NUOVI TRATTAMENTI DISPONIBILI NEGLI HTE: U=U

Silvia Nozza

I.R.C.C.S. Ospedale San Raffaele
Gruppo San Donato

UniSR
Università Vita-Salute San Raffaele

COI

La sottoscritto **NOZZA SILVIA**
in qualità di relatore
ai sensi dell’art. 76, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara
che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

ViiV HEALTHCARE
GILEAD SCIENCES
JANSSEN CILAG
MSD

PRESTIGIO REGISTRY

Baseline Characteristics

		Overall (n=229)
Age (years)		58,3 (53,6 – 61,6) min = 24,2 max = 81,3
Gender	Male	166 (72,5%)
	Female	63 (27,5%)
Nationality	Italian	210 (91,7%)
	Other	19 (8,3%)
Ethnicity	Caucasian	218 (95,2%)
	Black	9 (3,9%)
	Hispanic	2 (0,9%)

		Overall (n=229)
HIV risk factor	Hetero	59 (25,8%)
	MSM	59 (25,8%)
	IVDU	48 (21,0%)
	MTCT	21 (9,2%)
	Other	12 (5,2%)
	Unknown	30 (13,1%)
Years of HIV		21,6 (17,4 – 26,6)
Years of ART		18,1 (14,3 – 21,1)
Calendar year of ART start	< 1998	148 (64,6%)
	≥ 1998	81 (35,4%)

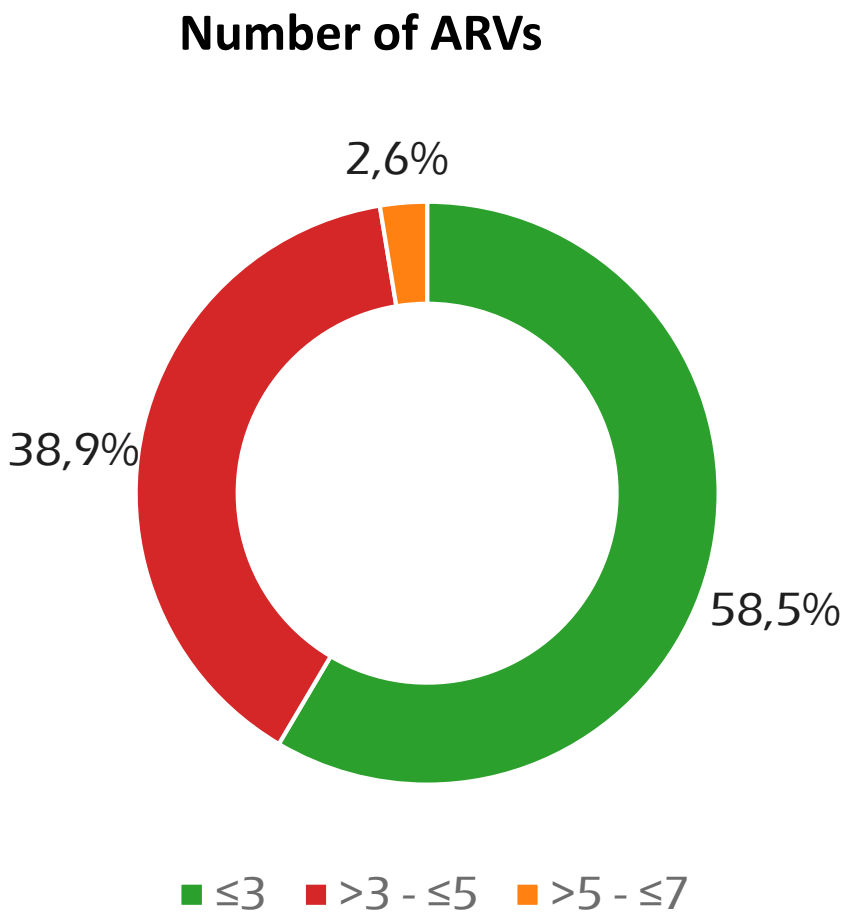
HCV infection in 81/229 patients enrolled

Castagna A., ICAR 2023

PRESTIGIO REGISTRY ANTIRETROVIRAL DRUGS

last available

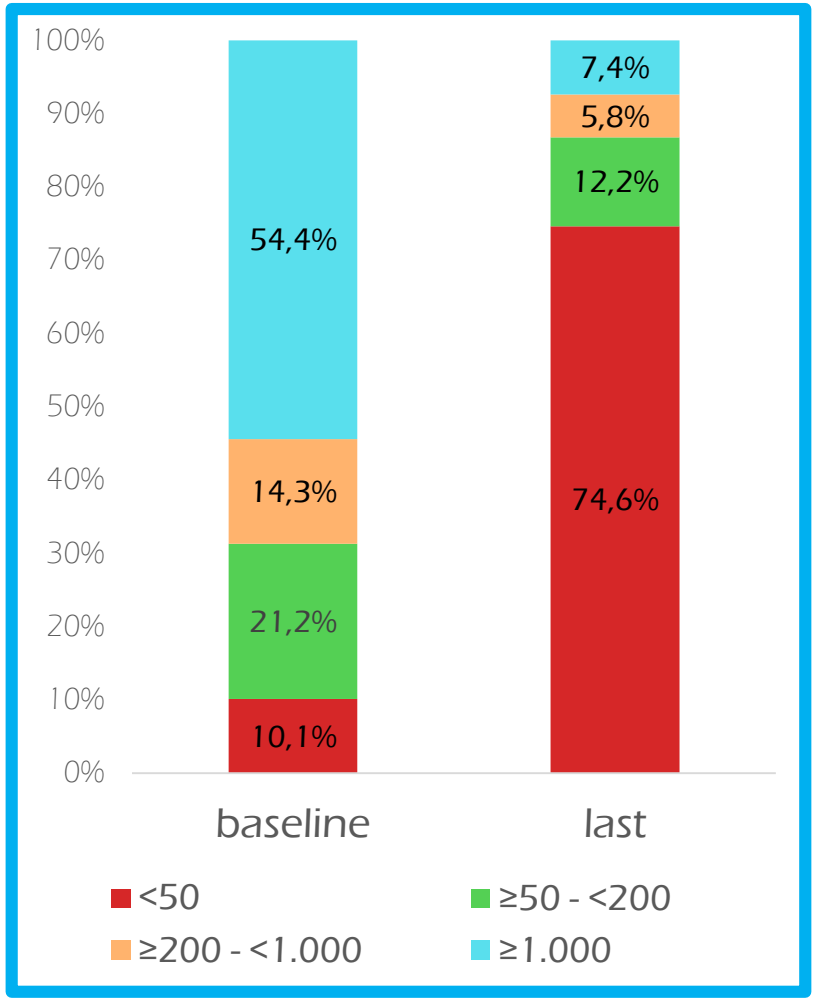
		Current regimen
Drugs	DTG	147 (77,4%)
	DRV/r	73 (38,4%)
	DRV/c	59 (31,1%)
	XTC	102 (54,0%)
	TAF	66 (34,9%)
	TDF	22 (11,6%)
	DOR	26 (13,7%)
	ETV	26 (13,7%)
	RPV	9 (4,7%)
	MVC	37 (19,5%)
	FTR	18 (9,5%)
	LEN	9 (4,7%)
	IBA	7 (3,7%)
	ISL	2 (1.1%)
	ENF	2 (1,1%)



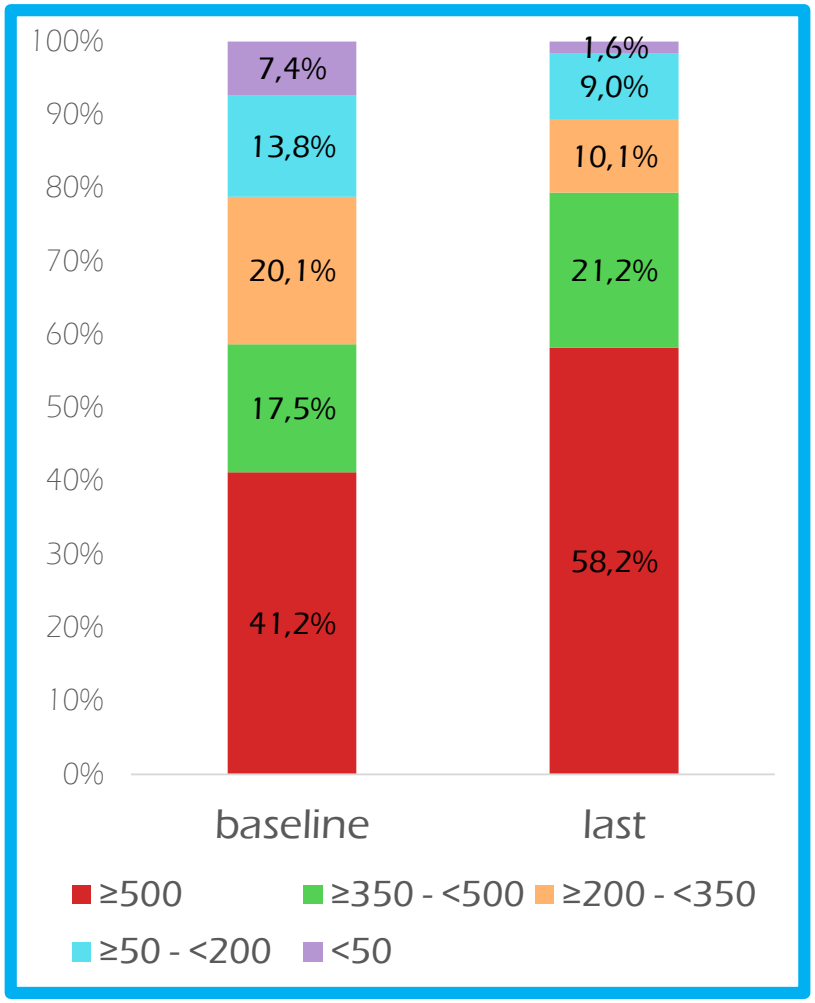
Castagna A., ICAR 2023

PRESTIGIO REGISTRY

HIV-RNA copies/mL



CD4+ cells/cmm



Castagna A., ICAR 2023

STIs SCREENING- EACS GUIDELINES

STI screening and treatment

STI screening should be offered to all sexually active persons at the time of HIV diagnosis, annually thereafter or at any time STI symptoms are reported and during pregnancy. More frequent screening at three-month intervals is warranted for persons at particularly high risk of STIs, including those with multiple or anonymous partners. Frequent HIV screening is also essential for those on PrEP, see Pre-exposure Prophylaxis (PrEP)
Diagnosis procedures should follow local or national guidelines. More comprehensive advice can be found at iusti.org/treatment-guidelines/

The following STIs should be universally considered in persons with HIV and their sexual partner(s):

Incident bacterial STIs

Cases	At baseline				At the time of STI				At last visit
	Age (years)	HIV VL (cps/mL)	CD4+ (cells/mm³)	ART	STI	HIV VL (cps/mL)	CD4+ (cells/mm³)	ART	Cumulative RAMs
Case 1	50	24810	252	3TC, ETV, RAL	Chlamydia	<50	334	FTC, TDF, DTG, MVC	M41L, T69D, M184V, L210W, T215DY, K219E - L100I, K103N, V108I, Y181C - V32I, L33F, M46I, I47V, I54M, Q58E, G73S, V82A, I84V, L89V, L90M - T97A, Y143R
					Mycoplasma	<50	294	FTC, TDF, DTG, MVC	
					Gonorrhea	<50	565	FTC, TAF, DTG, MVC	
Case 2	49	568	853	FTC, TDF, DRV/r, RAL	Syphilis	71	654	FTC, TAF, BIC, DOR	D67N, T69D, K70R, Q151M, M184V, K219Q - K103N, K238T - V32I, L33F, M46LV, I54V, G73C, V82A, L90M - history of virological failure to RAL-, DTG-, and BIC-containing regimens
Case 3	52	656	683	RAL, MVC	Syphilis	<50	797	DRV/r, DTG, MVC	M41L, D67N, K70R, V75M, F77L, M184V, T215F - K103N, V108I - M46I, I54V, G73S, V82T, I84V, L90M - N155H
					Syphilis	<50	774	DRV/r, DTG, MVC	
Case 4	55	49610	278	FTC, TDF, ATV	Chlamydia	<50	488	FTC, TDF, ETV, RAL	M41L, K70R, M184V, L210W, T215NSY, K219N - L100I, K103N, E138K - L10F, M46I, I47V, I54V, G73T, I84V, L90M - N155H
					Mycoplasma	<50	488	FTC, TDF, ETV, RAL	
					Mycoplasma	<50	530	FTC, TAF, ETV, RAL	
					Mycoplasma	<50	519	FTC, TAF, ETV, RAL	
Case 5	53	576176	122	3TC, DRV/r, DTG	Syphilis	<50	460	3TC, DRV/r, DTG	D67G, T69D, K70R, M184V, T215FI, K219Q - K101E, Y181CF, G190S - Q58E, L90M - T97A, N155H
Case 6	51	13900	427	FTC, TDF, NVP	Syphilis	<50	750	DRV/c, DTG	A62V, K65R, M184V - K103N, Y181C - K20T, L90M - F121Y

Clemente T AIDS 2023

Sexually transmitted infections in people with multidrug-resistant HIV

- Bacterial sexually transmitted infections (STIs) had an incidence of 1.3/100-person-years-of-follow-up (PYFU) in men (3.5/100-PYFU in MSM) whereas no STIs were diagnosed in women.

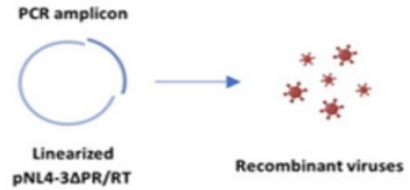
- Implementation of counseling and screening.

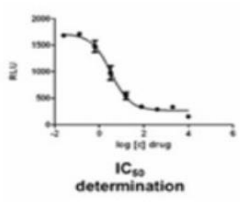
Residual susceptibility to doravirine in multidrug resistant HIV-1

METHODS

Plasma samples (n=22) collected from viremic individuals harboring HIV-1 resistant to NRTIs, NNRTIs, PIs and INSTIs enrolled in the Italian PRESTIGIO Registry

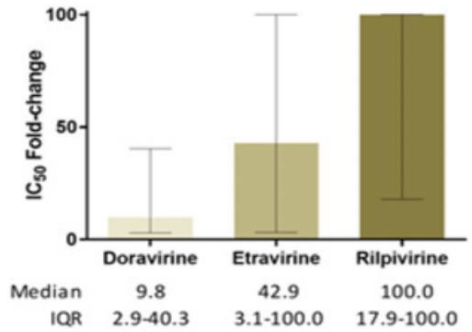
Generation of NL4-3-based recombinant viruses including clinically derived PR-RT coding region





Measurement of *in vitro* susceptibility to doravirine, rilpivirine and etravirine

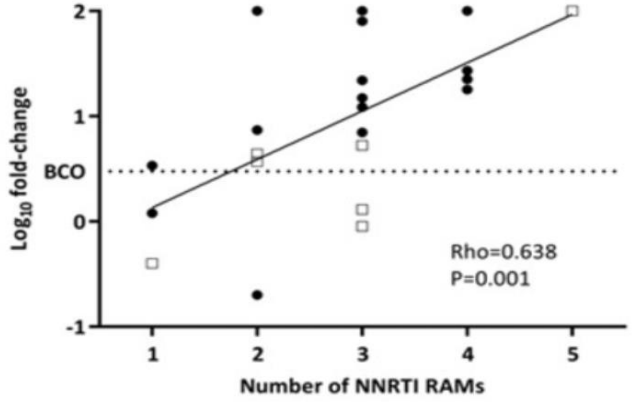
RESULTS



	Doravirine	Etravirine	Rilpivirine
Median	9.8	42.9	100.0
IQR	2.9-40.3	3.1-100.0	17.9-100.0

Median fold-change value of doravirine was lower than those of etravirine and rilpivirine

- According to the 3-fold biological cut-off, 5/22 (23%) of NNRTI-resistant viruses were fully susceptible to doravirine
- The higher the number of NNRTI RAMs, the higher the doravirine fold-change value, irrespective of the presence of doravirine RAMs (black circles)



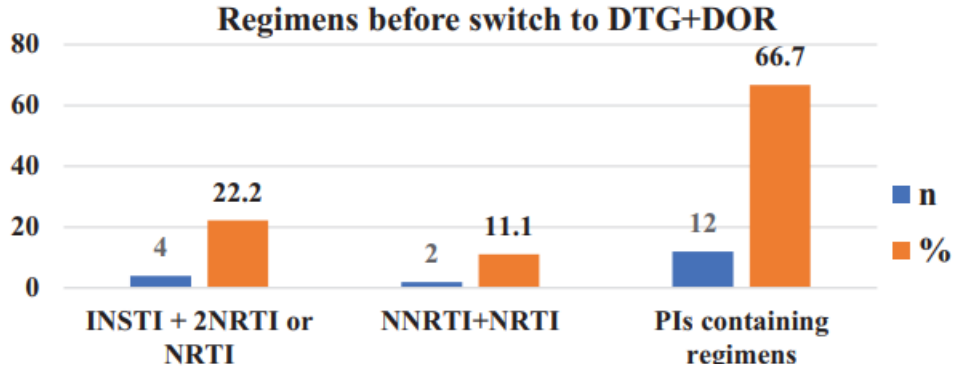
CONCLUSIONS

- Although doravirine remains the most active NNRTI against isolates exposed to previous drugs of the same class, its activity in salvage therapy may be compromised by the accumulation of NNRTI mutations
- A proportion of individuals with MDR HIV-1 and limited treatment options may benefit from the use of doravirine in salvage therapy

Saladini F, IJAA 2023

DTG+DOR: A possible simplification strategy

C



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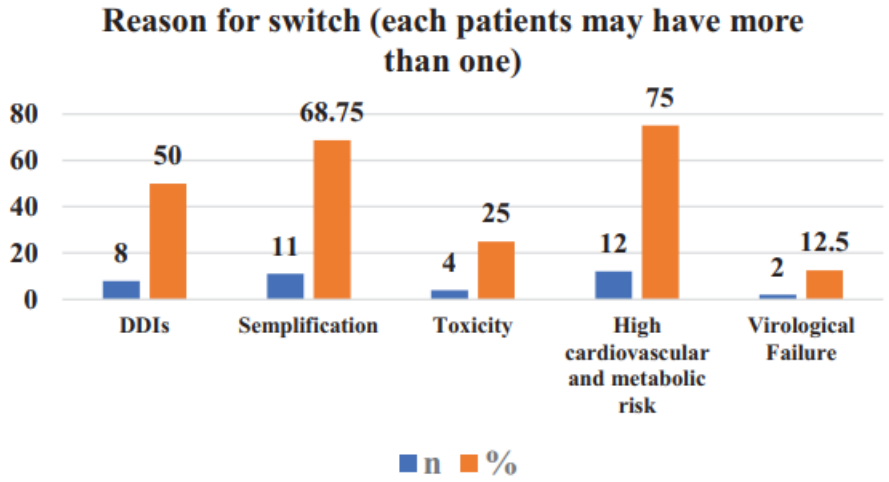


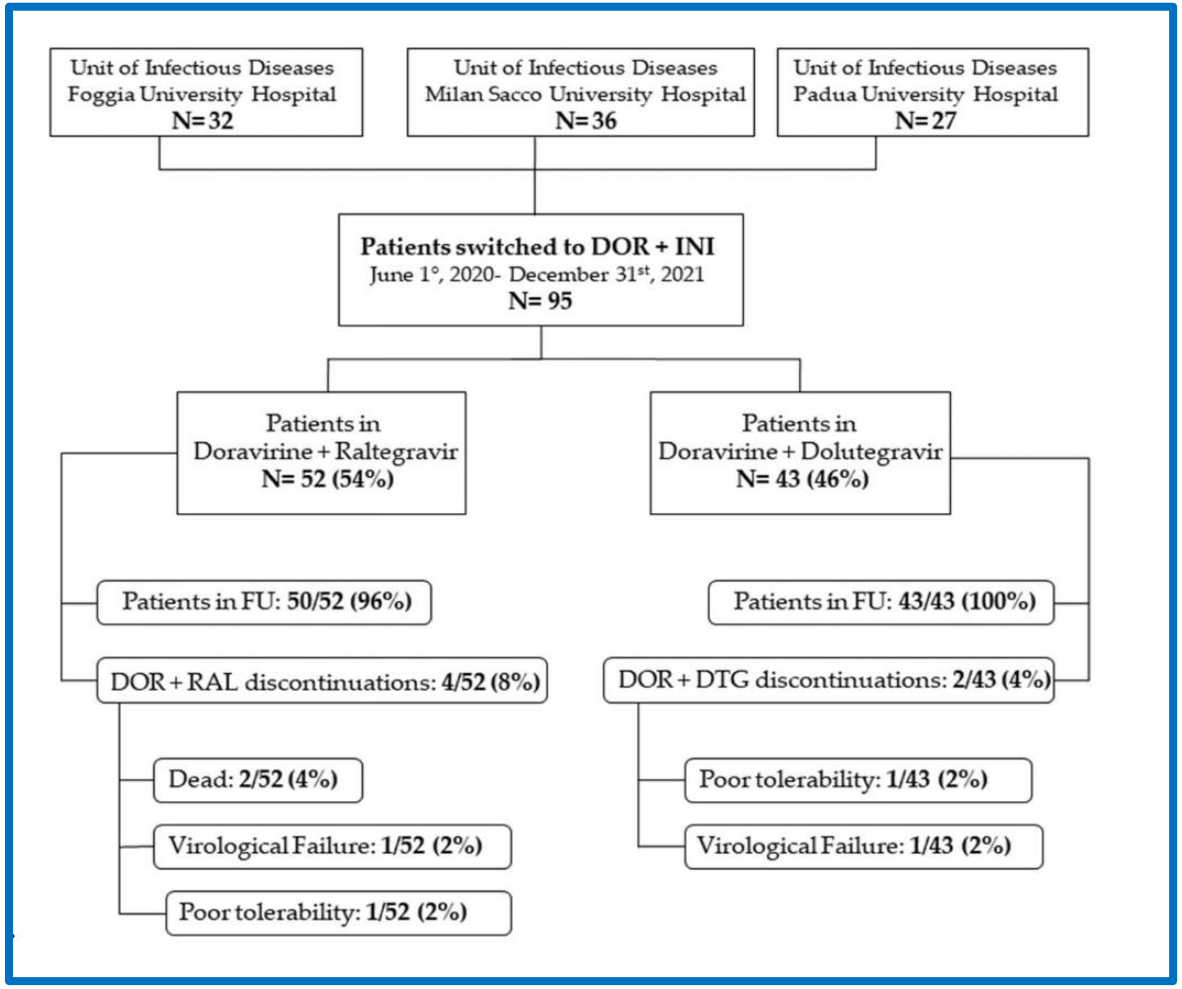
D

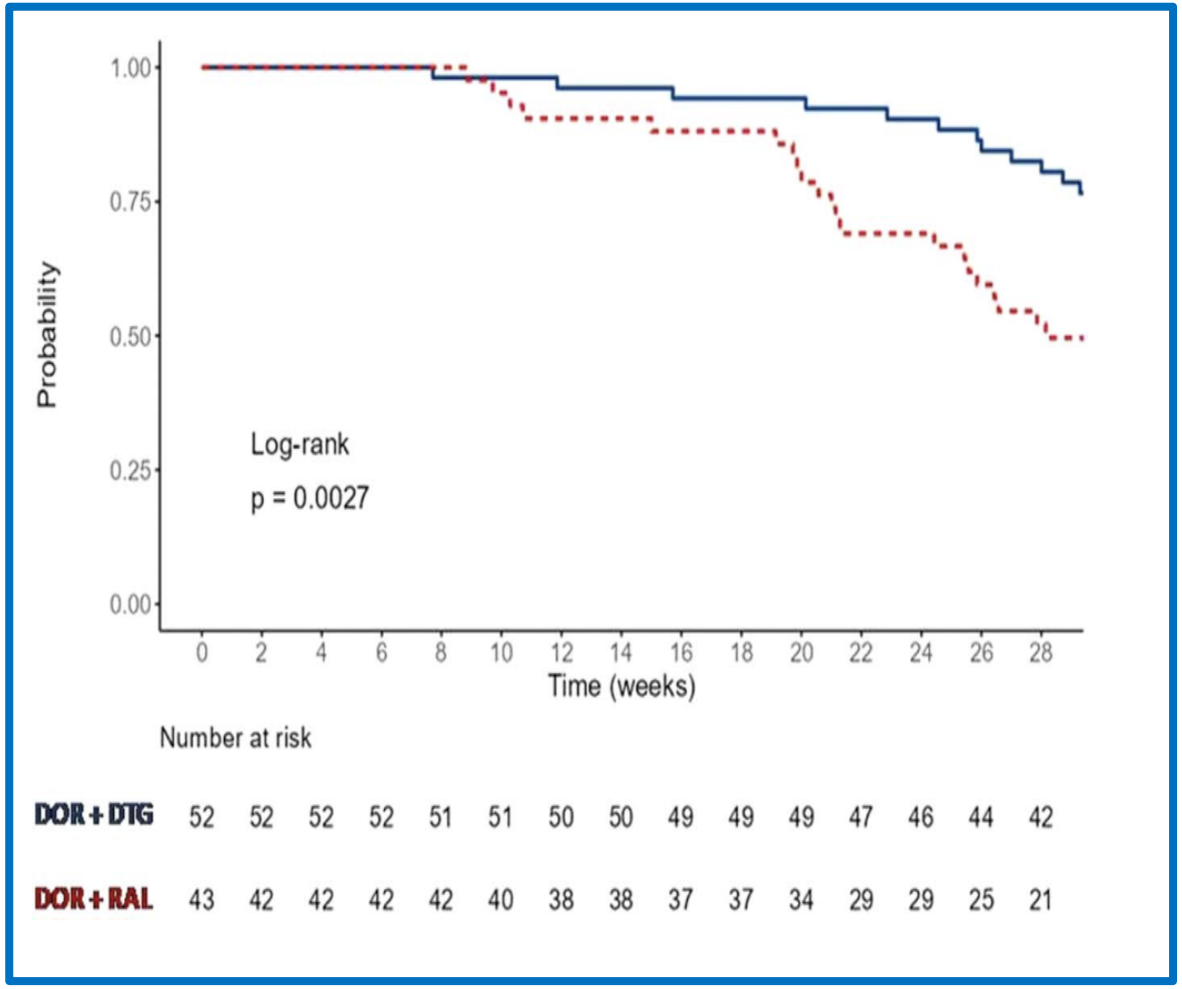
Parameter	Before switch, n(%)	After switch n (%)	p value
Undetectable HIV-RNA (Yes)	15 (88.2)	17 (100)	-
CD4+, cell/mm³, mean (SD)	607 (240)	629 (232)	0.37
Cholesterol, mmol/L, mean (SD)	5.1 (3.3)	4.8 (1.4)	0.1
HDL, mmol/L, mean (SD)	1.5 (0.7)	1.1 (0.4)	0.75
LDL, mmol/L, mean (SD)	3.1 (1)	2.9 (1.1)	0.49
Triglycerides, mmol/L, mean (SD)	1.41 (0.7)	1.5 (0.7)	0.2
Fasting glucose, mmol/L, mean (SD)	6.2 (1.7)	5.5 (1.4)	0.08
BMI, kg/m², mean (SD)	25.4 (3.2)	24.7 (3.3)	**<0.01**
Body weight, kg, mean (SD)	75.2 (11.6)	73.1 (11.6)	**<0.01**
Waist circumference, cm, mean (SD)	98.1 (10)	95.9 (9.8)	**<0.01**
Creatinine, umol/L	86.1 (22)	90.7 (23.4)	**0.04**
eGFR, ml/min, mean (SD)	79.4 (21)	75.2 (20.9)	**0.03**

Mazzitelli AM, Medicine, 2021

Doravirine Plus Integrase Strand Transfer Inhibitors as a 2-Drug Treatment–Switch Strategy in People Living with HIV: The Real-Life DORINI Multicentric Cohort Study

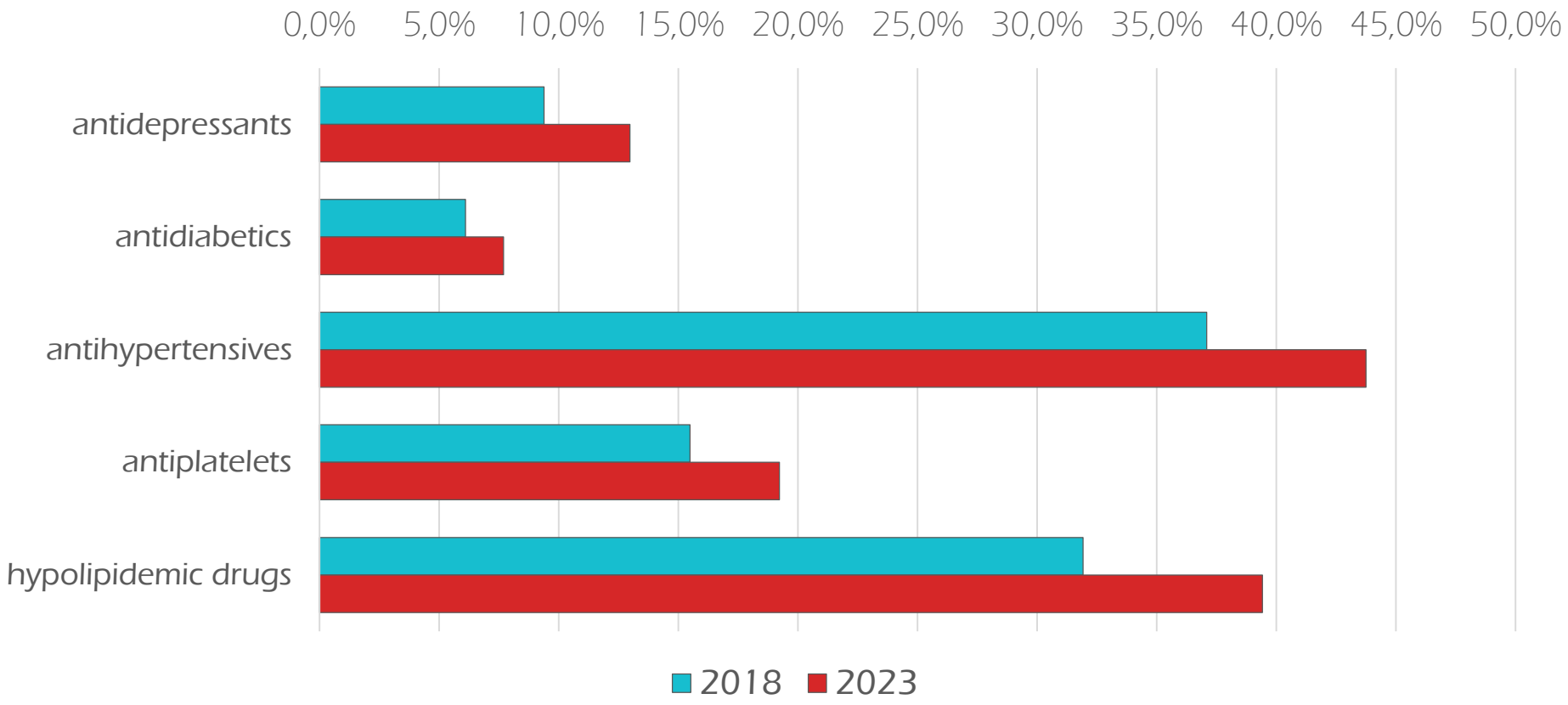
Most PLWH experienced many ART regimens (median of 6 treatment lines) and had a long history of HIV infection (mean 22 years)





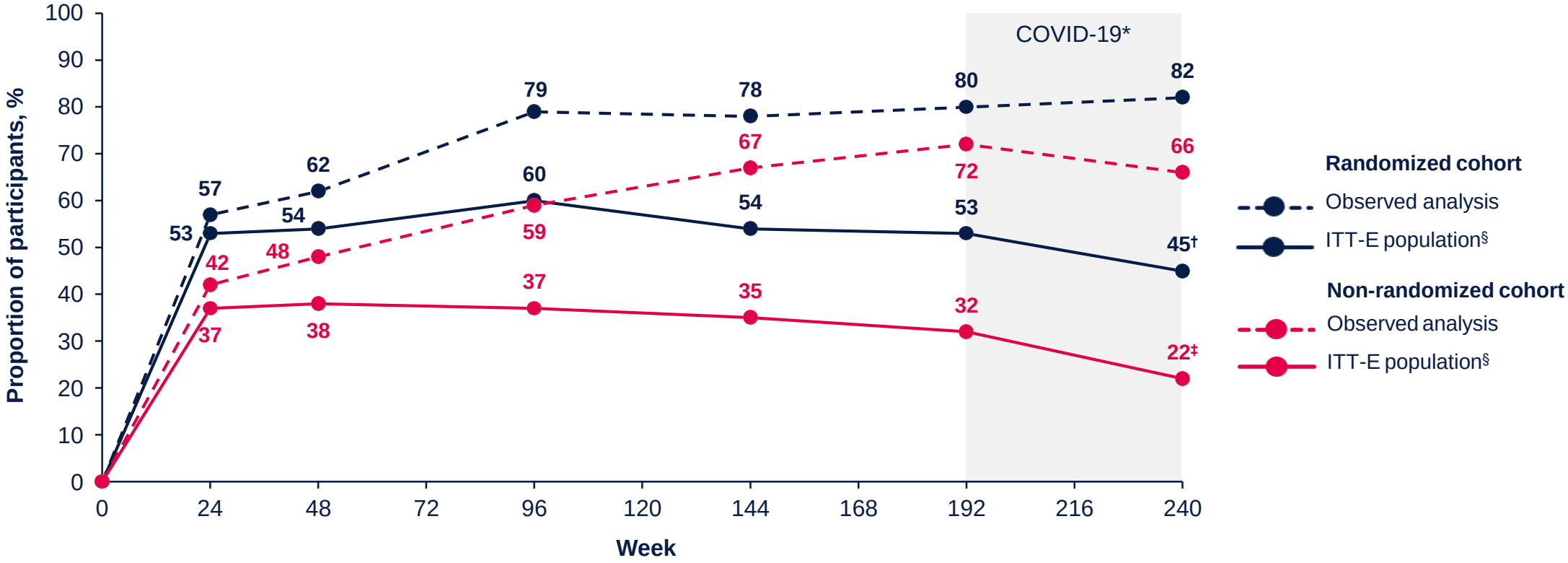
M. Polisseno, JAIDS 2023

CONCOMITANT THERAPIES



Castagna A., ICAR 2023

BRIGHTE: HIV-1 RNA <40 c/mL Through Week 240 by ITT-E Snapshot Analysis and Observed Analysis



- Rates of virologic suppression (by Snapshot analysis) were consistent through Week 192. Beyond Week 192, results were confounded by missing data related to inability to attend study visit(s) because of the COVID-19 pandemic
- In the randomized cohort at Week 240, of the 60% of participants who remained in the study with available efficacy data, >80% had HIV-1 RNA <40 c/mL
- Virologic response rates were partially confounded by missing data due to the COVID-19 pandemic, and changes in OBT that were classed as treatment failures

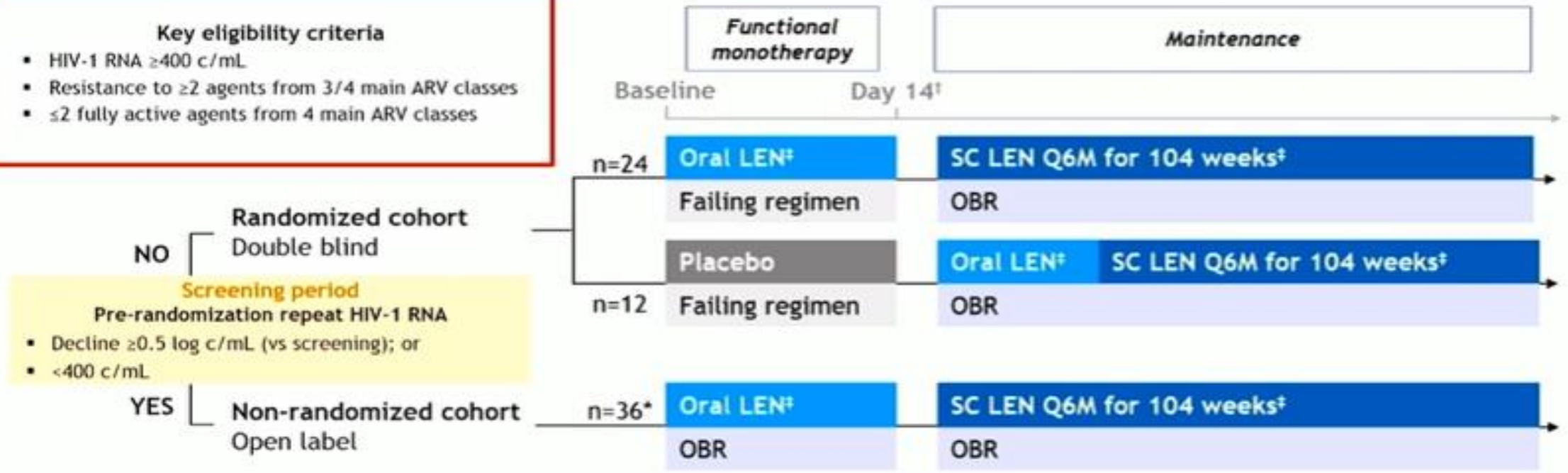
*The COVID-19 pandemic resulted in missing data related to inability to attend study visit(s)
†ITT-E population, N=267; ‡ITT-E population, N=92; §ITT-E participants without an HIV-1 RNA value at the relevant time point or those who changed OBT due to lack of efficacy up to each time point counted as failures

Aberg, J, et al. IAC 2022. Poster EPB160

CAPELLA Study Design[1]

Key eligibility criteria

- HIV-1 RNA ≥400 c/mL
- Resistance to ≥2 agents from 3/4 main ARV classes
- ≤2 fully active agents from 4 main ARV classes



- 82% of participants were suppressed at Week 104 (M=E)[2]
- Mean increase in CD4 cell count of 122 cells/μL from baseline to Week 104[2]

*Enrolled after not meeting criteria for randomized cohort, n=3; enrolled after randomized cohort enrollment was completed, n=33 (of those, n=28 met the randomization criteria). †Primary endpoint: HIV-1 RNA decrease ≥0.5 $\log_{10}$ c/mL in randomized cohort. ‡Oral LEN 600 mg on Days 1 and 2, and 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in abdomen on Day 15 then Q6M.

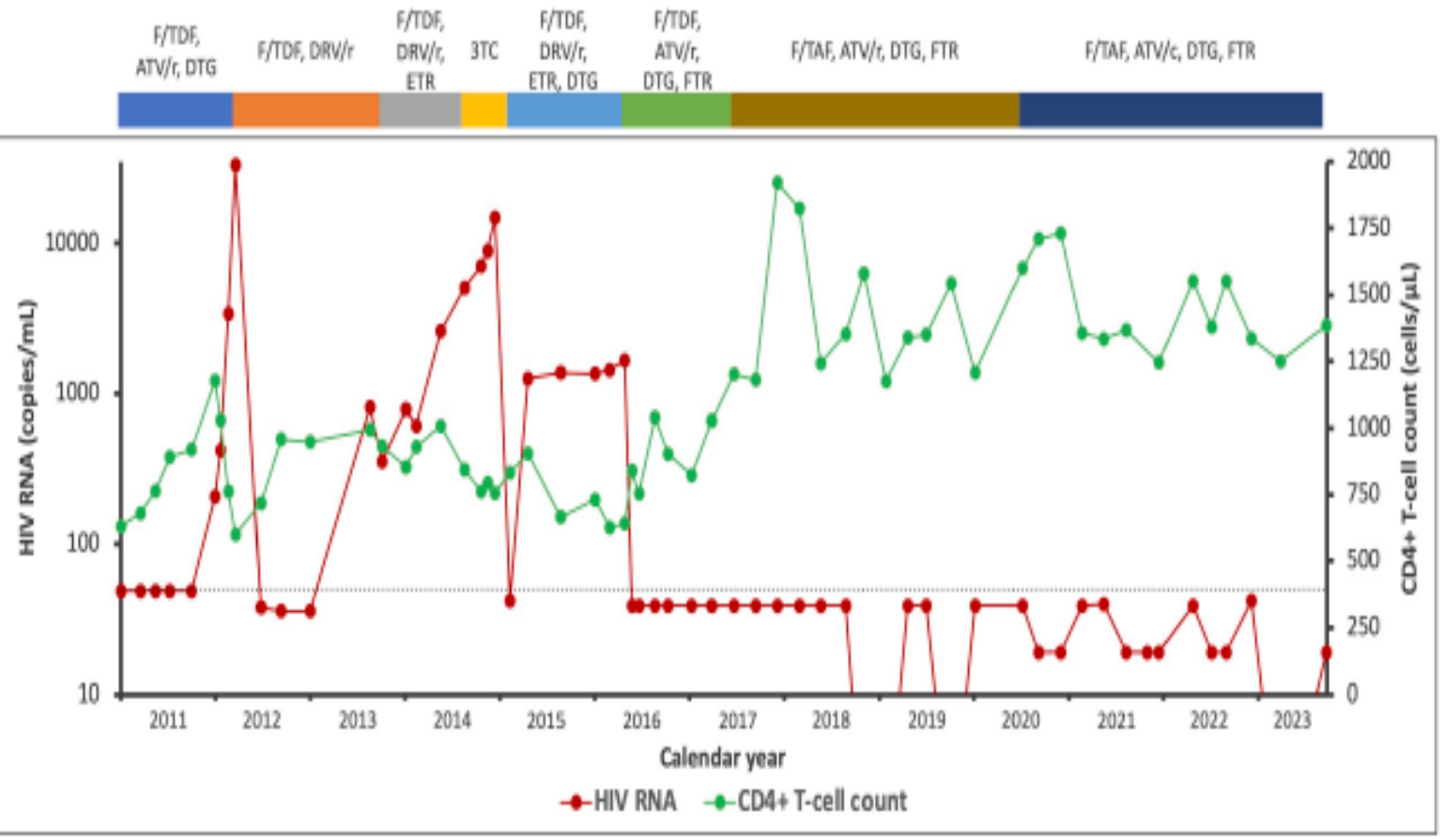
1. Segal-Maurer S, et al. *N Engl J Med* 2022;386:1793–803. 2. Ogbuago O, et al. Presented at IDWeek 2023; Poster 1596.

ARV, antiretroviral; c/mL, copies/mL; LEN, lenacapavir; M=E, missing=excluded; OBR, optimized background regimen; Q6M, every 6 months; SC, subcutaneous.

N. Margot, EACS 2023

How to choose the optimized background therapy with fostemsavir in viremic people with multidrug-resistant HIV?

Figure 1. HIV-1 RNA, CD4⁺ T-cell count, and antiretroviral therapy from January 2011 to September 2023



	Combined genotypic + phenotypic (April 2016)	
	Phenotype	Genotype
NRTI + NNRTI resistance-associated mutations	NRTI: M41L, A62V, D67N, V75I, M184V, L210W, T215Y, K219R – NNRTI: V90I, K103N, E138G, V179I, Y188L, K238T	
Abacavir (ABC)	Partially sensitive	Resistant
Didanosine (ddI)	Partially sensitive	Resistant
Emtricitabine (FTC)	Resistant	Resistant
Lamivudine (3TC)	Resistant	Resistant
Stavudine (d4T)	Resistant	Resistant
Zidovudine (AZT)	Resistant	Resistant
Tenofovir (TDF)	Partially sensitive	Resistant
Delavirdine (DLV)	Resistant	Resistant
Efavirenz (EFV)	Resistant	Resistant
Etravirine (ETR)	Resistant	Resistant
Nevirapine (NVP)	Resistant	Resistant
Rilpivirine (RPV)	Resistant	Resistant
Doravirine (DOR)	-	-
PI resistance-associated mutations	L10I, V11I, I13V, K20R, V32I, L33F, E35D, M36I, M46I, I47V, I50V, I54L, A71V, V82I, I85V, L90M	
Atazanavir (ATV)	Resistant	Resistant
Atazanavir/ritonavir (ATV/r)	Sensitive	Resistant
Darunavir/ritonavir (DRV/r)	Resistant	Resistant
Fosamprenavir/ritonavir (FPV/r)	Resistant	Resistant
Indinavir/ritonavir (IDV/r)	Sensitive	Resistant
Lopinavir/ritonavir (LPV/r)	Resistant	Resistant
Nelfinavir (NFV)	Resistant	Resistant
Ritonavir (RTV)	Resistant	Resistant
Saquinavir/ritonavir (SQV/r)	Partially sensitive	Resistant
Tipranavir/ritonavir (TPV/r)	Sensitive	Sensitive
INSTI resistance-associated mutations	T97A, E128K, G140S, Q148H	
Dolutegravir (DTG)	Resistant	Resistant
Elvitegravir (EVG)	Resistant	Resistant
Raltegravir (RAL)	Resistant	Resistant
Bictegravir (BIC)	-	-
Cabotegravir (CAB)	-	-

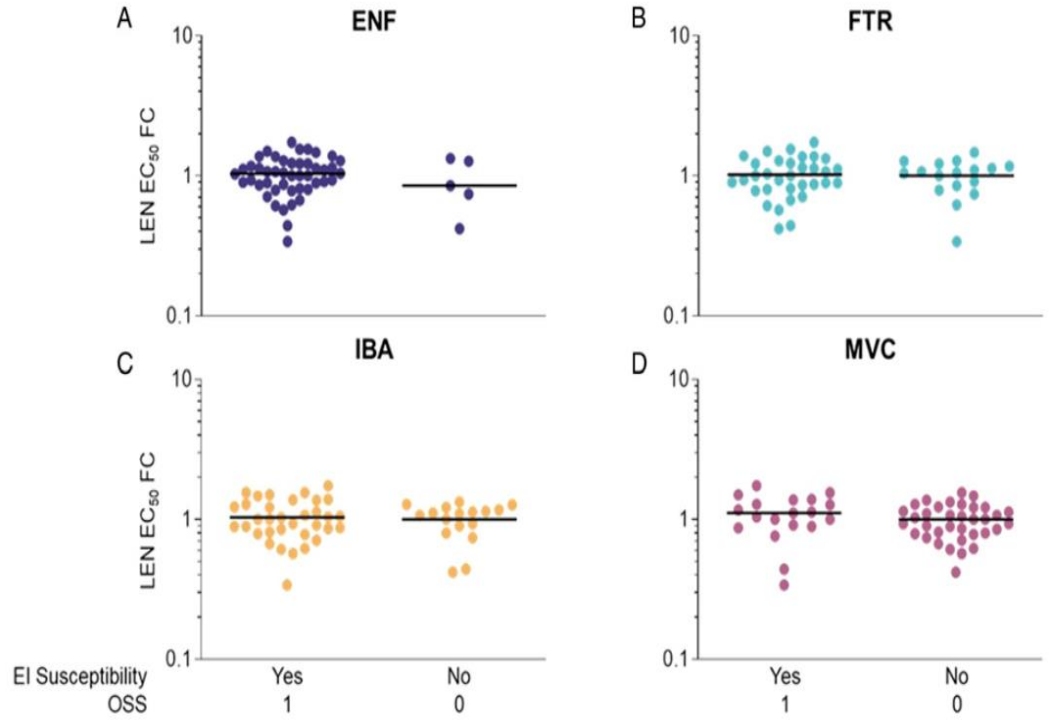
T. Clemente, EACS 2023 eP.CC.060

Cross-resistance to entry inhibitors and lenacapavir resistance through Week 52 in study CAPELLA

Table 1. Summary of LEN susceptibility by EI susceptibility.

	Samples susceptible to EI		Samples not susceptible to EI	
EI	*n*	Mean LEN FC (range)	*n*	Mean LEN FC (range)
ENF	46	1.0 (0.34–1.74)	5	0.9 (0.42–1.33)
FTR	33	1.0 (0.42–1.74)	17	1.0 (0.34–1.47)
IBA	34	1.0 (0.34–1.74)	17	1.0 (0.42–1.33)
MVC	19	1.1 (0.34–1.74)	35	1.0 (0.42–1.55)

EI: entry inhibitor; LEN: lenacapavir; FC: fold change; ENF: enfuvirtide; FTR: fostemsavir; IBA: ibalizumab; MVC: maraviroc.



Phenotypic resistance associated with the HIV-1 envelope is not associated with resistance in the capsid gene.

N. Margot, AVT 2023

Case Report

Lenacapavir with Fostemsavir in a Multidrug-Resistant HIV-Infected Hemodialysis Patient

We report a hemodialysis MDR HIV-infected patient switched to fostemsavir with lenacapavir plus lamivudine for more than a year. She maintained a suppressed viral replication and did not present any clinical or biological drug-related side efects. The combination of lenacapavir plus fostemsavir looks promising in terms of safety and efficacy even in patients with end-stage renal disease awaiting renal transplant. Both drugs are frst in class ARVs so that there is no cross resistance with previous drugs, maintaining their efficacy against MDR HIV

F. Bigirimana, Case reports in ID , 2023

Teropavimab and Zinlirvimab Sensitivity in People Living With MDR HIV-1: PRESTIGIO Registry Data

V. Spagnuolo, CROI 2024 Accepted

Oral weekly Islatravir plus Lenacapavir

Phase II, randomized, open-label

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	75 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	A Phase 2 Randomized, Open-Label, Active-Controlled Study Evaluating the Safety and Efficacy of an Oral Weekly Regimen of **Islatravir** in Combination With Lenacapavir in Virologically Suppressed People With HIV
Actual Study Start Date :	October 5, 2021
Estimated Primary Completion Date :	August 2023
Estimated Study Completion Date :	December 2027

Experimental: ISL+LEN

Participants will receive the following for at least 48 weeks:

- ISL 40 mg and LEN 600 mg on Days 1 and 2 (loading dose)
- ISL 20 mg and LEN 300 mg on Day 8 and every week thereafter

Experimental: B/F/TAF

Participants will receive the following for at least 48 weeks:

- bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) 50/200/25 mg once daily

After 48 weeks, participants will switch from B/F/TAF to ISL+LEN

- ISL 40 mg and LEN 600 mg (loading dose over 2 days)
- ISL 20 mg and LEN 300 mg 7 days after the first loading dose and every week thereafter

Participants who do not switch from B/F/TAF to ISL+LEN at Week 48 will be discontinued from the study.

Clin. Trial. Gov 2022

ACTIVE, NOT RECRUITING

Study to Compare Bictegravir/Lenacapavir Versus Current Therapy in People With HIV-1 Who Are Successfully Treated With a Complicated Regimen

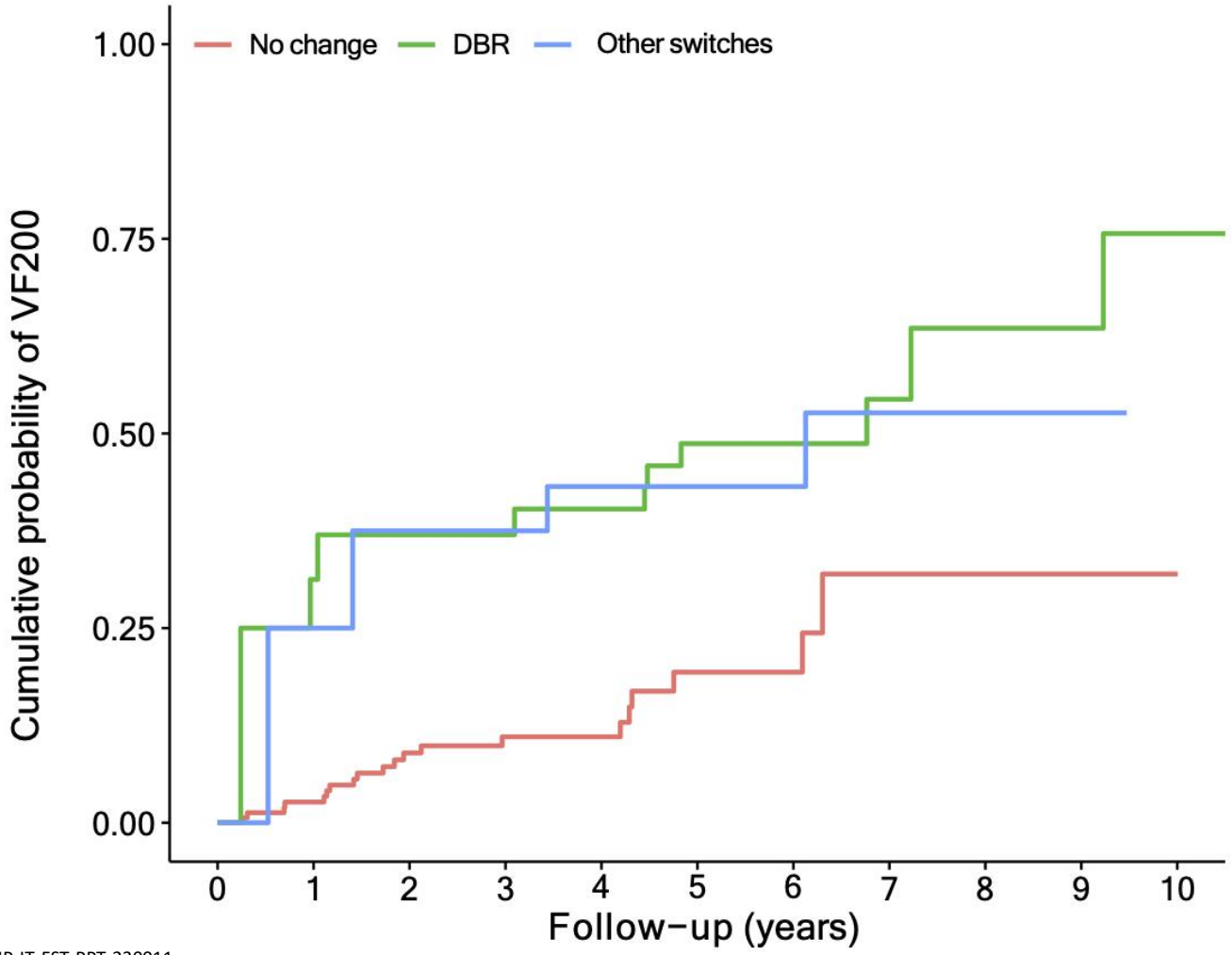
An Phase 2/3 Randomized, Open-label, Multicenter, Active-Controlled Study to Evaluate the Safety and Efficacy of Bictegravir/Lenacapavir Versus Stable Baseline Regimen in Virologically Suppressed People With HIV-1 on Stable Complex Treatment Regimens

Participants will switch from their stable baseline regimen to a regimen of BIC 75 mg plus LEN 25 (or 50 mg)
Participants will receive a 2-day loading dose regimen of LEN 600 mg, in addition to the daily doses of BIC 75 mg plus LEN 25 mg (or 50 mg) starting on Day 1 up to the end of randomized treatment (ERT) visit,

Following Randomized Period, the participants will have an option to participate in an Extension Period to receive BIC/LEN fixed dose combination (FDC) at the selected dos

Time to and risk of VF200 in 166 people with 4DR HIV and undetectable viral load

During a median FU of 3.8 (IQR=2.3-5.6) years, 34/166 (20.5%) individuals had VF200.



	Unadjusted Hazard ratio (95%CI)	P-value
DBR vs No change	2.20 (0.89-5.44)	0.08
DBR vs Other switches	1.19 (0.37-3.81)	0.76
Other switches vs No change	1.84 (0.54-6.24)	0.32

T. Clemente EACS 2023

RESCUE THERAPY

Table 2
Rescue regimens introduced after virological two-drug regimen (2DR) failure or discontinuation for toxicity in people living with human immunodeficiency virus (PLWH) included in the analysis according to reason of failure.

Rescue regimen after 2DR failure	Type of failed 2DR					
	Virological failure			Discontinuation for toxicity		
	Overall (n = 82)	INSTI-based 2DR (n = 47)	PI/b-based 2DR (n = 35)	Overall (n = 144)	INSTI-based 2DR (n = 51)	PI/b-based 2DR (n = 93)
INSTI-based 3DR	16 (19.5%)	15 (31.9%)	1 (2.9%)	31 (21.5%)	12 (23.5%)	19 (20.4%)
PI/b-based 3DR	3 (3.7%)	1 (2.1%)	2 (5.7%)	9 (6.3%)	9 (17.6%)	0
NNRTI-based 3DR	0	0	0	26 (18.1%)	9 (17.6%)	17 (18.3%)
INSTI-based 2DR	5 (6.1%)	2 (4.3%) changed to another INSTI-based 2DR	3 (8.6%)	30 (20.8%)	2 (3.9%) changed to another INSTI-based 2DR	28 (30.1%)
PI/b-based 2DR	0	0	0	35 (24.3%)	15 (29.4%)	20 (21.5%) changed to another PI/b-based 2DR
4-drug regimen	3 (3.7%)	3 (6.4%)	0	0	0	0
PI/b-based monotherapy	0	0	0	13 (9.0%)	4 (7.8%)	9 (9.7%)
No ART change	55 (67.1%)	26 (55.3%)	29 (82.9%)	0	0	0

3DR, three-drug regimen; ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI/b, boosted protease inhibitor.

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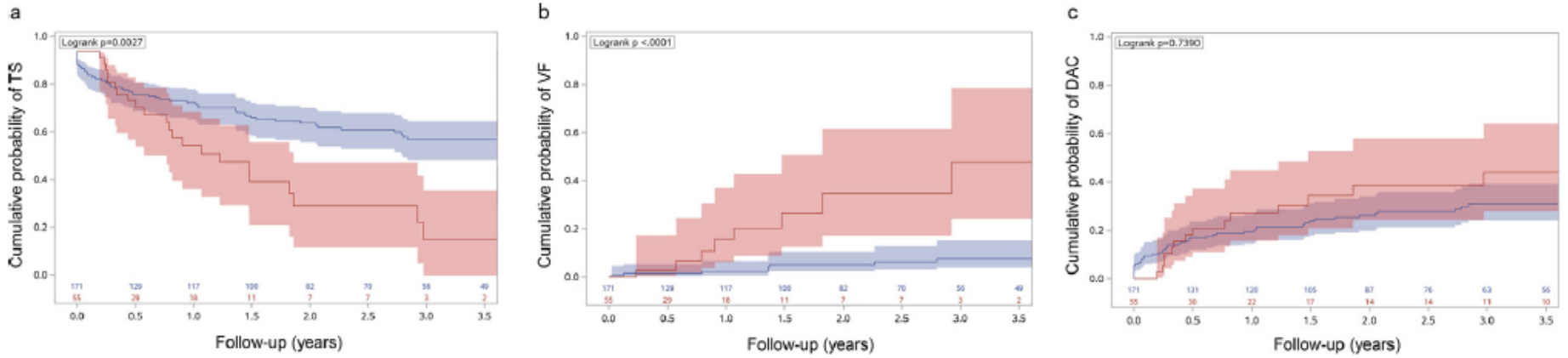
RESCUE THERAPY



% cumulative TS probabilities of rescue regimens (95%CI)		
Time Point	No ART modification	ART modified
6 months	79.5 (63.1 – 89.2)	82.0 (75.2 – 87.0)
12 months	60.7 (42.4 – 74.8)	78.7 (71.6 – 84.2)
18 months	45.7 (27.5 – 62.1)	72.4 (64.7 – 78.7)
24 months	35.5 (17.9 – 53.6)	70.0 (62.1 – 76.6)

% cumulative VF probabilities of rescue regimens (95%CI)		
Time Point	No ART modification	ART modified
6 months	2.6 (0.4 – 17.2)	1.3 (0.3 – 5.1)
12 months	15.5 (6.0 – 36.9)	2.1 (0.7 – 6.4)
18 months	26.3 (12.3 – 50.7)	4.8 (2.2 – 10.5)
24 months	34.5 (17.1 – 61.6)	4.8 (2.2 – 10.5)

% cumulative DAC probabilities of rescue regimens (95%CI)		
Time Point	No ART modification	ART modified
6 months	17.9 (19.0 – 34.0)	16.8 (11.9 -23.5)
12 months	27.0 (15.5 – 44.6)	19.4 (14.2 -26.4)
18 months	30.3 (17.9 – 48.4)	23.6 (17.8 – 31.1)
24 months	38.6 (24.0 – 57.9)	26.0 (19.8 – 33.7)

Fig. 1. Kaplan–Meier curves for probabilities of (a) overall treatment success (TS), (b) virological failure (VF) and (c) discontinuation for any other cause (DAC) in people living with human immunodeficiency virus who switched (blue line) or did not switch (red line) their two-drug antiretroviral therapy (ART) regimen after treatment failure. CI, confidence interval.

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TAKE HOME MESSAGES

- Defining HTE population.
- Acheiving undetectable viral load is essential.
- U=U and STIs.
- Simplification strategy is possible?

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PRESTIGIO Study Group

STEERING COMMITTEE: Antonella Castagna (Coordinator), Vincenzo Spagnuolo, Laura Galli, Franco Maggiolo, Leonardo Calza, Emanuele Focà, Filippo Lagi, Giovanni Cenderello, Antonio Di Biagio, Giulia Marchetti, Stefano Rusconi, Adriana Cervo, Roberta Gagliardini, Stefano Bonora, Anna Maria Cattelan, Maurizio Zazzi, Maria Mercedes Santoro

VIROLOGY TEAM AND BIOLOGICAL BANK: Maurizio Zazzi, Maria Mercedes Santoro, Andrea Galli, Francesco Saladini, Daniele Armenia

STUDY COORDINATORS: Elisabetta Carini, Sabrina Bagaglio

STATISTICAL AND MONITORING TEAM: Laura Galli, Riccardo Lolatto, Sara Diotallevi

ENROLLING CENTERS: *ANCONA*: Marcello Tavio, Alessandra Mataloni Paggi; *BARI*: Annalisa Saracino, Flavia Balena; *BERGAMO*: Franco Maggiolo, Laura Comi, Daniela Valenti, Claudia Suardi; *BOLOGNA*: Leonardo Calza, Malerba Federica; *BRESCIA*: Francesco Castelli, Emanuele Focà, Davide Minisci, Francesca Pennati, Anna Celotti, Francesca Brognoli; *BUSTO ARSIZIO*: Barbara Menzaghi, Maddalena Farinazzo; *CATANIA*: Bruno Cacopardo, Maurizio Celesia, Michele Salvatore Paternò Raddusa, Carmen Giarratana; CATANZARO: Carlo Torti, Paolo Fusco, Gabriele Bruno; *CREMONA*: Angelo Pan, Paola Brambilla, Chiara Fornabaio; *FIRENZE*: Alessandro Bartoloni, Filippo Lagi, Susanna Giachè, Francesca Vichi, Francesco Maria Fusco, Alessio Bellucci, Elisa Mirabelli, Paola Corsi, Seble Tekle Kiros, Filippo Ducci; *FOGGIA*: Teresa Santantonio, Sergio Lo Caputo, Sergio Ferrara, Marianna Narducci; *GENOVA*: Emanuele Pontali, Marcello Feasi, Antonio Sarà, Matteo Bassetti, Antonio Di Biagio, Sabrina Blanchi; *MILANO*: Antonella Castagna, Vincenzo Spagnuolo, Elisabetta Carini, Sabrina Bagaglio, Laura Galli, Riccardo Lolatto, Andrea Galli, Rebecka Papaioannu, Tommaso Clemente, Sara Diotallevi, Spinello Antinori, Tiziana Formenti, Andrea Giacomelli, Giulia Marchetti, Lidia Gazzola, Federica De Flaviis, Massimo Puoti, Cristina Moioli, Federico D'Amico; *MODENA*: Cristina Mussini, Adriana Cervo, Enrica Roncaglia, Giulia Nardini, Barbara Beghetto; *NAPOLI*: Elio Manzillo, Amedeo Lanzardo; *PADOVA*: Anna Maria Cattelan, Maria Mazzitelli; *PALERMO*: Antonio Cascio, Marcello Trizzino; *PARMA*: Elisa Fronti, Diletta Laccabue; *PAVIA*: Roberto Gulminetti, Andrea Zuccarini; *PERUGIA*: Daniela Francisci, Elisabetta Schiaroli, Giuseppe De Socio; *REGGIO EMILIA*: Elisa Garlassi, Romina Corsini; *ROMA*: Roberta Gagliardini, Marisa Fusto, Loredana Sarmati, Vincenzo Malagnino, Tiziana Mulas, Simona Di Giambenedetto, Silvia Lamonica; *SANREMO*: Giovanni Cenderello, Rachele Pincino; *SIENA*: Mario Tumbarello, Massimiliano Fabbiani, Francesca Panza, Ilaria Rancan; *TORINO*: Giovanni Di Perri, Stefano Bonora, Micol Ferrara; *VERONA*: Marina Malena, Marta Fiscon

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