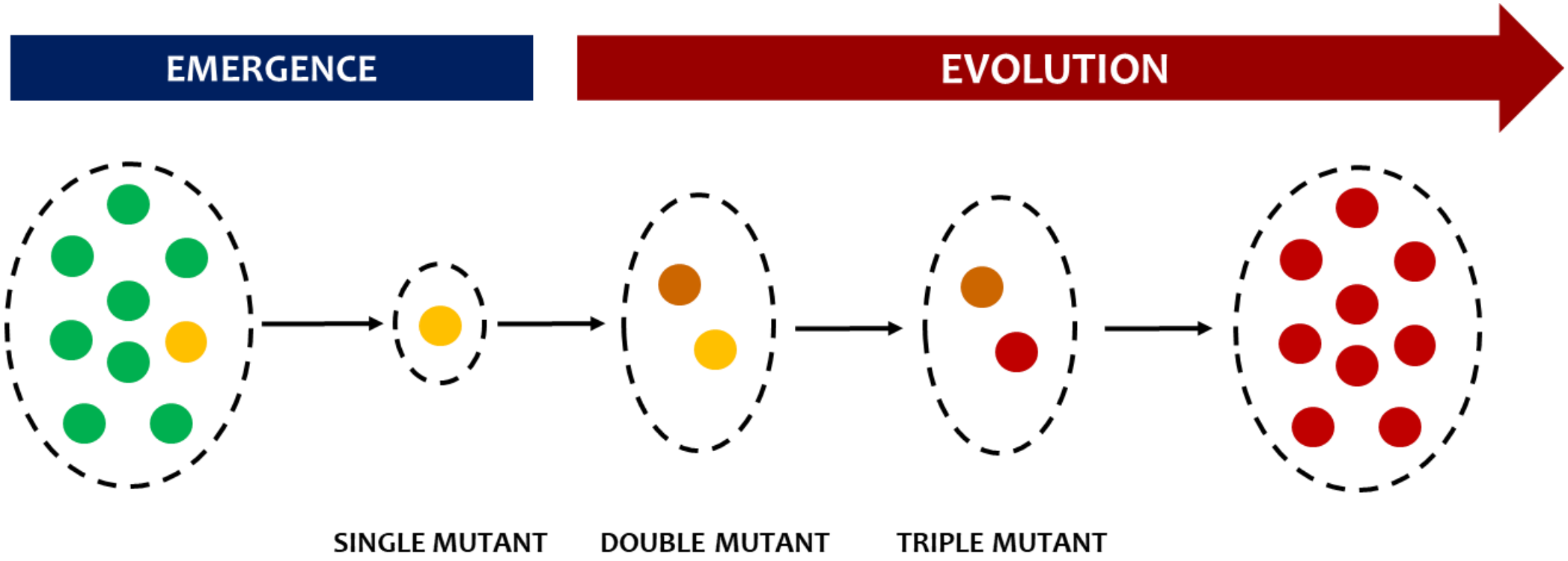


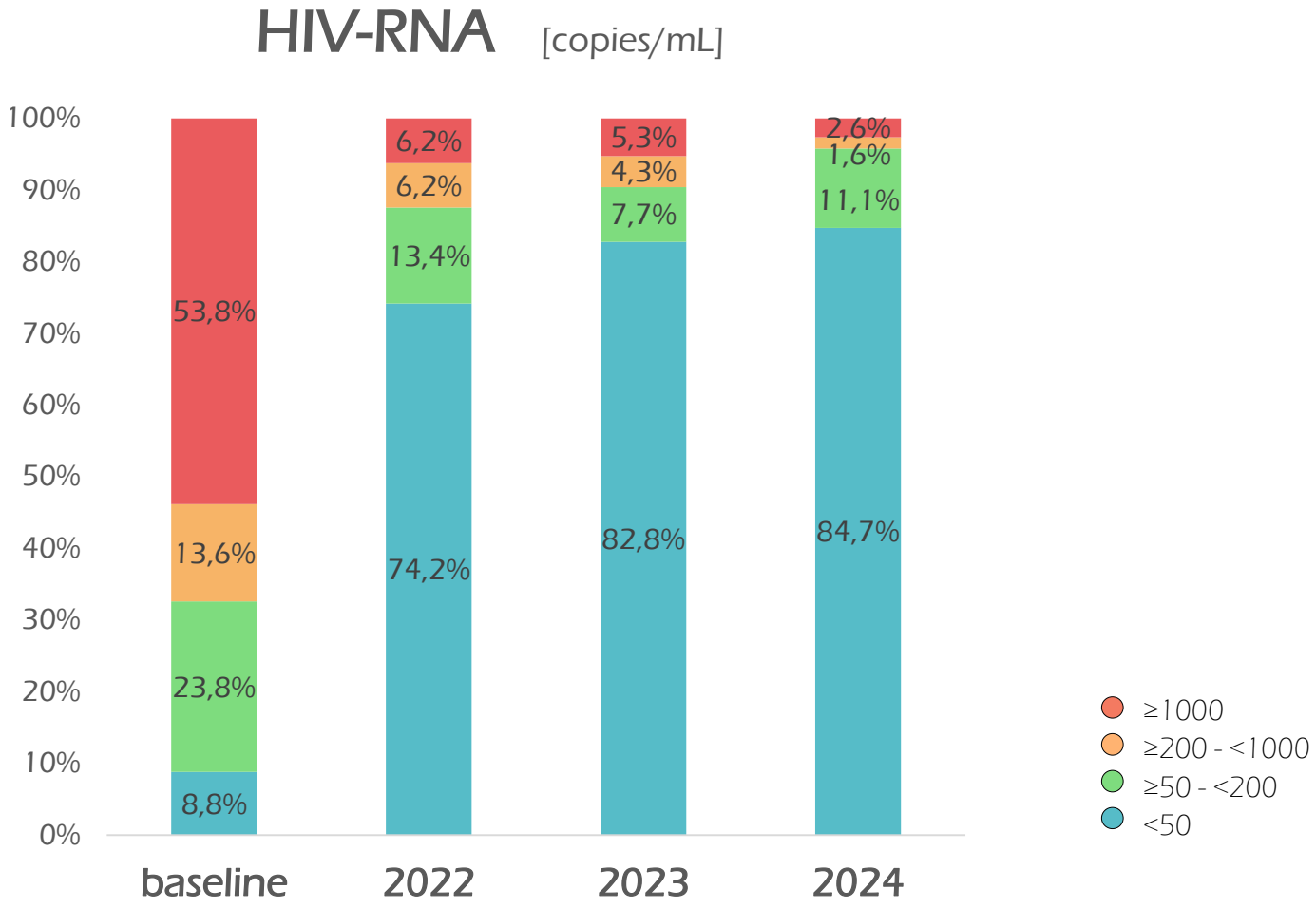
POSSIAMO OTTIMIZZARE IL PAZIENTE HTE? IL PUNTO DI VISTA DEL CLINICO

Vincenzo Spagnuolo

FINANCIAL DISCLOSURES

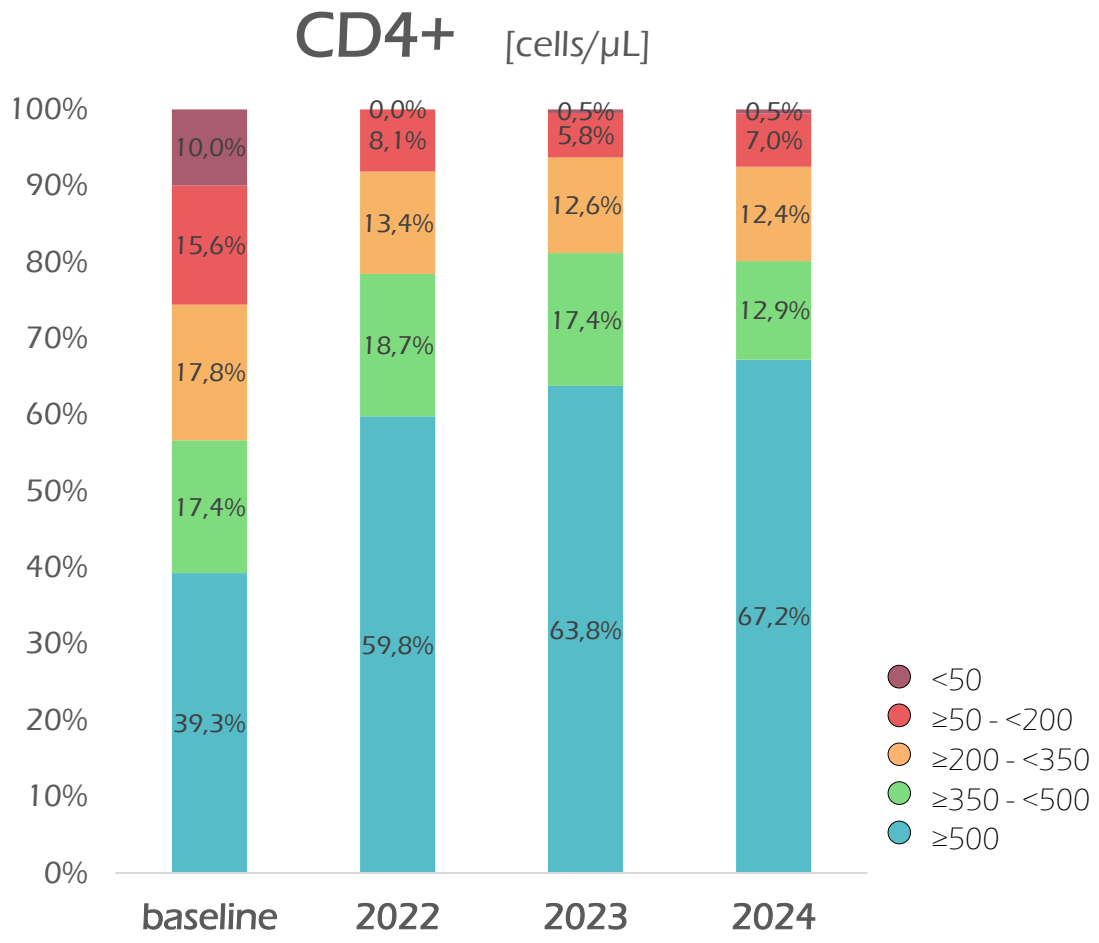
- Speakers' honoraria: Gilead Sciences, ViiV Healthcare and Merck Sharp and Dohme
- Advisory board: Gilead Sciences
- Research Grants: Gilead Sciences

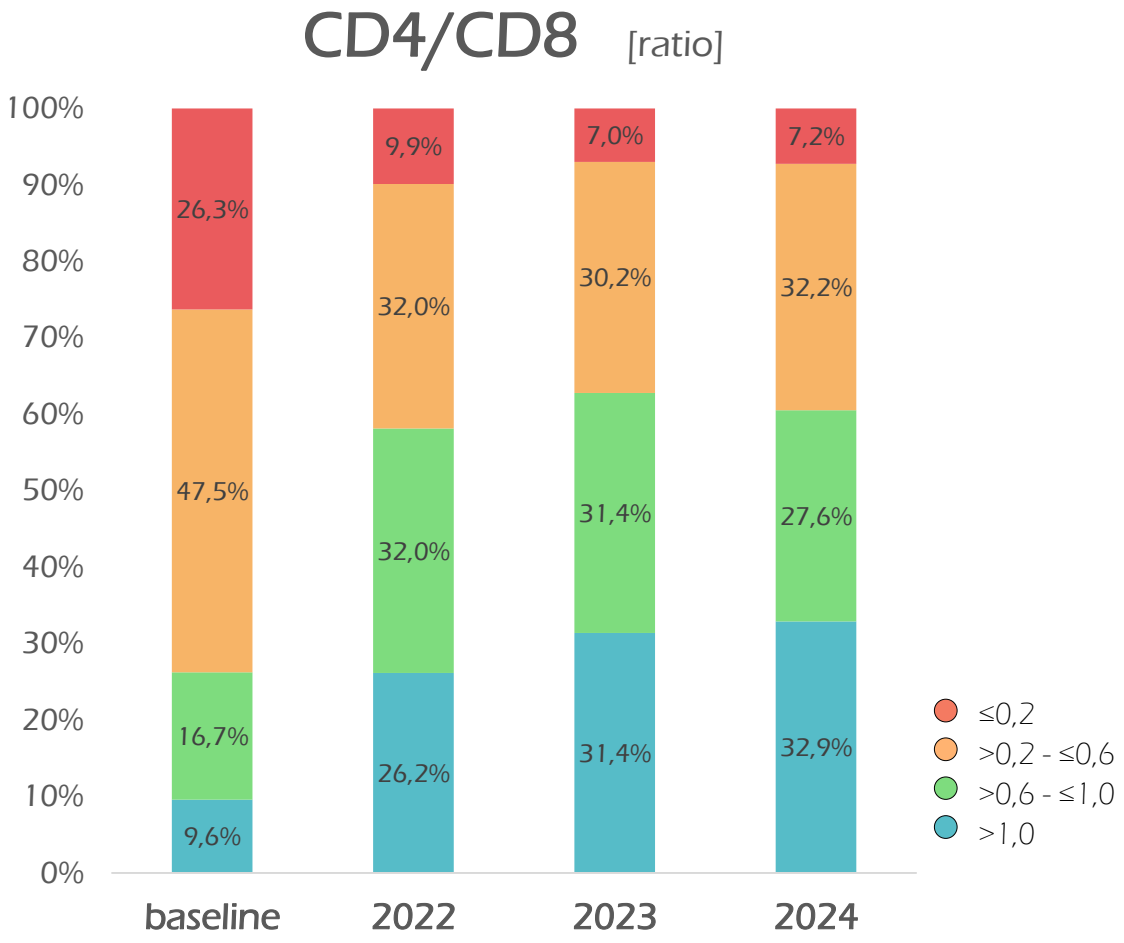
VIRAL LOAD



Data updated to May 1st, 2025

IMMUNOLOGICAL PROFILE





Data updated to May 1st, 2025

ANTIRETROVIRAL DRUGS PER YEAR

		2022 (n=224)	2023 (n=218)	2024 (n=216)
Drugs	DTG	172 (76,8%)	169 (77,5%)	161 (74,5%)
	DRV/r	81 (36,2%)	75 (34,4%)	70 (32,4%)
	DRV/c	73 (32,6%)	66 (30,3%)	64 (29,6%)
	XTC	118 (52,7%)	111 (50,9%)	113 (52,3%)
	TAF	81 (36,2%)	84 (38,5%)	87 (40,3%)
	TDF	20 (8,9%)	14 (6,4%)	13 (6,0%)
	DOR	37 (16,5%)	38 (17,4%)	38 (17,6%)
	ETV	24 (10,7%)	19 (8,7%)	18 (8,3%)
	RPV	15 (6,7%)	12 (5,5%)	10 (4,6%)
	MVC	45 (20,1%)	42 (19,3%)	41 (19,0%)
	FTR	20 (8,9%)	36 (16,5%)	41 (19,0%)
	LEN	8 (3,6%)	7 (3,2%)	14 (6,5%)
	IBA	7 (3,1%)	5 (2,3%)	5 (2,3%)
	ISL	2 (0,9%)	2 (0,9%)	2 (0,9%)
	ENF	2 (0,9%)	0 (0,0%)	0 (0,0%)

Data updated to May 1st, 2025

HOW TO SIMPLIFY?

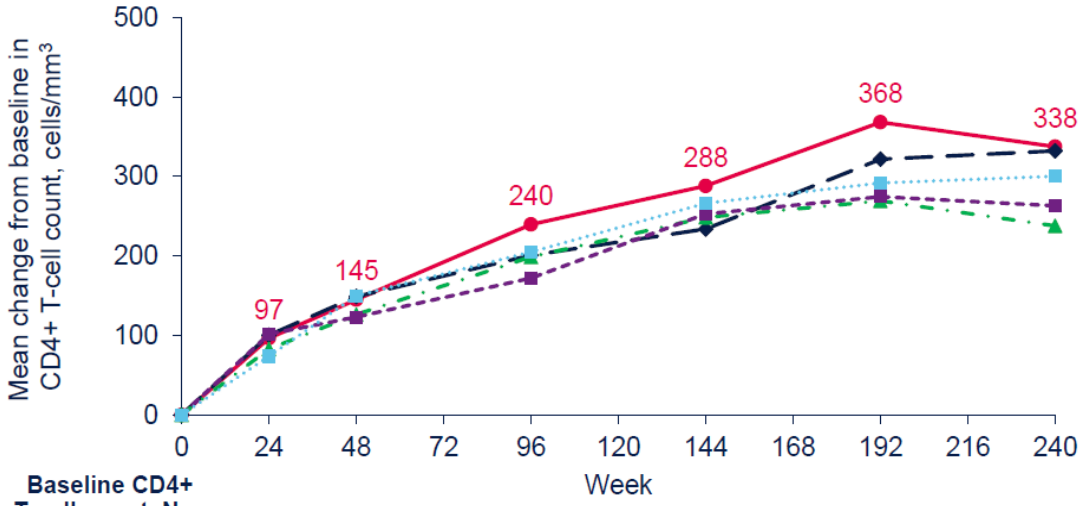
Is there a necessity for all these drugs?

Is the drug that I am going to stop or switch fully active and have a high genetic barrier?

Should I consider a drug with a new mechanism of action?

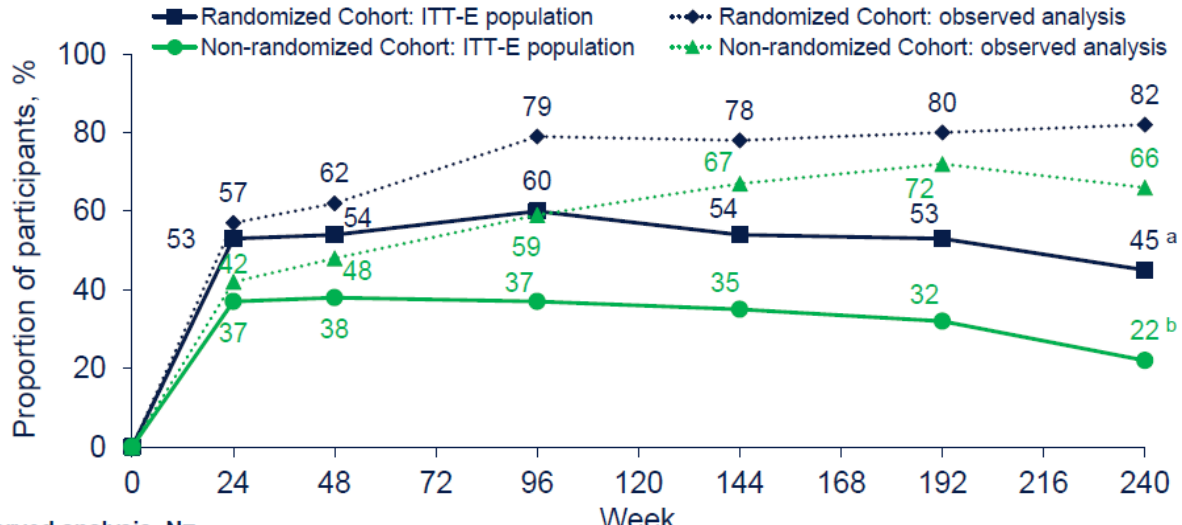
BRIGHTE STUDY: WEEK 240 EFFICACY AND IMMUNOLOGICAL RECOVERY

Figure 5. Change in CD4+ T-Cell Count From Baseline to Week 240 by Baseline CD4+ T-Cell Count (Randomized Cohort, Observed Analysis)



Baseline CD4+ T-cell count, N=						
<20 (n=72)	64	58	54	49	47	33
20 to <50 (n=25)	24	20	17	18	15	13
50 to <100 (n=39)	34	30	26	26	24	16
100 to <200 (n=63)	59	57	52	47	40	32
≥200 (n=73)	67	63	64	57	53	45

Figure 3. HIV-1 RNA <40 c/mL Through Week 240 by Snapshot Analysis (ITT-E) and Observed Analysis



Observed analysis, N=						
Randomized Cohort	247	233	214	206	195	164
Non-randomized Cohort	89	83	66	57	50	35

ITT-E participants without an HIV-1 RNA value at the relevant time point or those who changed OBT due to lack of efficacy up to each time point counted as failures. [a]ITT-E population, N=267. [b]ITT-E population, N=92.

Poster P061; HIV Drug Therapy Glasgow; October 23-26, 2022

WEEK 96 GENOTYPIC AND PHENOTYPIC RESULTS OF THE FOSTEMSAVIR PHASE 3 BRIGHTE STUDY IN HEAVILY TREATMENT-EXPERIENCED ADULTS LIVING WITH MULTIDRUG-RESISTANT HIV-1.

TABLE 3 Treatment-emergent genotypic changes among participants meeting PDVF criteria at Week 96[a]

Cohort	Randomized Cohort (N = 272)	Non-randomized Cohort (N = 99)
Participants meeting PDVF, *n* (%)	63 (23)	49 (49)
gp160 sequenced, *n*[b]	50	44
Treatment-emergent predefined amino acid substitutions in gp120, *n* (%)[c]		
None	26 (52)	11 (25)
Any	24 (48)	33 (75)
S375H/I/M/N/T	15 (30)	22 (50)
S375H	0	1 (2)
S375H/N	1 (2)[d]	1 (2)
S375M	0	3 (7)
S375N	7 (14)	8 (18)
S375N/T	1 (2)	2 (5)
S375S/I	0	1 (2)
S375S/M/T	1 (2)	0
S375S/N	4 (8)	6 (14)
S375S/T	1 (2)	0
M426L	16 (32)	21 (48)
M426L	10 (20)	13 (30)
M426M/L	7 (14)	8 (18)
M434I	5 (10)	4 (9)
M434I	1 (2)	1 (2)
M434M/I	4 (8)	3 (7)
M434M/I/T	1 (2)	0
M475I	6 (12)	5 (11)
M475I	4 (8)	1 (2)
M475M/I	2 (4)	4 (9)

[a]PDVF, protocol-defined virologic failure.
[b]Most missing genotypic data were the result of assay failure, usually because of low HIV-1 RNA levels.
[c]Predefined amino acid substitutions in gp120 are S375H/I/M/N/T, M426L/P, M434I/K, and M475I; M426P and M434K were not present in any baseline or on-treatment samples from this study population. Numbers include mixtures. The denominator is the number of participants with gp120 sequenced at baseline and on treatment. For each participant, results at additional on-treatment time points around the time of PDVF are included where available (not limited to only the PDVF time point).
[d]Only S375H was emergent; S375N was present at baseline.

Antimicrob Agents Chemother. 2022 Jun 21;66(6):e0175121

Table 3. Virologic outcomes

	Suppressed & High CD4 (VL <50, CD4 ≥350)	Suppressed & Low CD4 (VL <50, CD4 <350)	Viremic & High CD4 (VL ≥50, CD4 ≥350)	Viremic & Low CD4 (VL ≥50, CD4 <350)
6 months, N [a]	**29**	**20**	**40**	**39**
Viral load <50 copies/mL, n (%)	24 (83%)	18 (90%)	19 (48%)	12 (31%)
Median viral load change (IQR)	NA	NA	-100 (-745, -10)	-240 (-114, 713)
12-months, N [b]	**14**	**11**	**29**	**30**
Viral load <50 copies/mL, n (%)	9 (64%)	11 (100%)	15 (52%)	10 (33%)
Median viral load change (IQR)	NA	NA	-90 (-790, -20)	-335 (-14031, 2330)

IQR, interquartile range; mL, milliliters; N, number; VL, viral load
[a] Measured 91 to 270 days after FTR start
[b] Measured 271 to 455 days after FTR start

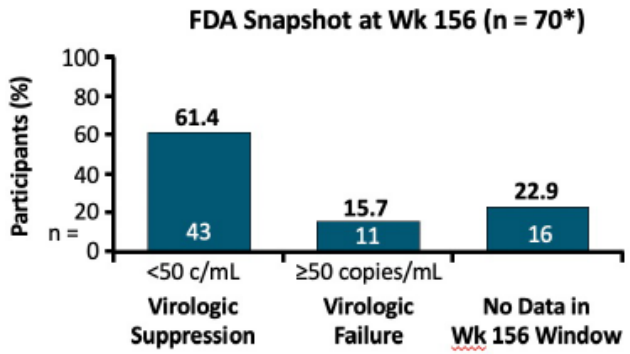
Table 4. Immunologic outcomes

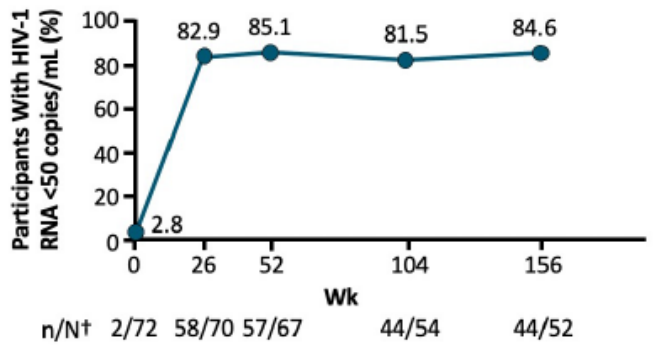
	Suppressed & High CD4 (VL <50, CD4 ≥350)	Suppressed & Low CD4 (VL <50, CD4 <350)	Viremic & High CD4 (VL ≥50, CD4 ≥350)	Viremic & Low CD4 (VL ≥50, CD4 <350)
6 months, N	**27**	**20**	**40**	**40**
CD4 ≥500 cells/μL, n (%)	16 (59%)	0 (0%)	23 (58%)	0 (0%)
CD4% ≥29%	13 (48%)	≤5 (≤25%)[a]	15 (38%)	0 (0%)
Median CD4% change (IQR)	-0.7 (-4.0, 3.0)	1.0 (-0.3, 2.8)	1.1 (-3.2, 3.7)	0.0 (-1.0, 2.7)
Mean CD4% change (SD)	-1.1 (5.4)	1.3 (2.6)	0.6 (5.3)	0.6 (3.3)
12-months, N	**14**	**10**	**28**	**30**
CD4 ≥500 cells/μL, n (%)	7 (50%)	≤5 (≤50%)[a]	12 (43%)	0 (0%)
CD4% ≥29%	6 (43%)	≤5 (≤50%)[a]	9 (32%)	0 (0%)
Median CD4% change (IQR)	0.0 (-2.4, 4.6)	1.9 (1.3, 3.9)	0.5 (-1.2, 3.4)	0.1 (-1.3, 2.8)
Mean CD4% change (SD)	-0.2 (5.7)	2.5 (1.7)	0.8 (4.7)	0.8 (3.7)

IQR, interquartile range; mL, milliliters; N, number; VL, viral load
[a] Measured 91 to 270 days after FTR start
[b] Measured 271 to 455 days after FTR start

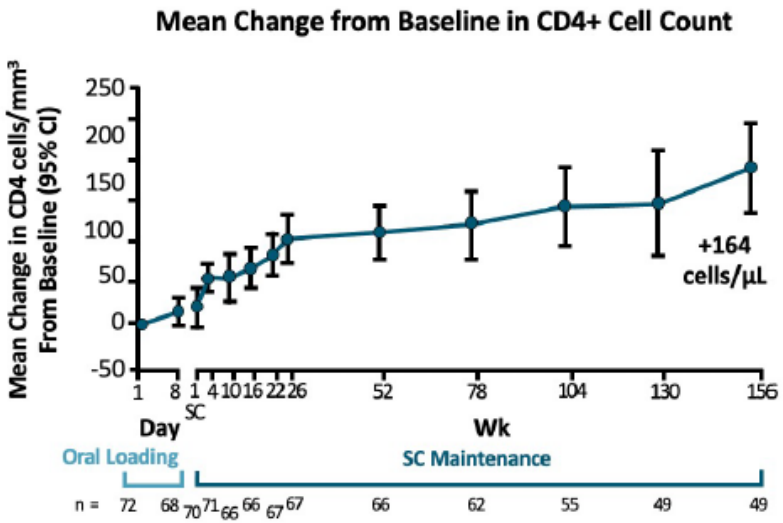
Hsu et al. 2025

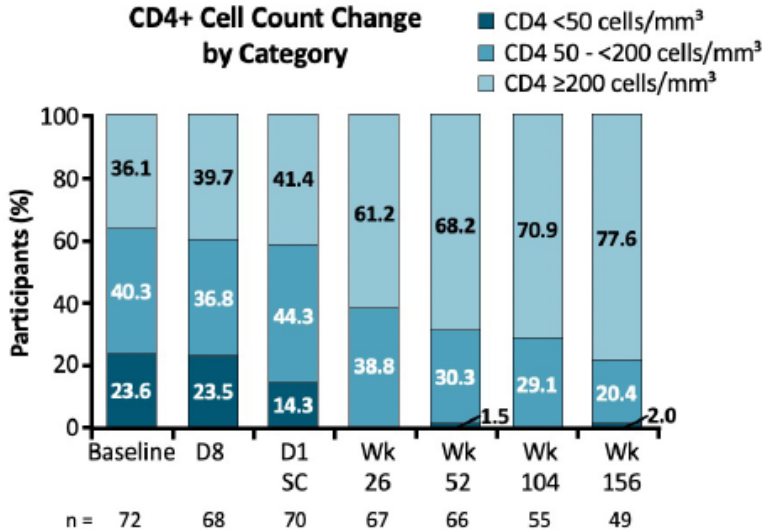
CAPELLA study - Week 156 results





*2 participants excluded (missing HIV-1 RNA at Wk 156 but completed study before reaching upper limit of analysis window).
†Denominator for percentages is number of persons with nonmissing HIV-1 RNA values at each time point.





Ogbuagu. IDWeek 2024. Abstr 155. Reproduced with permission.

Slide credit: clinicaloptions.com

Resistance Analysis Population and Emerging LEN RAMs at Week 104

- Genotypic/phenotypic analyses (capsid, protease, RT, integrase) performed at virologic failure*

Category, n (%)	CAPELLA (N=72)
Resistance analysis population	**27** (38)
LEN RAM emergence	**14** (19)
M66I	6 (8)
Q67H/K/N	8 (11)
K70H/N/R/S	7 (10)
N74D/H/K	3 (4)
A105T/S	4 (6)
T107A/C/N/S	3 (4)
No LEN RAM emergence	**13** (18)

- Plasma OBR drug concentrations quantification (LC-MS/MS methods)
  - DRV, DTG, TAF/TFV, FTC

*Virologic failure defined as confirmed rebound ≥50 copies/mL or <1 $\log_{10}$ decline from baseline at Week 4. Resistance assays conducted at Monogram Biosciences.
DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LEN, lenacapavir; OBR, optimized background regimen; RAM, resistance-associated mutation; RT, reverse transcriptase; TAF, tenofovir alafenamide; TFV, tenofovir.

Margot N et al. Oral PS8 O4; EACS 2023, Warsaw

CAPELLA study - Resistance analysis

- 14 participants developed emergent LEN resistance (9 participants by Wk 52, 5 participants between Wk 52 and 104, none between Wk 104 and 156)
  - Mutations: M66I; Q67H/K/N; K70H/N/R/S; N74D/H/K; A105S/T; T107A/C/N/S
  - 2 participants with earlier resistance developed additional mutations
    - 1 participant with emergent K70R+T107N with existing Q67H: LEN susceptibility reduced from 4.5- to 85-fold of WT
    - 1 participant with emergent T107T/N with existing K70N + N74K resulting: no LEN susceptibility data for triple mutant
  - All participants with no fully active drugs in OBR or inadequate OBR adherence
  - Median change in CD4+ cell count change: 82 cells/mm³ (IQR: 48-399 cells/mm³)

Characteristic, n	Total Population (N = 72)
OBR	
▪ No fully active agents in OBR	4
▪ Inadequate adherence to OBR*	10
Resuppressed after LEN resistance emergence while continuing LEN	5
▪ With OBR change	2
▪ Without OBR change	3
Not resuppressed after LEN resistance emergence	9
▪ Continued LEN†	6
▪ Discontinued LEN for reasons unrelated to efficacy (death, nonadherence, LTFU)	3

*Based on OBR plasma concentrations. †Returned to baseline HIV-1 RNA (n = 2), HIV-1 RNA >1 log reduction (n = 3); mean HIV-1 RNA log reduction from Day 1 for the 4 participants who did not return to baseline: -1.64.

Slide credit: clinicaloptions.com

Igbuagu. IDWeek 2024. Abstr 155.

Patient Clones and Site-Directed Mutants						
#	Genotype				RC (%)[a]	LEN FC[a]
A.	M66I				0.6	>869.0
B.	M66I	A105T			1.2	>869.0
C.	M66I				1.5	>869.0
D.	M66I	Q67H	K70R		3.1	>869.0
E.	M66I				12.0	>869.0
F.	M66I	T107S			24.0	>869.0
G.	M66I	K70S			*AF*	*AF*
H.	A105T				*AF*	*AF*
I.	K70R				9.7	1.2
J.	K70H				9.8	154.2
K.	K70H				37	84.8
L.	K70S				*AF*	*AF*
M.	N74D				49.0	17.0
N.	Q67H				58.0	4.8
O.	Q67H	K70R	T107S		109.0	46.3

Margot N, et al. *EACS 2023* (Abs. PS8.O4)

DELFINO Study

Doravirine + Lenacapavir + Fostemsavir
in PWH enrolled in the Prestigio Registry

A bPI, INSTI (and NRTI) sparing strategy to improve QOL

40 People with HIV-1:

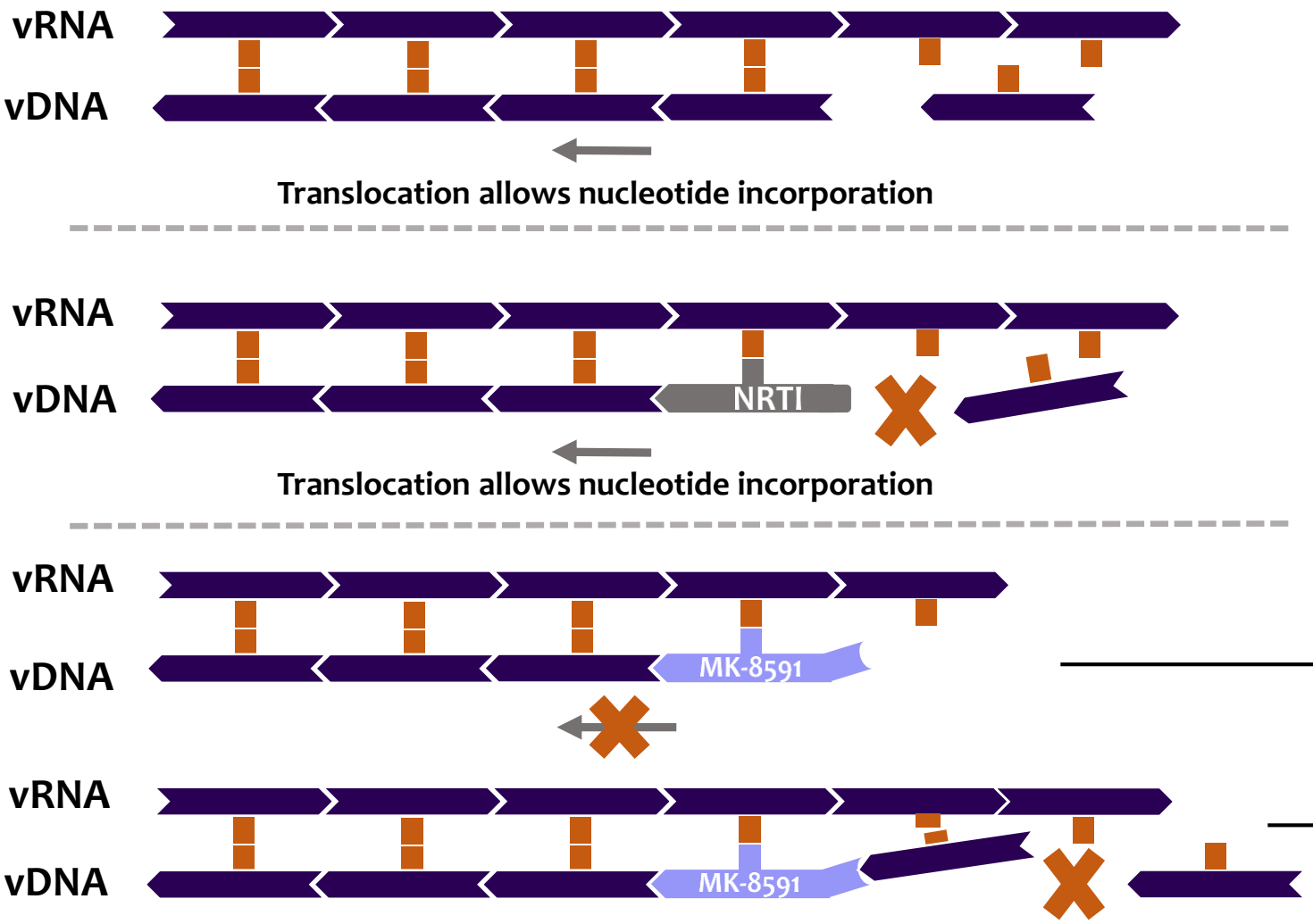
- age ≥18 years
- Enrolled in PRESTIGIO Registry
- Need to change ART
- non-CRF_01AE strain
- HBsAg negative
- no previous exposure to LEN- and/or FTR-containing regimens
- Susceptibility to DOR (Stanford score <15)

→ DOR + LEN + FTR

Primary endpoint HIV-RNA < 50 copies/mL at 26 weeks

ISLATRAVIR: The first NRTTI (Nucleoside Reverse Transcriptase Translocation Inhibitor)

Acosta-Hoyas AJ, et al. *Viruses*. 2010;2(2):372-394.
Arts EJ, et al. *Cold Spring Harb Perspect Med*. 2012;2(4):a00761.
Iyidogan P, et al. *Viruses*. 2014;6(10):4095-4139.
Michailidis E, et al. *J Biol Chem*. 2014;289(35):24533-24548.



Normal HIV Replication
Next nucleotide incorporates into the vDNA and continues to build the vDNA chain

NRTI: Single mechanism of action
Following translocation, the NRTI is incorporated into the vDNA, blocking the next nucleotide from attaching, which RESULTS IN CHAIN TERMINATION

MK-8591 (NRTTI): Multiple mechanisms of action
TRANSLOCATION BLOCKED
MK-8591 is incorporated into the vDNA preventing nucleotide binding and incorporation. This results in IMMEDIATE CHAIN TERMINATION

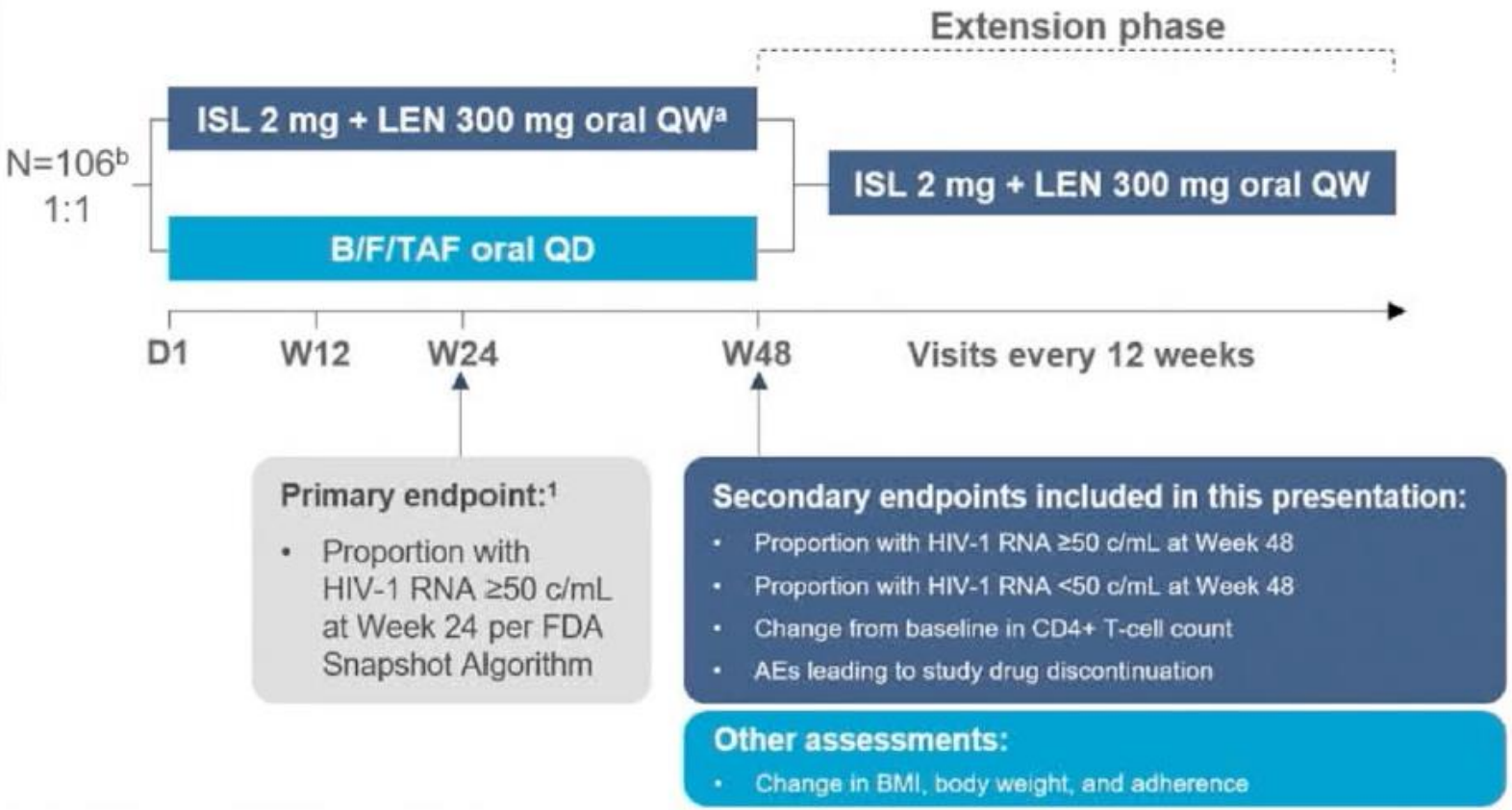
In the event that tanslocation does occur and additional nucleotides are incorporated, MK-8591 causes structural change to vDNA resulting in DELAYED CHAIN TERMINATION

Grobler J et al. Efficacy of MK-8591 against diverse HIV-1 subtypes and NRTI-resistant clinical isolates; HIV Glasgow 28-31 October 2018

ISL+LEN: a phase II trial - Week 48 results

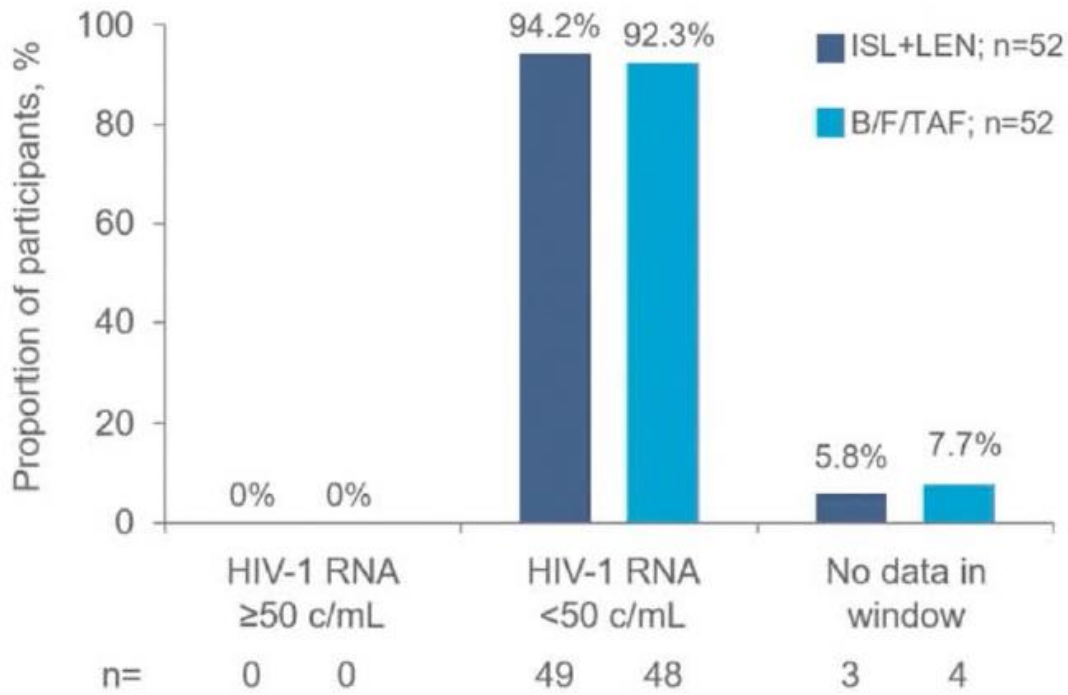
Eligibility criteria

- Aged ≥18 years
- On B/F/TAF for >6 months
- HIV-1 RNA <50 c/mL for >6 months
- No history of virologic failure
- CD4+ T-cell count ≥350 cells/µl
- Lymphocyte count ≥900 cells/µl
- No HBV infection



Colson A, et al. *HIV Glasgow 2024* (Abs. O21)

ISL+LEN: a phase II trial - Week 48 results



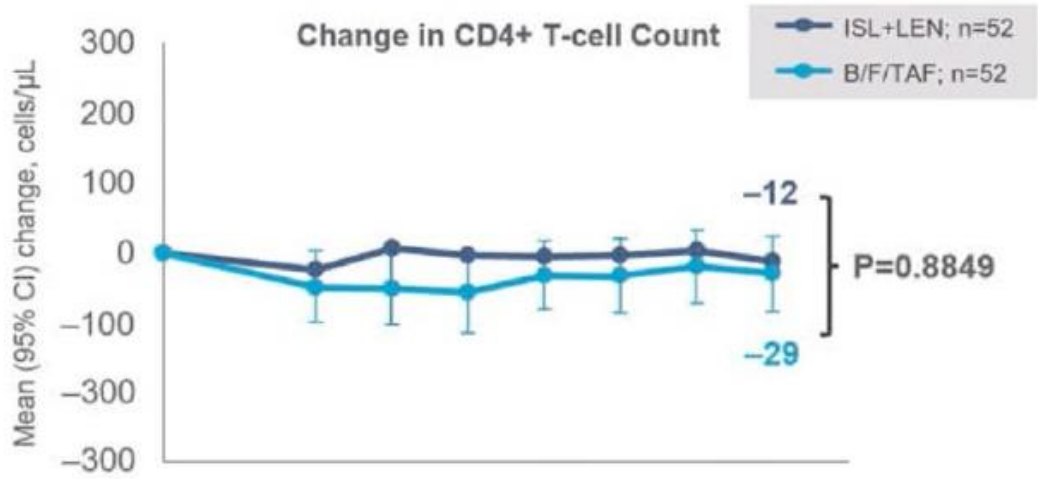
Visit	HIV-1 RNA (c/mL)
Screening	<50
Day 1	251
Week 24	64
Week 30	<50

- Adequate plasma ISL and LEN levels
- No resistance selection

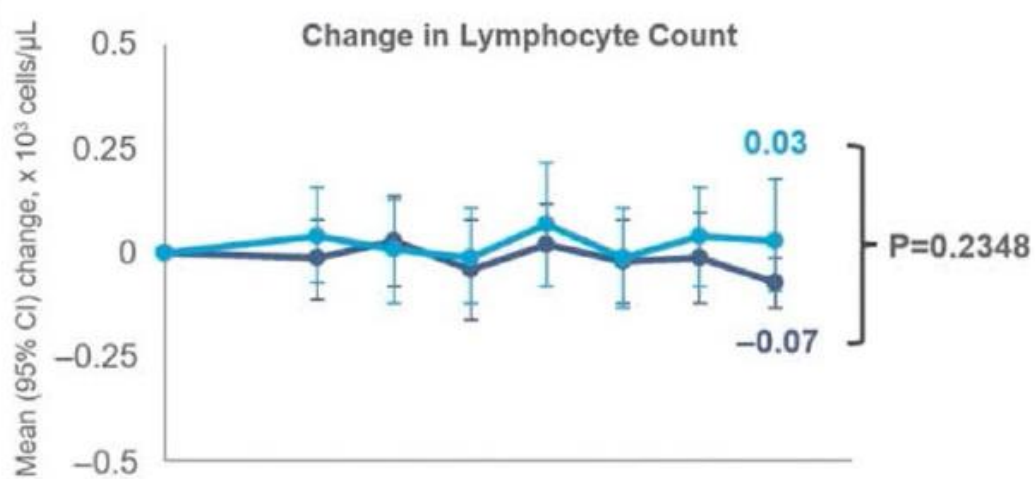
Colson A, et al. *CROI 2024* (Abs. 208)

Colson A, et al. *HIV Glasgow 2024* (Abs. O21)

ISL+LEN: a phase II trial - Week 48 results



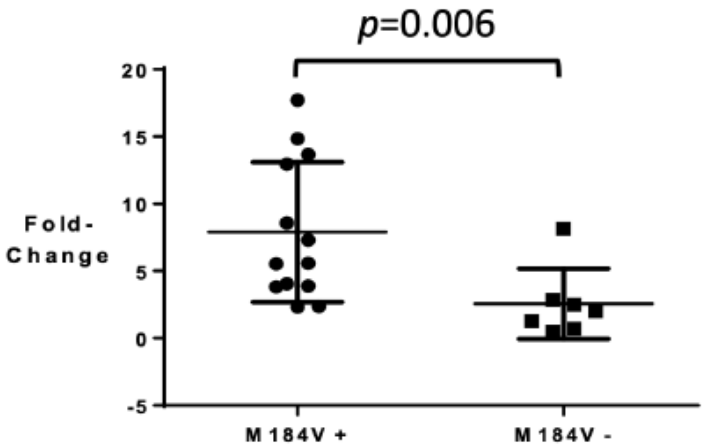
Mean Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	755	732	766	755	754	756	761	746
B/F/TAF	818	758	767	761	785	783	797	787

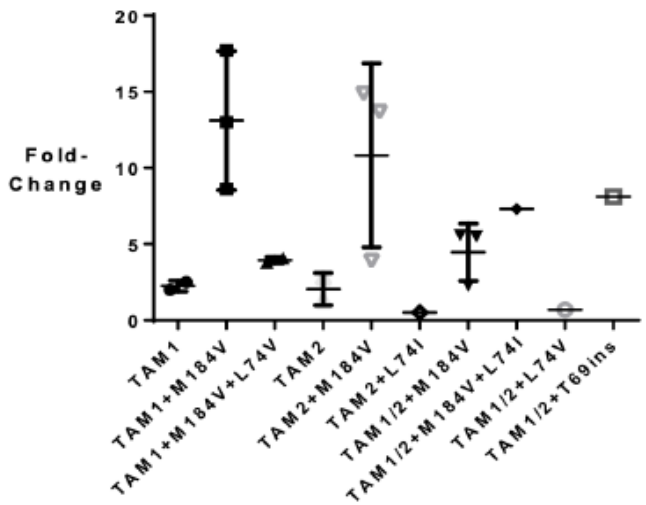


Mean Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	1.94	1.94	1.98	1.92	1.96	1.94	1.93	1.88
B/F/TAF	1.95	1.99	1.97	1.96	2.03	1.96	2.00	1.99

Colson A, et al. *HIV Glasgow 2024* (Abs. O21)

ISL susceptibility in MDR-PWH





NRTI RAMs	NNRTI RAMs	IC_{50} Fold Change		Predicted susceptibility	Phenotypic susceptibility
		TAF	ISL	TAF	TAF
M41L, M184V, L210W, T215Y	none	2.7	6.8	I	I
M41L, D67G, S68G, K70R, L74I, M184V, T215Y, K219E	A98G, K103N, Y181C, P225H	3.9	7.3	I	I
K70Q, M184MV, T215F	E138Q, V179E, Y181C	1.0	3.9	LLR	S
M41L, M184V, T215Y	V106I, Y188L, K238N	2.4	22.6	LLR	I
K65R, Y115F, M184V	Y181C, H221Y, M230I	7.7	2.4	R	R
D67N, K70R, M184V, T215F, K219Q	A98G	2.6	13.7	I	I
M41L, E44D, L74V, M184V, L210W, T215Y, K219N	L100I, E138R, V179L	1.6	3.8	R	I
K65R, D67G, M184V, K219Q	none	4.9	3.4	I	R
M41L, E44D, D67N, T69D, M184V, L210W, T215Y, K219KR	K103N, Y181I	4.9	8.0	R	R
M41L, E44D, D67N, K70Q, V75M, F77L, M184I, L210W, T215Y, K219R	E138A, G190A	4.2	37.8	R	R
M41L, A62AV, D67N, K70G, V75I, M184MV, L210W, T215Y, K219Q	K101E, Y181C, G190A	3.3	2.3	R	I
D67G, S68G, K70R, M184V, T215F, K219E	Y188L	0.5	8.9	I	S
M184V	none	1.2	9.0	S	S
M41L, S68G, M184V, L210W, T215C, K219E	Y181I	0.5	5.5	LLR	S
M41L, M184V, L210W, T215Y, K219E	K101E, E138A, G190Q	4.5	9.8	I	R

Gianmarino F, et al. *European Meeting on HIV and Hepatitis 2020* (Abs. 28)
Bartolini N, et al. *ICAR 2024* (Abs. SC27)

Efficacy and Safety of Lenacapavir, Teropavimab, and Zinlirvimab: Phase 2 Week 26 Primary Outcome

Onyema Ogbuagu[1*], Aditya Gaur[2], James H. McMahon[3], Linda Gorgos[4], Javier O. Morales-Ramirez[5], Kimberly Workowski[6], Jason Brunetta[7], Kwad Mponponsuo[8], Sean E. Collins[8], Laurie A. VanderVeen[8], Hailin Huang[8], Jared Baeten[8], Joseph Eron[9]

[1]Yale School of Medicine, New Haven, CT, USA; [2]St. Jude Children's Research Hospital, Memphis, TN, USA; [3]The Alfred Hospital and Monash University, Melbourne, Australia; [4]AXCES Research Group, Santa Fe, NM, USA; [5]Clinical Research Puerto Rico Inc., San Juan, Puerto Rico; [6]Department of Medicine, Emory University, Atlanta, GA, USA; [7]Maple Leaf Medical Clinic, Toronto, ON, Canada; [8]Gilead Sciences, Inc., Foster City, CA, USA; [9]University of North Carolina, Chapel Hill, NC, USA.

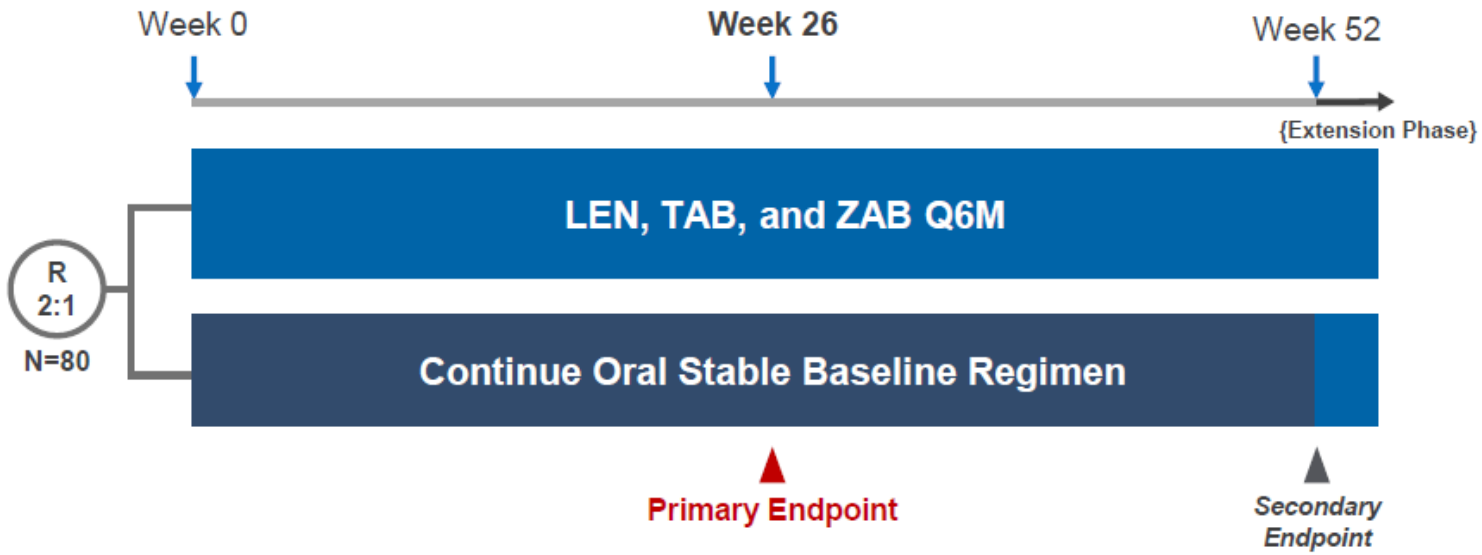
*Presenting author

32nd Conference on Retroviruses and Opportunistic Infections (CROI), March 9–12, 2025, San Francisco, California, USA

Phase 2 Study Design[a]

Key inclusion criteria

- Age 18–65 years
- HIV-1 RNA <50 copies/mL for ≥12 months
- On stable oral ART (≤2 classes) for ≥12 months
- CD4+ T-cell count ≥200 cells/µL
- HBV negative
- Highly susceptible to **both** bNAbs (IC_{90} ≤2 µg/mL)[b]

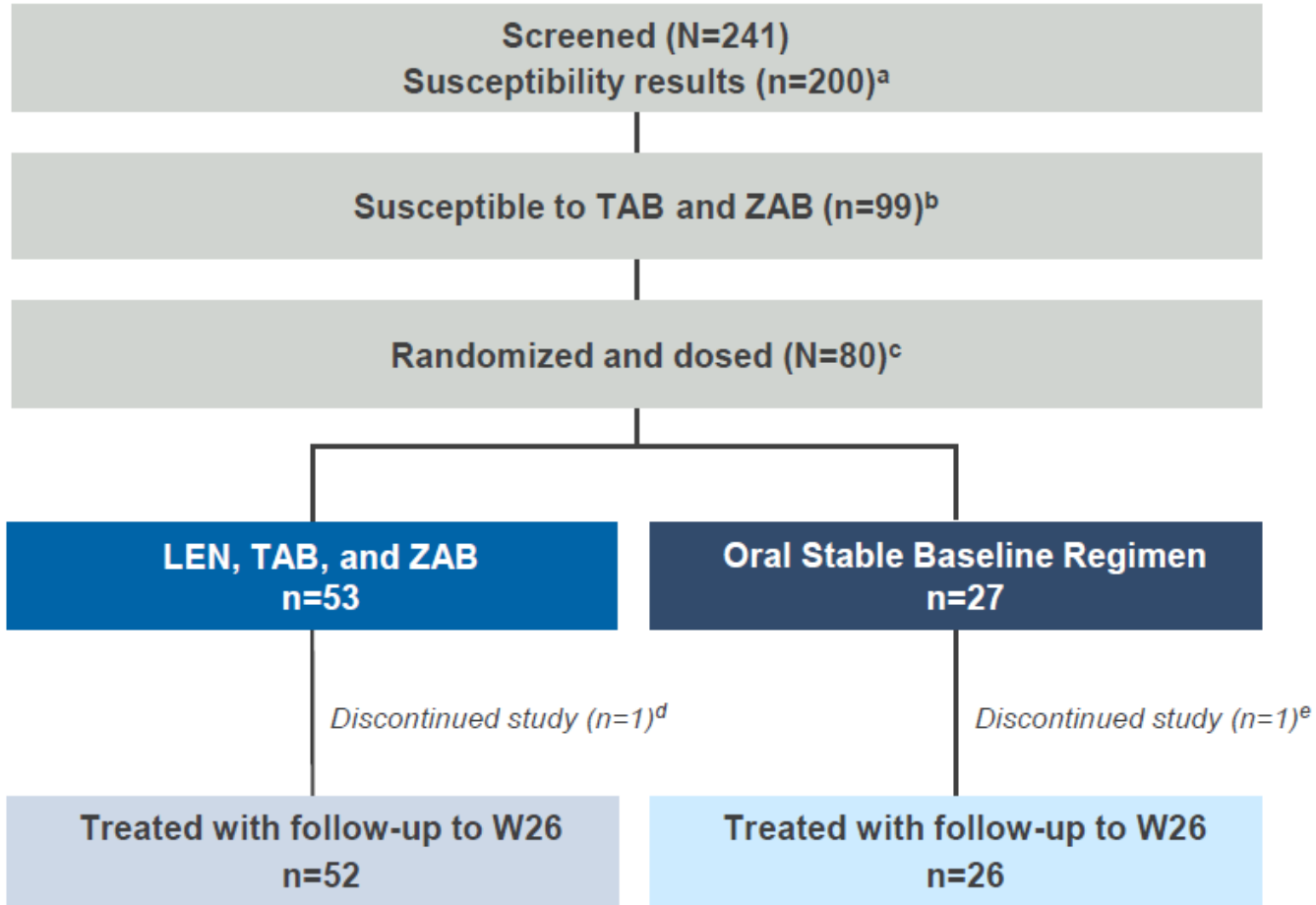


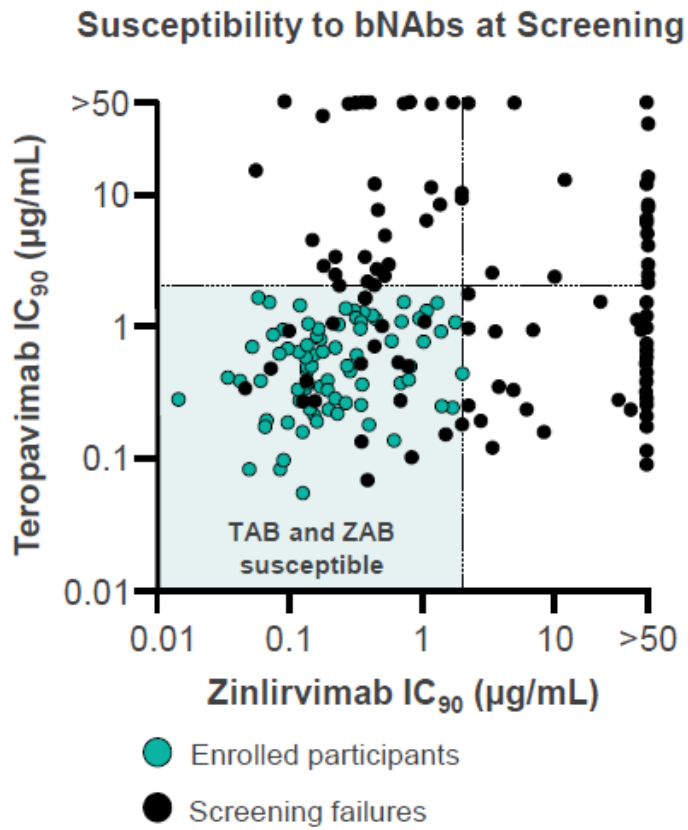
Primary Outcome (Efficacy): HIV-1 RNA ≥50 copies/mL at Week 26 per FDA snapshot algorithm

Secondary Outcomes: Safety (adverse events); change from baseline in CD4+ T-cell count, PK of LEN, TAB, and ZAB; anti-drug antibodies (ADAs) at Week 26

[a]NCT05729568. [b]By PhenoSense® mAb Assay (Monogram Biosciences).
ADAs, anti-drug antibodies; **ART**, antiretroviral therapy; **bNAb**, broadly neutralizing antibody; **HBV**, hepatitis B virus; **IC_{90}**, 90% inhibitory concentration; **LEN**, lenacapavir; **PK**, pharmacokinetics; **Q6M**, every 6 months; **R**, randomized; **TAB**, teropavimab; **ZAB**, zinlirvimab.

Participant Disposition and bNAb Susceptibility





[a]41 with assay failure, 195 with screening data and 5 with results from the Phase 1b study; [b]TAB only: 47 (24%); ZAB only: 31 (16%); neither: 23 (12%). [c]84 participants met all eligibility criteria; 1 eligible but not randomized (participant decision); 3 randomized but not dosed (participant decision). [d]Discontinued study drug and study due to investigator's discretion (relocation). [e]Discontinued oral stable baseline regimen and study due to adverse event (metastatic pancreatic carcinoma).

bNAb, broadly neutralizing antibody; **IC_{90}**, 90% inhibitory concentration; **LEN**, lenacapavir; **TAB**, teropavimab; **W**, week; **ZAB**, zinlirvimab.

Week 26 Virologic Outcomes (FDA Snapshot Algorithm)

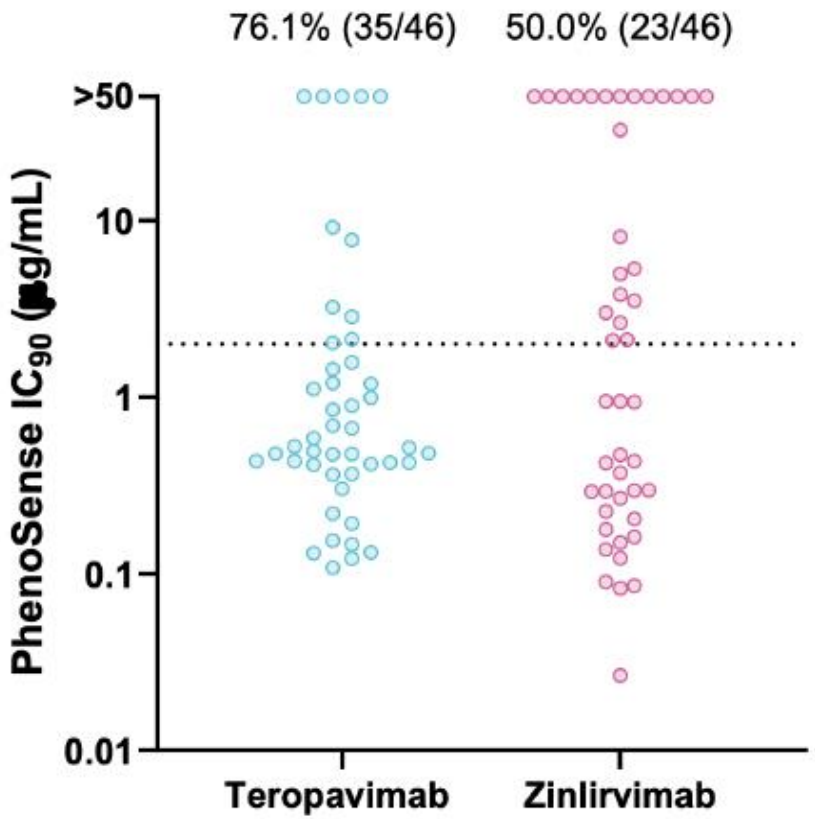
Participants, n (%)	LEN, TAB, and ZAB n=53	Oral Stable Baseline Regimen n=27
HIV-1 RNA ≥50 copies/mL	1 (1.9)	0
HIV-1 RNA <50 copies/mL	51 (96.2)	26 (96.3)
No virologic data in Week 26 window[a]	1[b] (1.9)	1[c] (3.7)

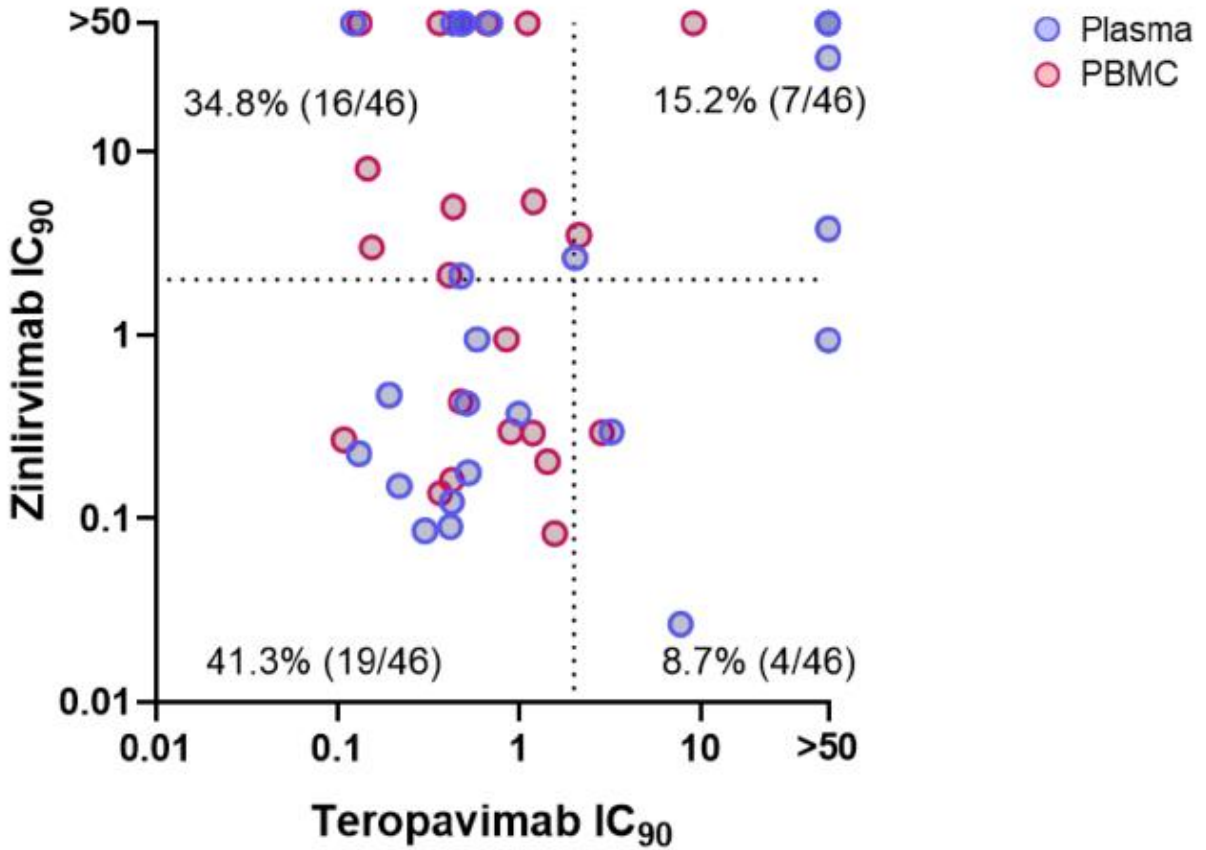
— Mean CD4+ T-cell counts increased at Week 26 in both treatment arms with no difference between groups (p=0.2)[d]

Efficacy of LEN, TAB, and ZAB at Week 26 was comparable to continuing daily oral ART

[a]Last available HIV-1 RNA was <50 copies/mL for both participants with no virologic data in the Week 26 window. [b]Discontinued study drug due to investigator's discretion (relocation). [c]Discontinued stable baseline regimen due to adverse event (metastatic pancreatic carcinoma). [d]The difference was calculated as the difference in least-squares means. Mean (SD) change: +23 (143) cells/μL in the LEN, TAB, and ZAB group and +69 (203) cells/μL in the stable baseline regimen group.
LEN, lenacapavir; **TAB,** teropavimab; **ZAB,** zinlirvimab.

TAB & ZAB susceptibility in MDR-PWH

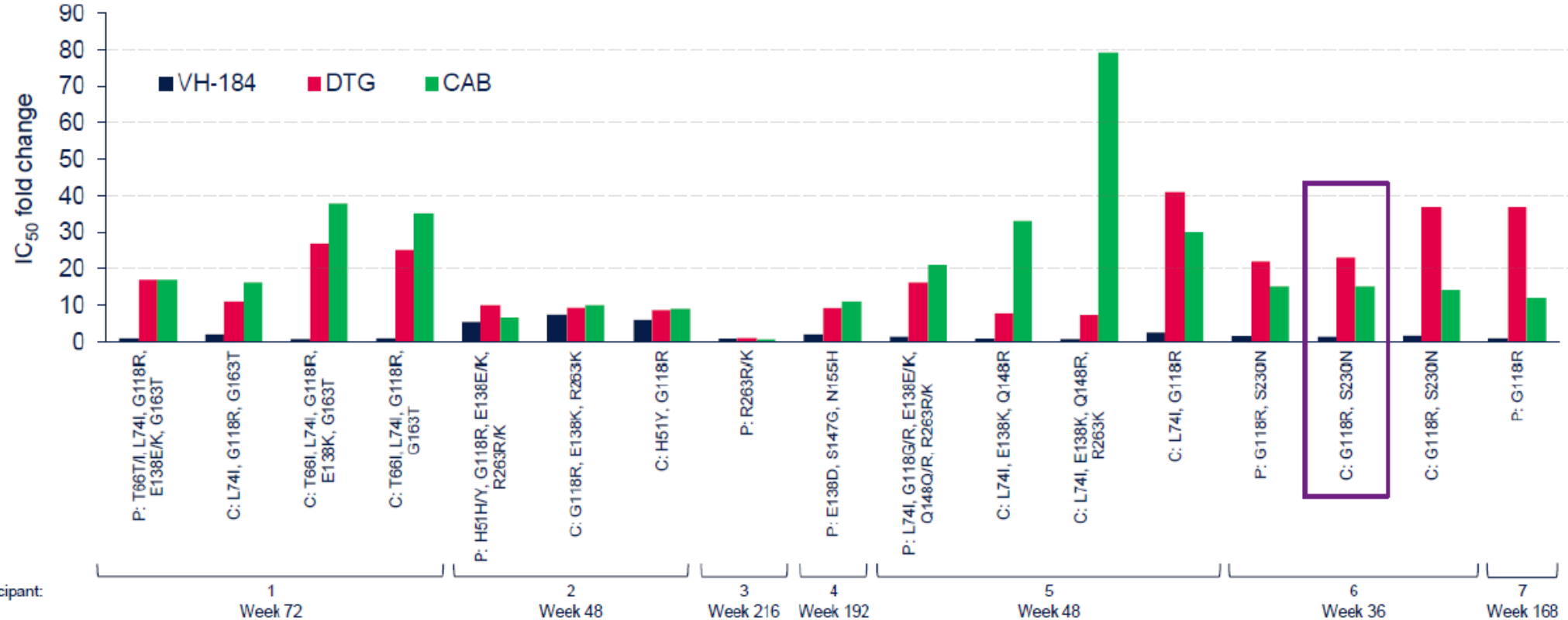




Spagnuolo V, et al. *CROI 2024* (Abs. 691)

VH-184 Demonstrated Potent Antiviral Activity Against DTG-Selected INSTI-Resistant Isolates

Antiviral activity of VH-184 against a panel of HIV-1 clinical isolate populations[a] and clonal variants[b] from 7 participants in the phase 3 DAWNING study



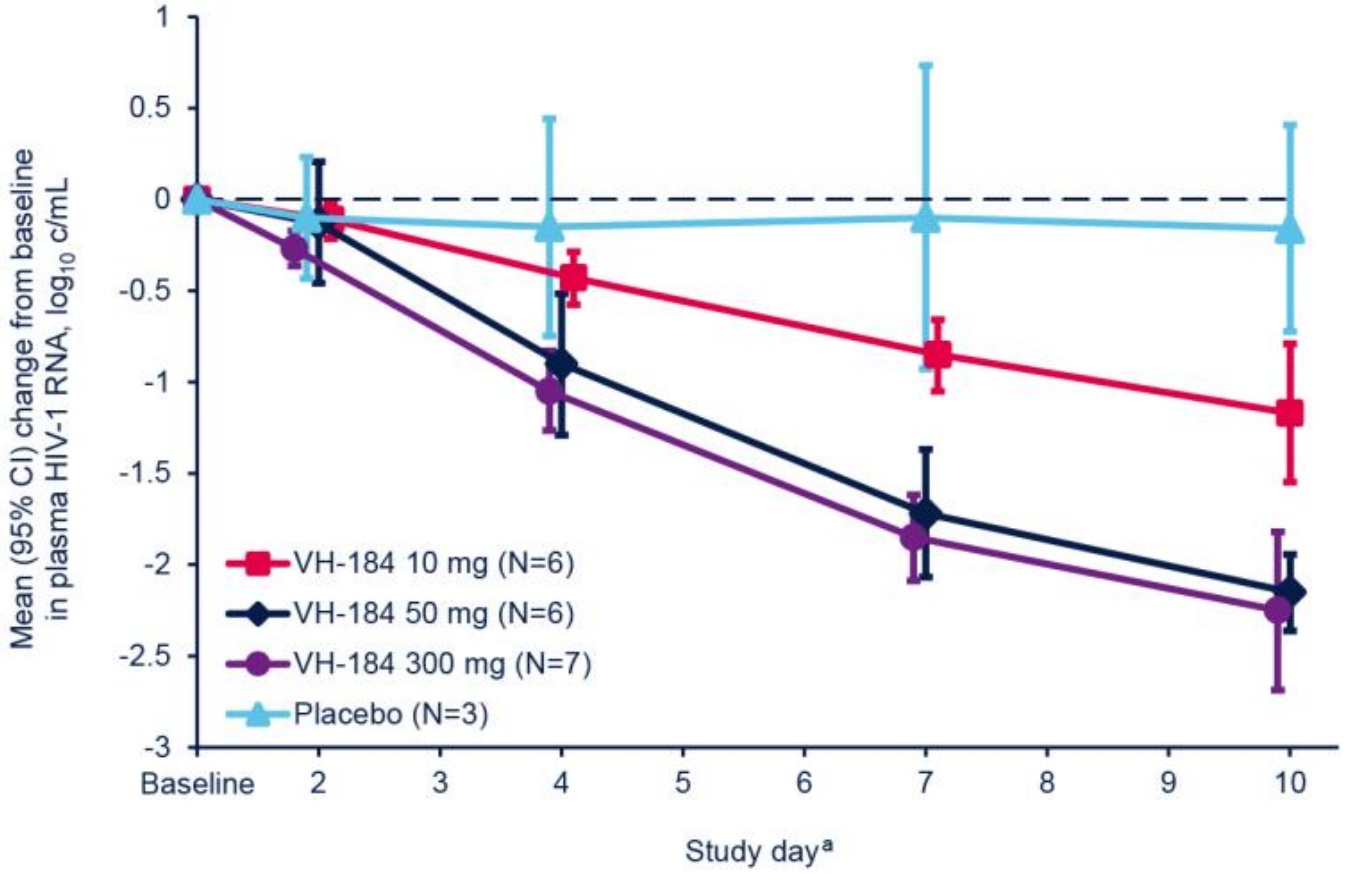
C, clonal variant; CAB, cabotegravir; DTG, dolutegravir; IC_{50}, half-maximal inhibitory concentration; INSTI, integrase strand transfer inhibitor; P, population; VH-184, VH4524184.

[a]Indicated with a "P" along the x-axis. [b]Indicated with a "C" along the x-axis.

Underwood et al. *Antimicrob Agents Chemother*. 2022;66:e0164321.

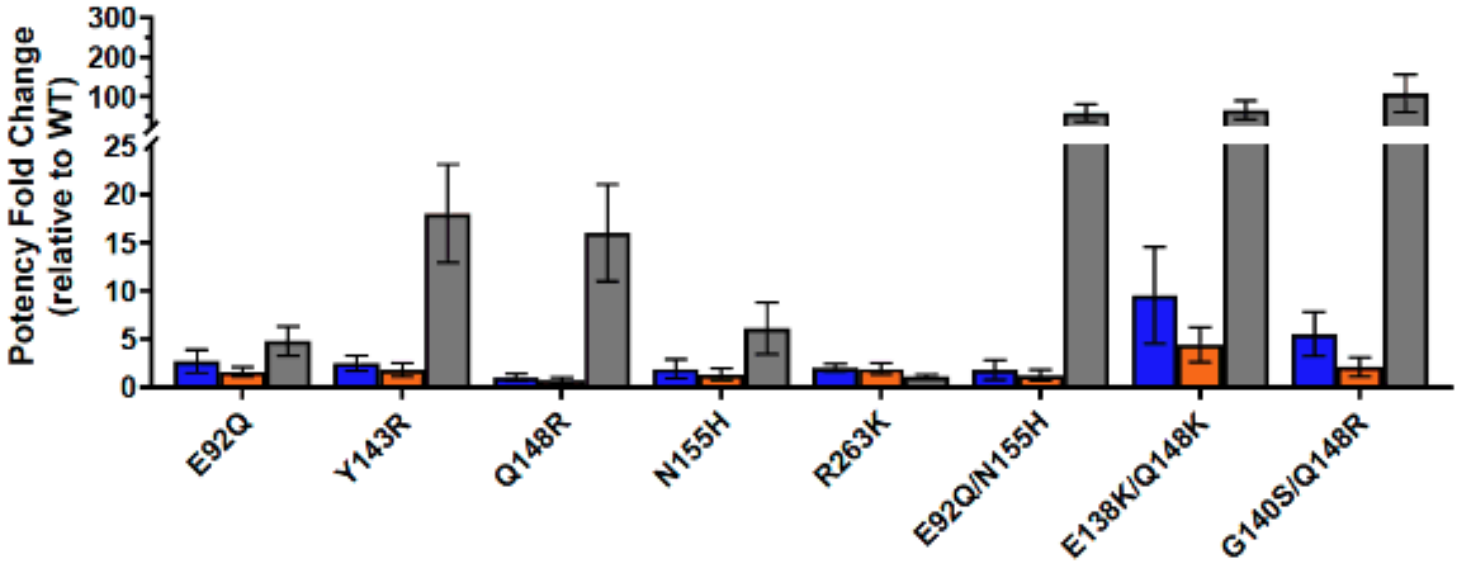
Rogg et al. AIDS 2024; Munich, Germany. Oral presentation OAB2603.

VH4524184: Potent Antiviral Activity with No Resistance



- ✓ An exposure-response relationship was observed for plasma HIV-1 RNA decrease
- ✓ No VH-184 genotypic or phenotypic resistance was detected at Day 10, the end of monotherapy
- ✓ No AEs leading to withdrawal, serious AEs, or deaths were reported during monotherapy or follow-up

GS-1720 Retains Activity Comparable to Bictegravir Against Common INSTI-r Site-Directed HIV-1 Mutants



	Mean EC_{50} Fold Change (relative to WT)[a]							
	E92Q	Y143R	Q148R	N155H	R263K	E92Q/ N155H	E138K/ Q148K	G140S/ Q148R
GS-1720	2.7	2.5	1.0	1.9	2.0	1.8	9.5	5.5
Bictegravir	1.6	1.8	0.7	1.3	1.9	1.2	4.4	2.1
Raltegravir	4.8	18	16	6.1	1.1	58	65	108

a Mean FC values (+ SD), in bar graph) from at least 3 independent experiments assayed in quadruplicate

Hansen D et al. AIDS 202

M, **65 anni**, trasmissione sessuale

In anamnesi:
- **protesi valvolare aortica meccanica** in TAO (2019)
- **CAD** con pregressa **CABG** (2019)
- IPA
- pregresso **adenocarcinoma polmonare** trattato con lobectomia (2015)
- **linfoma di Hodgkin** trattato con cicli ABVD (2008)

Plurime linee terapeutiche

Dal 2011 (VIKING III) in terapia con: ENF (sospeso dopo pochi mesi), DTG 50mg bid, MVC

Impostato TDF/FTC per riattivazione HBV (2011)

Dal 2012 al 2019 in ART con: **TDF/FTC, DTG bid, MVC**

2019

11/06/2019	**68** Copie/mL [-]	TIVICAY*50MG 30 CPR DESCOVY*200/25MG 30 CPR RIV. CELSENTRI*300MG 60CPR RIV
26/04/2019	**80** Copie/mL [-]	TIVICAY*50MG 30 CPR DESCOVY*200/25MG 30 CPR RIV. CELSENTRI*300MG 60CPR RIV
2018		
23/10/2018	**39** Valore compreso tra 1-40 Copie/mL [-]	TIVICAY*50MG 30 CPR DESCOVY*200/25MG 30 CPR RIV. CELSENTRI*300MG 60CPR RIV
05/03/2018	**39** Valore compreso tra 1-40 [-]	TIVICAY*50MG 30 CPR DESCOVY*200/25MG 30 CPR RIV. CELSENTRI*300MG 60CPR RIV
2017		
12/09/2017	**39** Valore compreso tra 1-40 [-]	TRUVADA*30CPR 200/245MG TIVICAY*50MG 30 CPR CELSENTRI*300MG 60CPR RIV
10/01/2017	**51** Copie/mL [-]	TRUVADA*30CPR 200/245MG TIVICAY*50MG 30 CPR CELSENTRI*300MG 60CPR RIV
2016		
14/06/2016	**39** Valore compreso tra 1-40 [-]	TRUVADA*30CPR 200/245MG TIVICAY*50MG 30 CPR CELSENTRI*300MG 60CPR RIV
11/01/2016	**39** Valore compreso tra 1-40 [-]	TRUVADA*30CPR 200/245MG TIVICAY*50MG 30 CPR CELSENTRI*300MG 60CPR RIV
2015		
01/10/2015	**0.9** Negativo [-]	TRUVADA*30CPR 200/245MG TIVICAY*50MG 30 CPR CELSENTRI*300MG 60CPR RIV
06/07/2015	**173** Copie/mL [-]	TRUVADA*30CPR 200/245MG TIVICAY*50MG 30 CPR CELSENTRI*300MG 60CPR RIV
07/05/2015	**39** Valore compreso tra 1-40 [-]	TRUVADA*30CPR 200/245MG TIVICAY*50MG 30 CPR CELSENTRI*300MG 60CPR RIV
2014		
29/12/2014	**49** Copie/mL [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV
06/10/2014	**49** Copie/mL [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV ING112574(VIKING-3) DOLUTEGRAVIR 50 MG
14/07/2014	**49** Copie/mL [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV ING112574(VIKING-3) DOLUTEGRAVIR 50 MG
28/04/2014	**49** Copie/mL [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV ING112574(VIKING-3) DOLUTEGRAVIR 50 MG
27/01/2014	**49** Copie/mL [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV ING112574(VIKING-3) DOLUTEGRAVIR 50 MG

Nota: Esame eseguito su DNA estratto da PBMC

Sequenza aminoacidica della regione V3loop di HIV-1

C T R P H N N T R K R I H/R I A/G P R/G R A F F A F - Y A I G D I/V R Q A H/Y C

Analisi secondo algoritmo Geno2pheno

Predizione del tropismo corecettoriale	FPR
CXCR4	0.7%

nota: il valore FPR (false positive rate) si riferisce alla probabilità che il risultato di tropismo CXCR4 sia un falso positivo. In questo senso tanto maggiore è il valore FPR quanto maggiore è la probabilità che la sequenza predica un tropismo CCR5, Il livello di cut-off utilizzato è 10% FPR.

Conclusioni diagnostiche

Gli antagonisti di CCR5 come Maraviroc (Celsentri/Selzentry) non dovrebbero essere utilizzati

CD4+ > 500cellule/mm^3

2019 GENOTIPO CUMULATIVO

Drug resistance interpretation: RT

HIVDB 9.6 (2024-03-09)

NRTI Mutations: **M41L** • **T69D** • **M184V** • **L210W** • **T215Y**
NNRTI Mutations: **K103KN** • **V108VI** • **Y181C**
RT Other Mutations: V90VI • K101N • V118I • E138M

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	High-Level Resistance
zidovudine (AZT)	High-Level Resistance
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Intermediate Resistance

Non-nucleoside Reverse Transcriptase Inhibitors

doravirine (DOR)	Intermediate Resistance
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Intermediate Resistance
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Intermediate Resistance

Drug resistance interpretation: PR

PI Major Mutations: **V32I** • **M46I** • **I47V** • **I54M** • **V82A** • **I84V** • **L90M**
PI Accessory Mutations: **L33F** • **Q58E** • **G73S** • **L89V**
PR Other Mutations: L10I • A71V • I85V

Protease Inhibitors

atazanavir/r (ATV/r)	High-Level Resistance
darunavir/r (DRV/r)	High-Level Resistance
lopinavir/r (LPV/r)	High-Level Resistance

Drug resistance interpretation: IN

INSTI Major Mutations: **Y143R**
INSTI Accessory Mutations: **L74M** • **T97A**
IN Other Mutations: None

Integrase Strand Transfer Inhibitors

bictegravir (BIC)	Susceptible
cabotegravir (CAB)	Intermediate Resistance
dolutegravir (DTG)	Susceptible
elvitegravir (EVG)	Intermediate Resistance
raltegravir (RAL)	High-Level Resistance

AVRESTE MODIFICATO LA TERAPIA?

SE SI, COME?

Stop MVC, introduce **F/TAF/DRV/c,** prosegue **DTG bid**

2020		
31/10/2020	**133** Copie/mL [-]	SYMTUZA*800/150/200/10MG 30CPR TIVICAY*50MG 30 CPR
21/09/2020	**64** Copie/mL [-]	SYMTUZA*800/150/200/10MG 30CPR TIVICAY*50MG 30 CPR
18/08/2020	**29** Copie/mL [-]	SYMTUZA*800/150/200/10MG 30CPR TIVICAY*50MG 30 CPR
10/07/2020	**534** Copie/mL [-]	SYMTUZA*800/150/200/10MG 30CPR TIVICAY*50MG 30 CPR
01/06/2020	**23** Copie/mL [-]	SYMTUZA*800/150/200/10MG 30CPR TIVICAY*50MG 30 CPR
04/05/2020	**69** Copie/mL [-]	SYMTUZA*800/150/200/10MG 30CPR TIVICAY*50MG 30 CPR
05/02/2020	**39** Valore compreso tra 1-40 Copie/mL [-]	SYMTUZA*800/150/200/10MG 30CPR TIVICAY*50MG 30 CPR
2019		
16/09/2019	**92** Copie/mL [-]	SYMTUZA*800/150/200/10MG 30CPR TIVICAY*50MG 30 CPR

Potenzia a **DRV/r 600/100mg** BID, prosegue **F/TAF, DTG 50mg bid**

FOLLOW UP

25/06/2024	**26** Copie/mL [-]	RITONAVIR ACH*100MG 30 CPRR DARUNAVIR ACC*600MG 60CPR TIVICAY*50MG 30 CPR DESCOVY*200/10MG 30 CPR RIV.
03/01/2024	**19** Valore compreso fra 1-20 copie/mL [-]	RITONAVIR ACH*100MG 30 CPRR DARUNAVIR ACC*600MG 60CPR TIVICAY*50MG 30 CPR DESCOVY*200/10MG 30 CPR RIV.
2023		
18/08/2023	**123** Copie/mL [-]	RITONAVIR ACH*100MG 30 CPRR DARUNAVIR ACC*600MG 60CPR TIVICAY*50MG 30 CPR DESCOVY*200/10MG 30 CPR RIV.
21/04/2023	**101** Copie/mL [-]	RITONAVIR ACH*100MG 30 CPRR DARUNAVIR ACC*600MG 60CPR TIVICAY*50MG 30 CPR DESCOVY*200/10MG 30 CPR RIV.
2022		
19/12/2022	**50** Copie/mL [-]	RITONAVIR ACH*100MG 30 CPRR DARUNAVIR ACC*600MG 60CPR TIVICAY*50MG 30 CPR DESCOVY*200/10MG 30 CPR RIV.
22/08/2022	**37** Copie/mL [-]	RITONAVIR ACH*100MG 30 CPRR DARUNAVIR ACC*600MG 60CPR TIVICAY*50MG 30 CPR DESCOVY*200/10MG 30 CPR RIV.
24/05/2022	**50** Copie/mL [-]	RITONAVIR ACH*100MG 30 CPRR DARUNAVIR ACC*600MG 60CPR TIVICAY*50MG 30 CPR DESCOVY*200/10MG 30 CPR RIV.
19/04/2022	**53** Copie/mL [-]	RITONAVIR ACH*100MG 30 CPRR DARUNAVIR ACC*600MG 60CPR TIVICAY*50MG 30 CPR DESCOVY*200/10MG 30 CPR RIV.
04/02/2022	**84** Copie/mL [-]	RITONAVIR ACH*100MG 30 CPRR DARUNAVIR ACC*600MG 60CPR TIVICAY*50MG 30 CPR DESCOVY*200/10MG 30 CPR RIV.
2021		
16/12/2021	**59** Copie/mL [-]	RITONAVIR ACH*100MG 30 CPRR DARUNAVIR ACC*600MG 60CPR TIVICAY*50MG 30 CPR DESCOVY*200/10MG 30 CPR RIV.
07/09/2021	**159** Copie/mL [-]	RITONAVIR ACH*100MG 30 CPRR DARUNAVIR ACC*600MG 60CPR TIVICAY*50MG 30 CPR DESCOVY*200/10MG 30 CPR RIV.
09/04/2021	**72** Copie/mL [-]	RITONAVIR ACH*100MG 30 CPRR DARUNAVIR ACC*600MG 60CPR TIVICAY*50MG 30 CPR DESCOVY*200/10MG 30 CPR RIV.

Nota: Esame eseguito su DNA estratto da PBMC

Drug resistance interpretation: PR
HIVDB 9.4 (2022-12-07)
PI Major Mutations:

V32I, **M46I**, **I47V**, **I54M**, **V82A**, **I84V**, **L90M**

PI Accessory Mutations:

L33F, **Q58E**, **G73S**, **L89V**

PR Other Mutations:

L10I, **V11L**, I13V, I15V, G16A, L19V, K20R, M36I, G51GE, L63P, A71V, I72V, I85V

Protease Inhibitors

atazanavir/r (ATV/r)	High-Level Resistance
darunavir/r (DRV/r)	High-Level Resistance
fosamprenavir/r (FPV/r)	High-Level Resistance
indinavir/r (IDV/r)	High-Level Resistance
lopinavir/r (LPV/r)	High-Level Resistance
nelfinavir (NFV)	High-Level Resistance
saquinavir/r (SQV/r)	High-Level Resistance
tipranavir/r (TPV/r)	High-Level Resistance

Nota: Esame eseguito su DNA estratto da PBMC

Drug resistance interpretation: IN

HIVDB 9.0 (2021-02-22)
IN Major Resistance Mutations:
None
IN Accessory Resistance Mutations:
None
Other Mutations:
S17N, V31I, L101I, T112I, S119P, T122I, T124N

Integrase Strand Transfer Inhibitors

bictegravir (BIC)	Susceptible
cabotegravir (CAB)	Susceptible
dolutegravir (DTG)	Susceptible
elvitegravir (EVG)	Susceptible
raltegravir (RAL)	Susceptible

TERAPIA CONCOMITANTE

- Irbesartan
- Warfarin
- ASA
- Bisoprololo
- Atorvastatina→ colesterolo LDL > 100mg/dL
- Pregabalin

Chiede di semplificare: CD4 > 500; HIV-RNA < 30cp/mL

COME? COSA CONSIDERARE?

- Switch DRV/r→FTR
- Switch DRV/r→LEN
- Switch DRV/r→LEN + FTR

- Da Luglio 2024: F/TAF, DTG 50mg BID, **LEN**
- Agosto 2024: HIV-RNA 80cp/mL 

Settembre 2024: HIV-RNA < 30cp/mL→Marzo 2025: 32cp/mL

- 2016: RB, **male, 53** years old, MSM
- HIV infection: **January 1995; Stage B2;** Nadir CD4 305/µL
- First antiretroviral therapy: **May 1996** (AZT,ddC,SQV)
- Drug Allergies: **amoxicillin, ticlopidine**
- Family History: **father** died of **myocardial infarction** at **52**
- Previous exposure to:

NRTIs	NNRTIs	PIs	INSTIs	EIs
AZT 3TC ddC d4T ddI TDF	EFV ETV	SQV IDV NFV fAPV/r ATV/r DRV/r	RAL DTG	ENF MVC

COMORBIDITIES

- Hypertension
- Lipoatrophy
- Dyslipidemia
- Carotid stenosis: Right 50%; Left 40%
- Impaired fasting glucose (105-110mg/dL)
- December 2011 (Age 48): non-ST segment elevation myocardial infarction →percutaneous transluminal coronary angioplasty and double stent placement

MEDICATIONS

- Rosuvastatin 20mg QD
- Metoprolol 25mg BID
- ASA 100mg QD

ART: **DTG** 50mg BID; **ETV** 200mg BID; **DRV/r** 600/100mg BID, **TDF/FTC**

MAY 2016:

- CD4 641 (22.3%), HIV-RNA 1668cp/mL , CD4/CD8: 0.6
- Cholesterol 202mg/dL; HDL 47mg/dL; LDL 103mg/dL; triglycerides 280mg/dL; Glucose 105mg/dL; ALT 41 U/L; creatinine 0.72 mg/dL

GENOTYPIC RESISTANCE TESTING (December 2015)

Drug Resistance Interpretation: PR

PI Major Resistance Mutations:	**V32I, M46IM, I47IV, I50IV, I54IL, L90M**
PI Minor Resistance Mutations:	**L10I, L33FL, A71V**
Other Mutations:	I13V, G16EG, L19I, K20R, E35D, M36I, P39PS, L63P, I66FI, V82IV, I85V, Q92QR

Protease Inhibitors

atazanavir/r (ATV/r)	High-level resistance
darunavir/r (DRV/r)	High-level resistance
fosamprenavir/r (FPV/r)	High-level resistance
indinavir/r (IDV/r)	High-level resistance
lopinavir/r (LPV/r)	High-level resistance
nelfinavir (NFV)	High-level resistance
saquinavir/r (SQV/r)	High-level resistance
tipranavir/r (TPV/r)	Intermediate resistance

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	**M41L, A62AV, D67N, V75I, M184V, L210W, T215Y, K219R**
NNRTI Resistance Mutations:	**V90I, K103N, E138EG, Y188L, K238T**
Other Mutations:	I31L, T39A, K43Q, K122E, S162Y, R172KR, V179I, G196E, T200A, E203D, R211K, D237DN

Nucleoside RTI

lamivudine (3TC)	High-level resistance
abacavir (ABC)	High-level resistance
zidovudine (AZT)	High-level resistance
stavudine (D4T)	High-level resistance
didanosine (DDI)	High-level resistance
emtricitabine (FTC)	High-level resistance
tenofovir (TDF)	High-level resistance

Non-Nucleoside RTI

efavirenz (EFV)	High-level resistance
etravirine (ETR)	Low-level resistance
nevirapine (NVP)	High-level resistance
rilpivirine (RPV)	High-level resistance

Drug Resistance Interpretation: IN

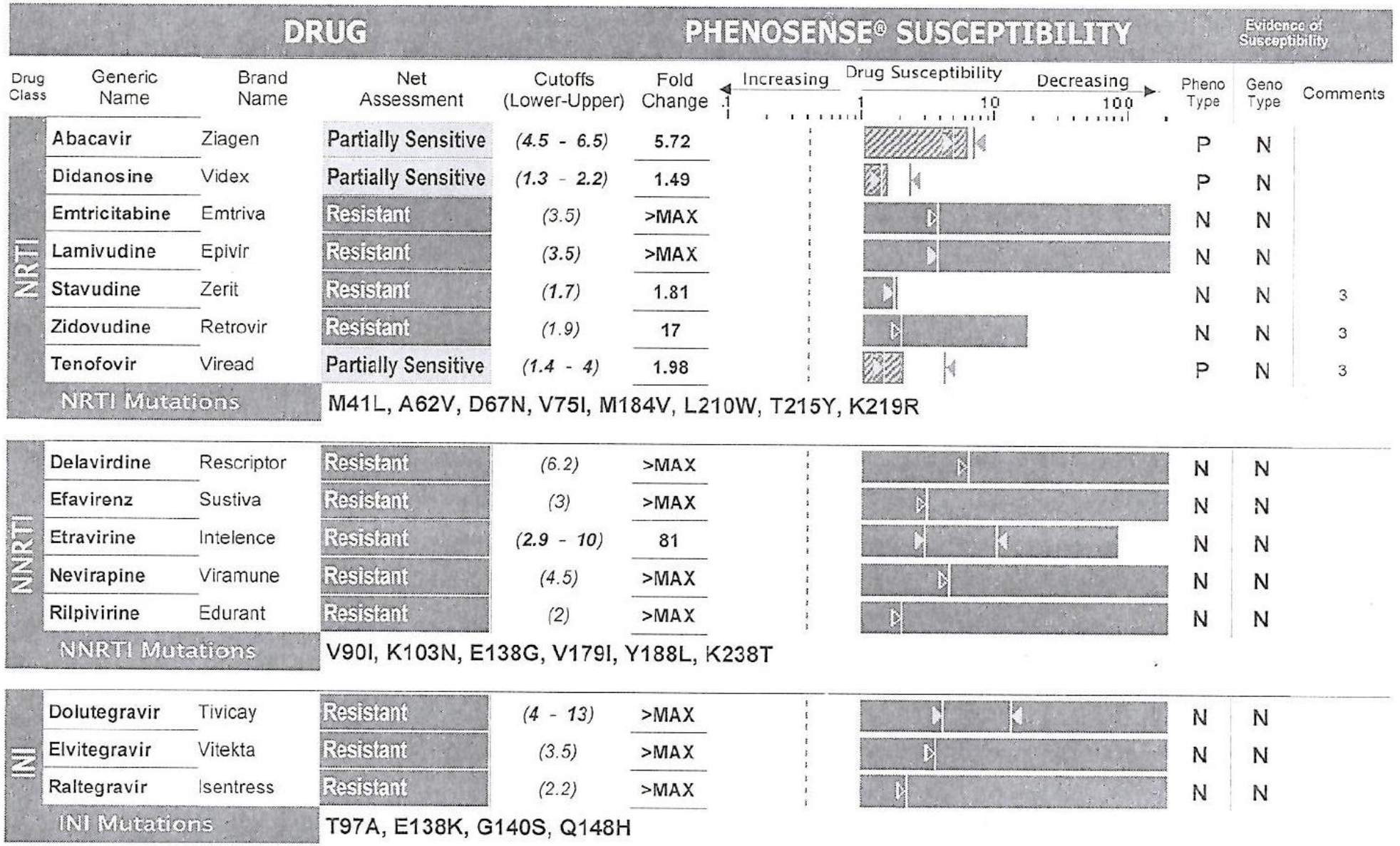
Major Resistance Mutations:	**Q148HQ**
Accessory Mutations:	**G140GS**
Other Mutations:	D3DE, E10D, M154I, V165I, V201I, I208L

Integrase Inhibitors

dolutegravir (DTG)	Intermediate resistance
elvitegravir (EVG)	High-level resistance
raltegravir (RAL)	High-level resistance

HIV DB Stanford

GENOTYPIC + PHENOTYPIC RESISTANCE TESTING (April 2016)

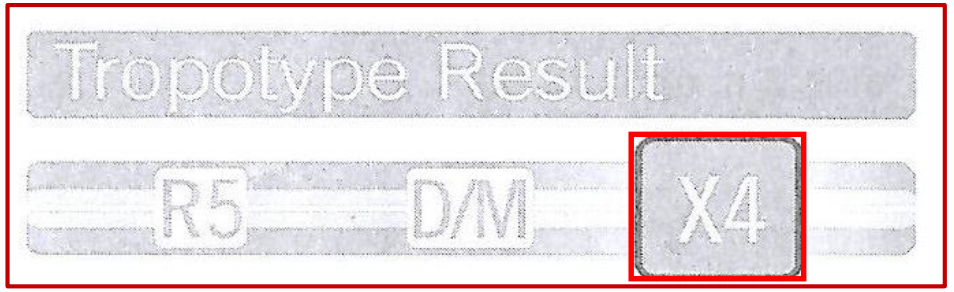


DRUG			PHENOSENSE® SUSCEPTIBILITY				Evidence of Susceptibility		
Drug Class	Generic Name	Brand Name	Net Assessment	Cutoffs (Lower-Upper)	Fold Change	Increasing Drug Susceptibility Decreasing (1 / 10 / 100)	Pheno Type	Geno Type	Comments
NRTI	Abacavir	Ziagen	Partially Sensitive	(4.5 - 6.5)	5.72		P	N	
NRTI	Didanosine	Videx	Partially Sensitive	(1.3 - 2.2)	1.49		P	N	
NRTI	Emtricitabine	Emtriva	Resistant	(3.5)	>MAX		N	N	
NRTI	Lamivudine	Epivir	Resistant	(3.5)	>MAX		N	N	
NRTI	Stavudine	Zerit	Resistant	(1.7)	1.81		N	N	3
NRTI	Zidovudine	Retrovir	Resistant	(1.9)	17		N	N	3
NRTI	Tenofovir	Viread	Partially Sensitive	(1.4 - 4)	1.98		P	N	3
NRTI Mutations	M41L, A62V, D67N, V75I, M184V, L210W, T215Y, K219R								
NNRTI	Delavirdine	Rescriptor	Resistant	(6.2)	>MAX		N	N	
NNRTI	Efavirenz	Sustiva	Resistant	(3)	>MAX		N	N	
NNRTI	Etravirine	Intelence	Resistant	(2.9 - 10)	81		N	N	
NNRTI	Nevirapine	Viramune	Resistant	(4.5)	>MAX		N	N	
NNRTI	Rilpivirine	Edurant	Resistant	(2)	>MAX		N	N	
NNRTI Mutations	V90I, K103N, E138G, V179I, Y188L, K238T								
INI	Dolutegravir	Tivicay	Resistant	(4 - 13)	>MAX		N	N	
INI	Elvitegravir	Vitekta	Resistant	(3.5)	>MAX		N	N	
INI	Raltegravir	Isentress	Resistant	(2.2)	>MAX		N	N	
INI Mutations	T97A, E138K, G140S, Q148H								

GENOTYPIC + PHENOTYPIC RESISTANCE TESTING (April 2016)

DRUG			PHENOSENSE® SUSCEPTIBILITY					Evidence of Susceptibility	
Drug Class	Generic Name	Brand Name	Net Assessment	Cutoffs (Lower-Upper)	Fold Change	Increasing Drug Susceptibility Decreasing (.1 — 1 — 10 — 100)	Pheno Type	Geno Type	Comments
PI	Atazanavir	Reyataz	Resistant	(2.2)	2.99		N	N	
PI	Atazanavir	Reyataz / r‡	Sensitive	(5.2)	2.99		Y	N	16
PI	Darunavir	Prezista / r‡	Resistant	(10 - 90)	>MAX		N	N	
PI	Fosamprenavir	Lexiva / r‡	Resistant	(4 - 11)	>MAX		N	N	
PI	Indinavir	Crixivan / r‡	Sensitive	(10)	2.37		Y	N	16
PI	Lopinavir	Kaletra‡	Resistant	(9 - 55)	90		N	N	
PI	Nelfinavir	Viracept	Resistant	(3.6)	13		N	N	
PI	Ritonavir	Norvir	Resistant	(2.5)	>MAX		N	N	
PI	Saquinavir	Invirase / r‡	Partially Sensitive	(2.3 - 12)	7.77		P	N	
PI	Tipranavir	Aptivus / r‡	Sensitive	(2 - 8)	0.52		Y	Y	
PI Mutations	L10I, V11V/I, I13V, K20R, V32I, L33F, E35D, M36I, M46I, I47V, I50V, I54L, A71V, V82I, I85V, L90M								

TROFILE



FOLLOW-UP

A therapy with **TDF/FTC, ATV/r, FTR** and **DTG 100mg BID** was started (BRIGHTE Study; FTR/Placebo BL→Day8).

At BL:

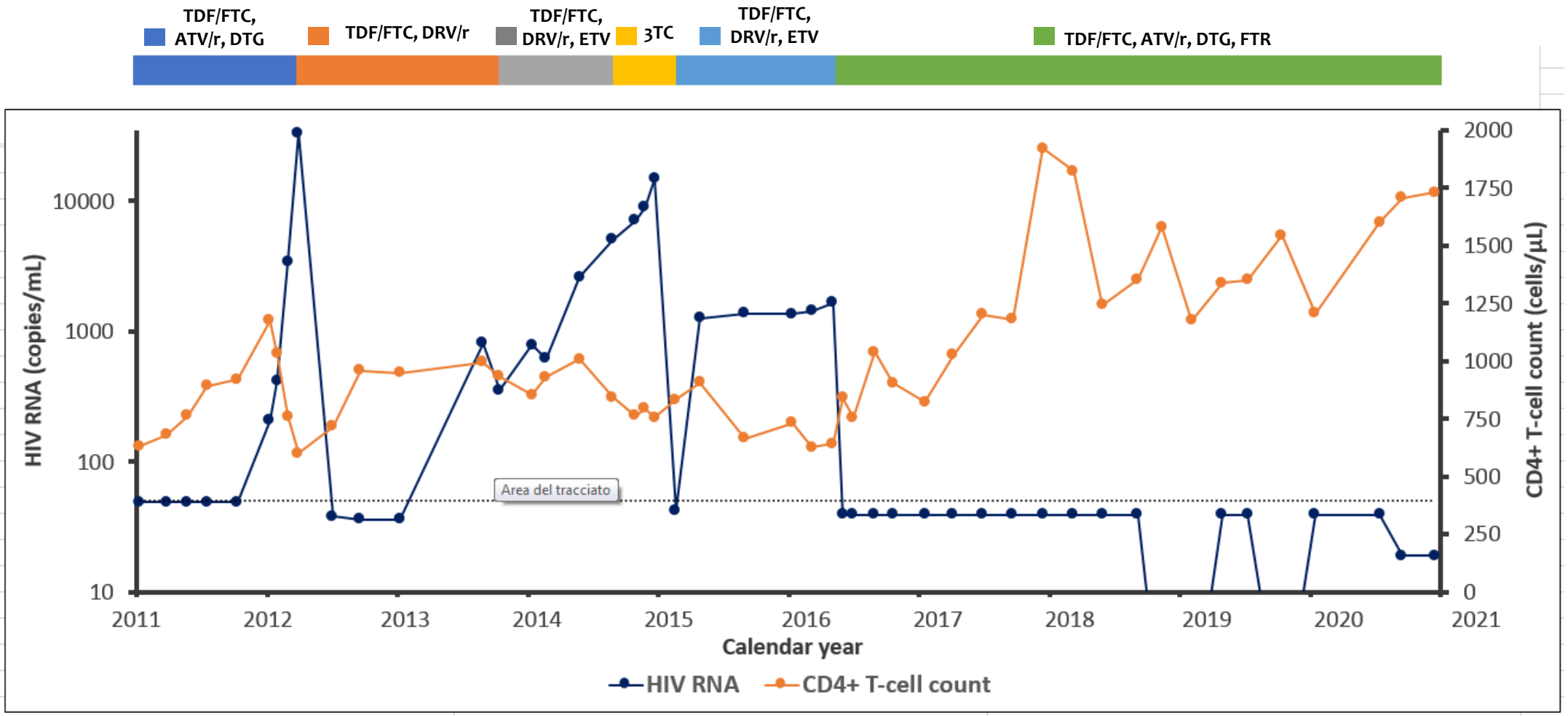
- CD4 641 (22%)
- HIV-RNA 1668 cp/mL

At week 4:

- CD4 840 (26%)
- HIV-RNA <40cp/mL
- Cholesterol 160mg/dL; HDL 46mg/dL LDL 76mg/dL
- Triglycerides 200mg/dL
- ALT 51 U/L; Total bilirubin 2.1mg/dL; Creatinine 0.92mg/dL; glucose 110mg/dL

Treatment well-tolerated; **dizziness** (Grade 1) in the first two weeks of therapy

FOLLOW-UP (2)



Dolutegravir C_{trough}: 15843 ng/mL

Dose of rosuvastatin reduced to 10mg die

November 2021 (>5 years of HIV-RNA<50cp/mL)

ART: DTG 50mg BID; **FTV, ATV/c, F/TAF**

- CD4 1245 (36.0%), HIV-RNA <20 cp/mL , CD4/CD8: 0.85
- Cholesterol 179mg/dL; HDL 49mg/dL; LDL 88mg/dL; triglycerides 290mg/dL;
- Fasting Glucose 123mg/dL; HBA1c 55mmol/mol
- Nephrolithiasis (May 2021)

Recent Diagnosis of **TYPE 2 DIABETES (January 2021)**

QUESTIONS. Current therapy: F/TAF,ATV/c,FTR, DTG

1. DO YOU WANT TO SIMPLIFY AND HOW?

-No

-Yes, stop ATV/c

-Yes, stop ATV/c and switch to another PI/b

- Yes, stop DTG

Discontinuation of ATV/c→ DTG 50mg BID + FTR + F/TAF

Test	ART Change	Week 4	Week 8	Week 10
HIV-RNA (cp/ml)	19	19	3883	4740
CD4 (cells/mm³)	1245	1120	1604	

SO, WHAT TO DO NOW?

Reintroduction of ATV/c (10 weeks after discontinuation)→ DTG 50mg BID + FTR + F/TAF+ATV/c
Resistance testing not available

Test	ATV/c reintroduction	Week 4	Week 12	Week 48	Week 144
HIV-RNA (cp/ml)	**4740**	98	**39**	**19**	**19**
CD4 (cells/mm³)		1420	1534	1310	1510

QUESTIONS. Current therapy: F/TAF,ATV/c,FTR, DTG

2. IS THIS AN UNSIMPLIFIABLE REGIMEN?

-Yes

-No, switch from ATV/c to LEN

-No, switch from FTR to LEN

- Why do I need to switch?

DISCUSSION

MDR PWH at higher risk of mortality, cancer and CV disease compared to PWH without MDR[1,2,3].

PI/b has been associated with an increased risk of CV (although this risk is less pronounced for ATV)[4,5].

In this case, considering the history of CAD and renal toxicity, ATV/c should be removed if possible and the use of a new drug with full susceptibility should be considered in its place.

1. doi: 10.1093/ofid/ofaa456.
2. doi: 10.1097/QAD.0000000000003952.
3.doi: 10.1093/jac/dkae465.
4. doi: 10.1093/ofid/ofae485.
5. doi: 10.1097/QAD.0000000000003786.


THANK YOU