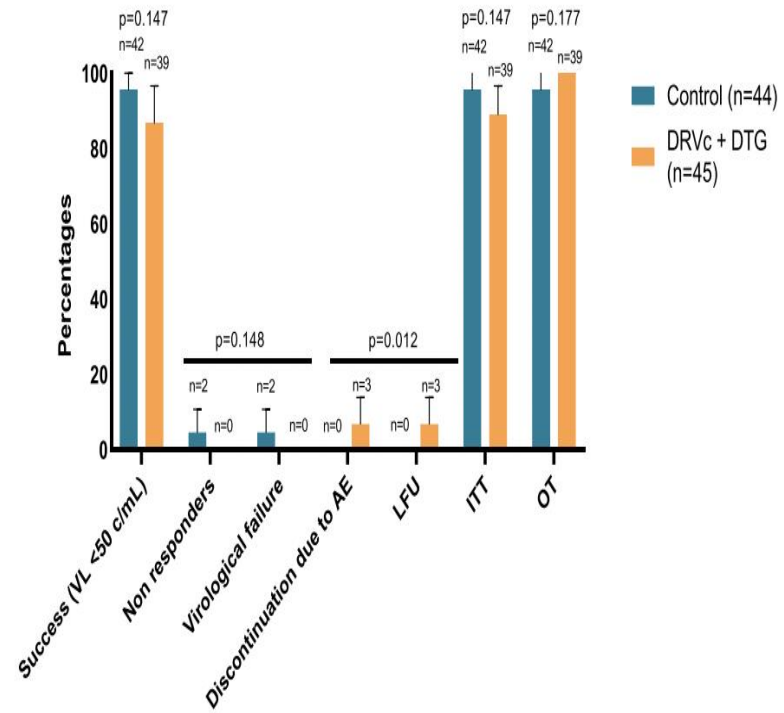


Inclusion criteria:

CONCLUSIONS

- Dual therapy with DTG+DRV/c maintains viral suppression in highly treatment experienced subjects with multiclass drug resistance, as long as they retain DRV- and INSTI-susceptible HIV-1.
- More frequently observed AEs in the DRV/c+DTG arm has to be interpreted with caution due to the open label design.
- AES leading to treatment discontinuation were unfrequent.

Figure 3. Virological outcome at week 48 according to FDA snapshot analysis

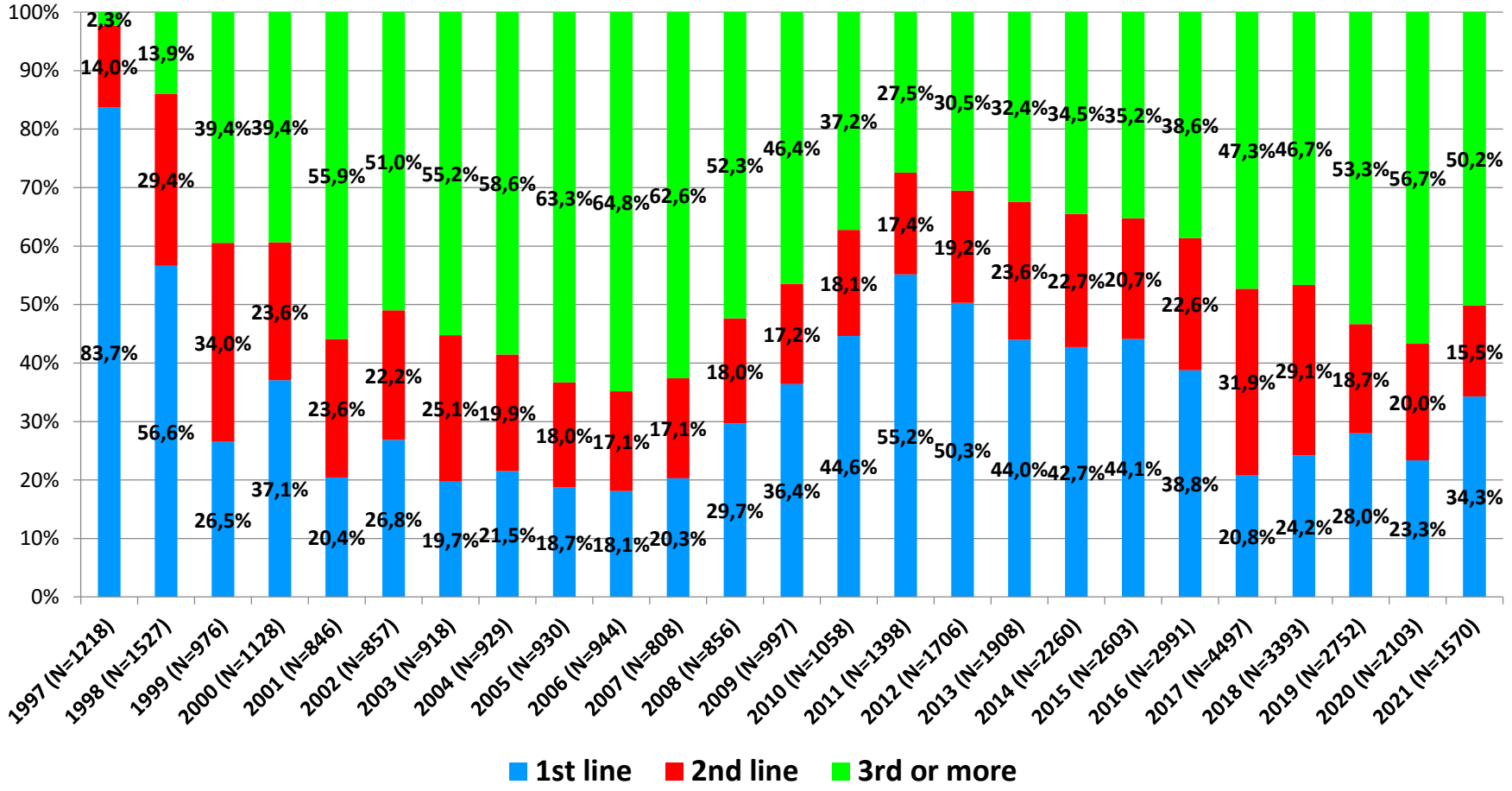


VL, viral load; LFU, loss to follow-up; ITT: M = F, intention to treat: missing equal to failure; OT: M ≠ F, On-treatment: missing censored

CROI 2022

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Proportion of patients under different ART regimen lines according to calendar year



BIC+DRV or DTG+DRV		
Years of ART strata	n	percent
0-4	38	0,9%
5-9	44	1,3%
10-14	16	1,4%
15-19	6	1,4%
20-24	17	2,9%

Dec 2021 Report

Take-home Message

- HTE subjects are a challenging population, especially those with a pan-resistant virus
- New options with specific MoA are available (DOR, FTR, IBA), others will hopefully (LEN, ISL, LER..bNABS…MI…) come
- We need for new tools for correctly managing these options
- We need a multidisciplinary approach for managing HTE PLWH with the ultimate goal to achieve and maintain undetectability and possibly to simplify complex regimens