Sistema Socio Sanitario
Regione Lombardia
ASST Ovest Milanese

Advanced naive e terapia antiretrovirale

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COIs

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MEDICI CON L'AFRICA CUAMM

Background

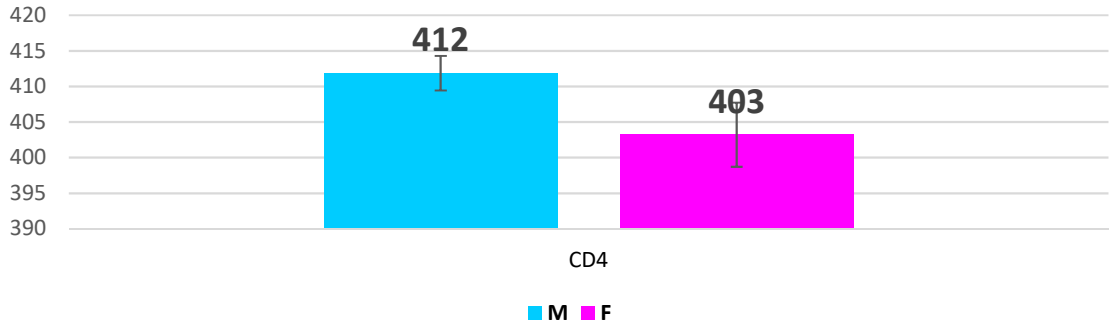
- Gli individui treatment-naive, nella pratica clinica, possono essere individuati:

- in ambiente ambulatoriale nell'ambito di campagne di screening -> tipicamente pazienti asintomatici con CD4+ > 200/mm^3

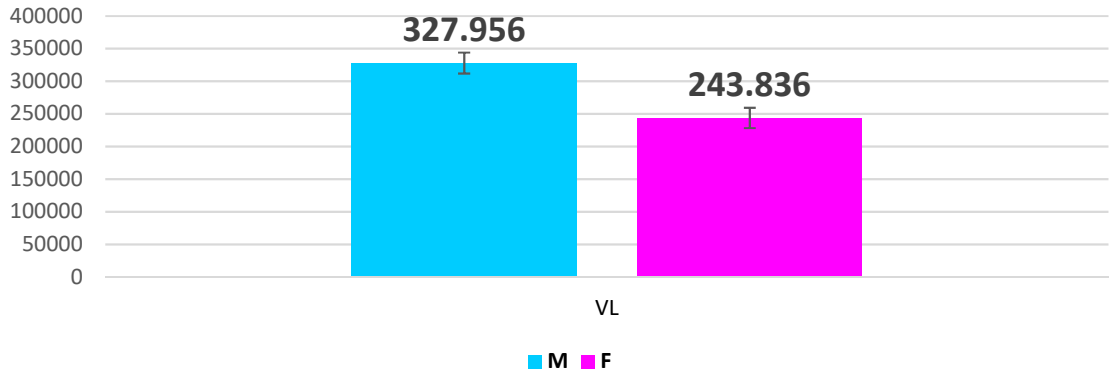
- in ambiente ospedaliero -> pazienti sintomatici/con infezione opportunistica e conta dei CD4+ < 200 mm^3

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Mean CD4 count and HIV-RNA viral load at enrolment



CD4 [cells/mmc] ±SD



HIV-RNA [copies/mL] ±SD

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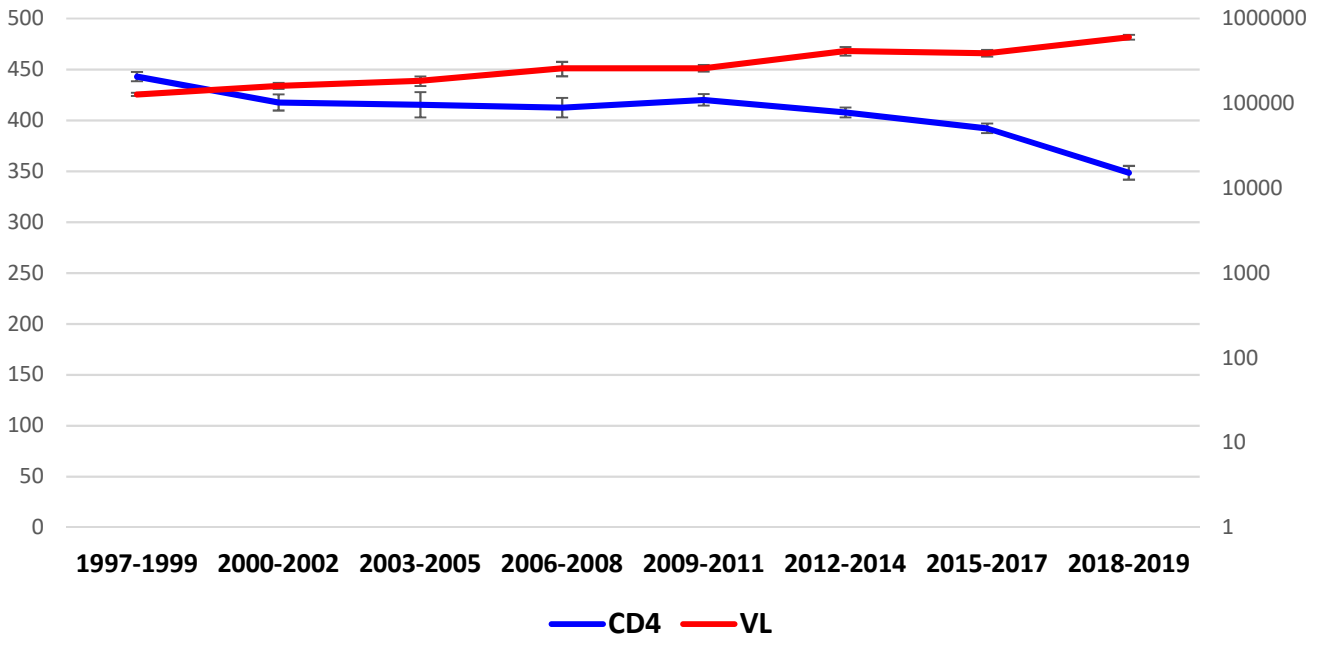
Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Mean CD4 count and HIV-RNA viral load at enrolment according to calendar period



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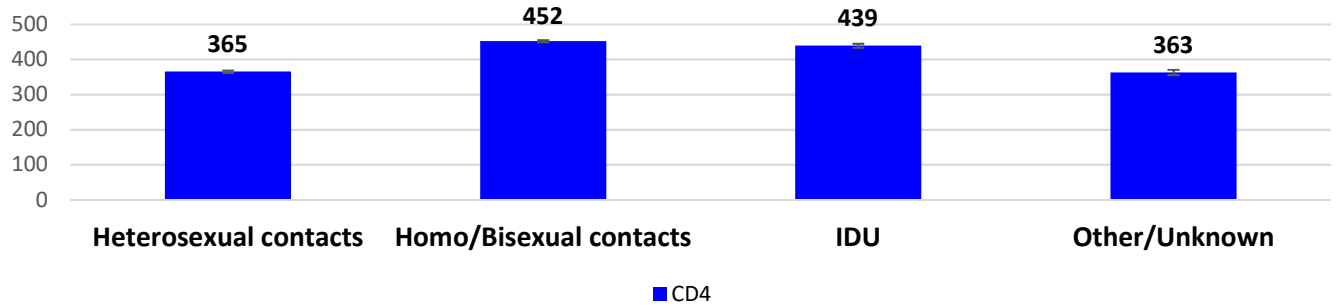
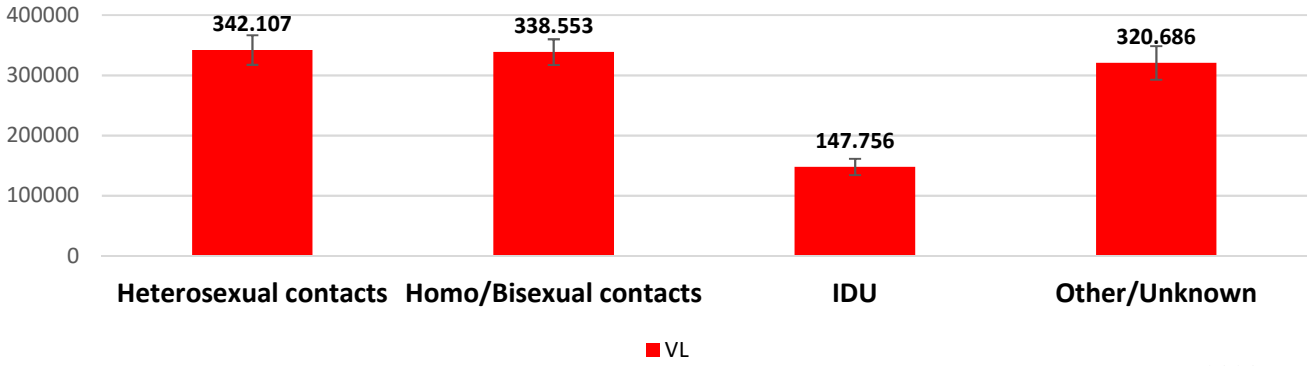
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Mean CD4 count at enrolment according to mode of HIV transmission



Mean HIV-RNA (cp/mL) at enrolment according to mode of HIV transmission



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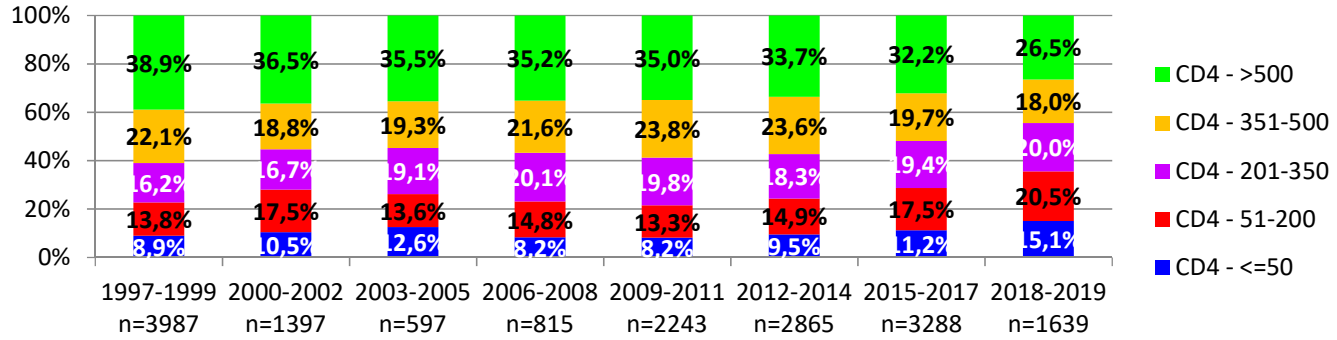
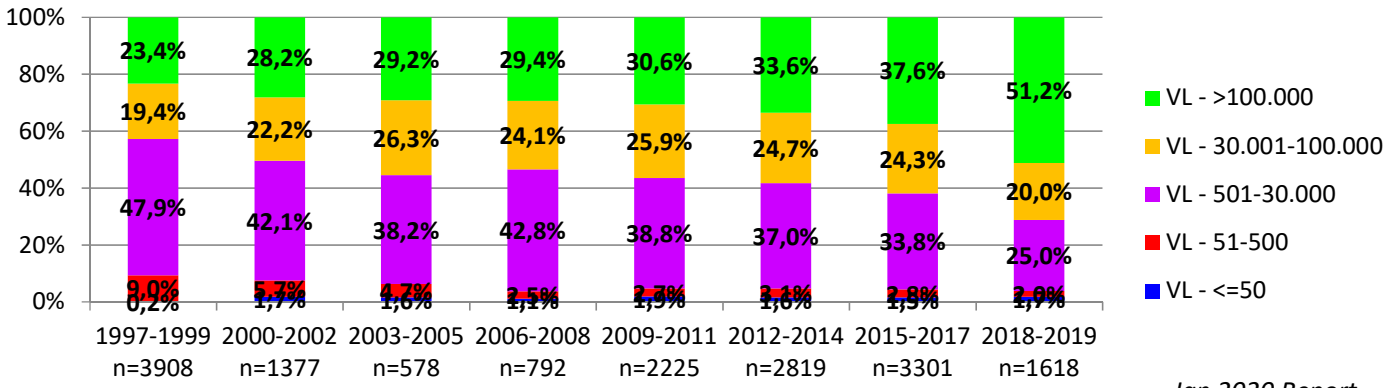
ITALIAN COHORT NAIVE ANTIRETROVIRALS

CD4 cells/mmc count strata at enrolment according to calendar period



HIV-RNA strata at enrolment according to calendar period



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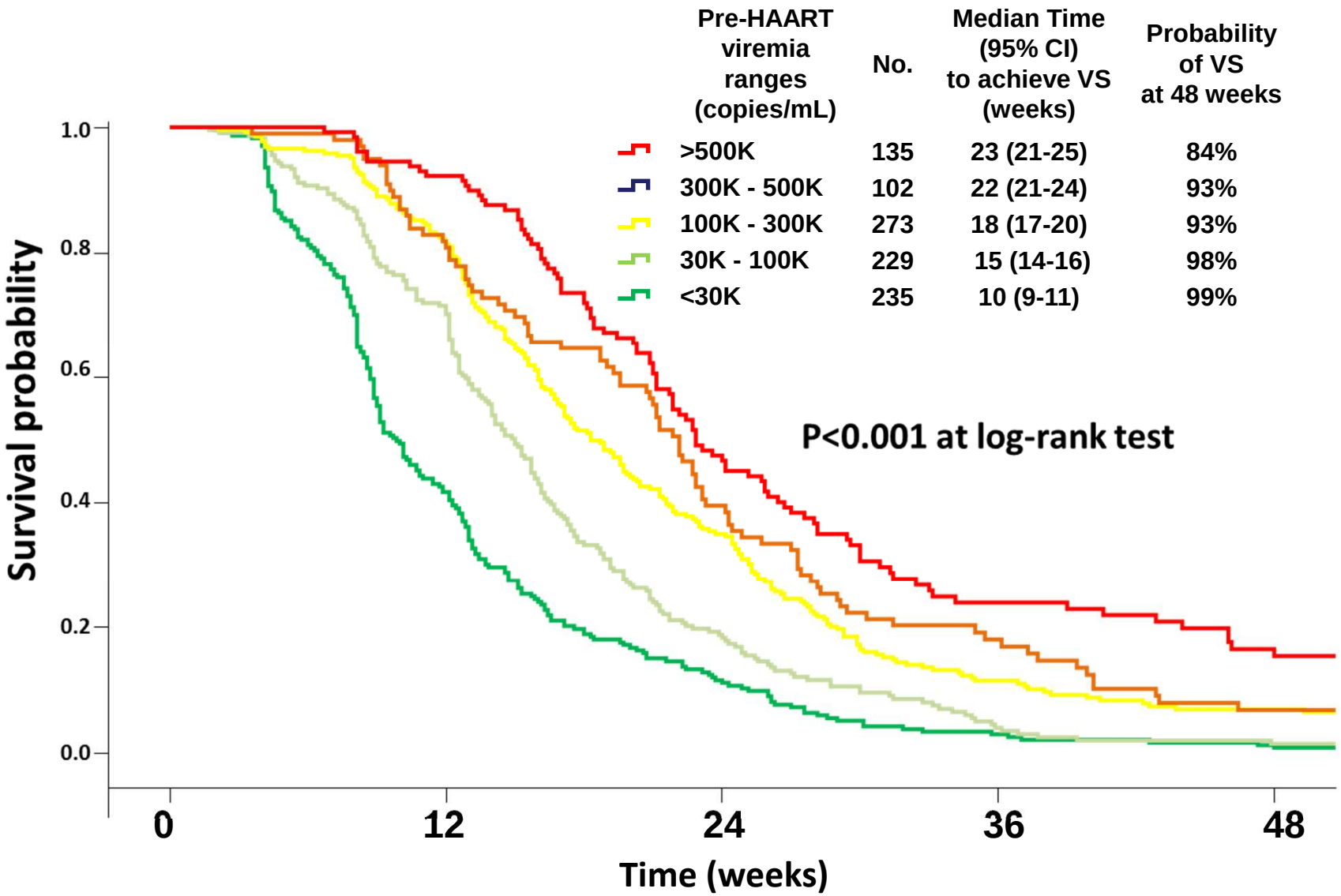
The time to achieve virological undectability and the rate of success at 48 weeks are pre-HAART viremia dependent



Santoro MM, et al. Antivir Ther. 2013;18:867-76

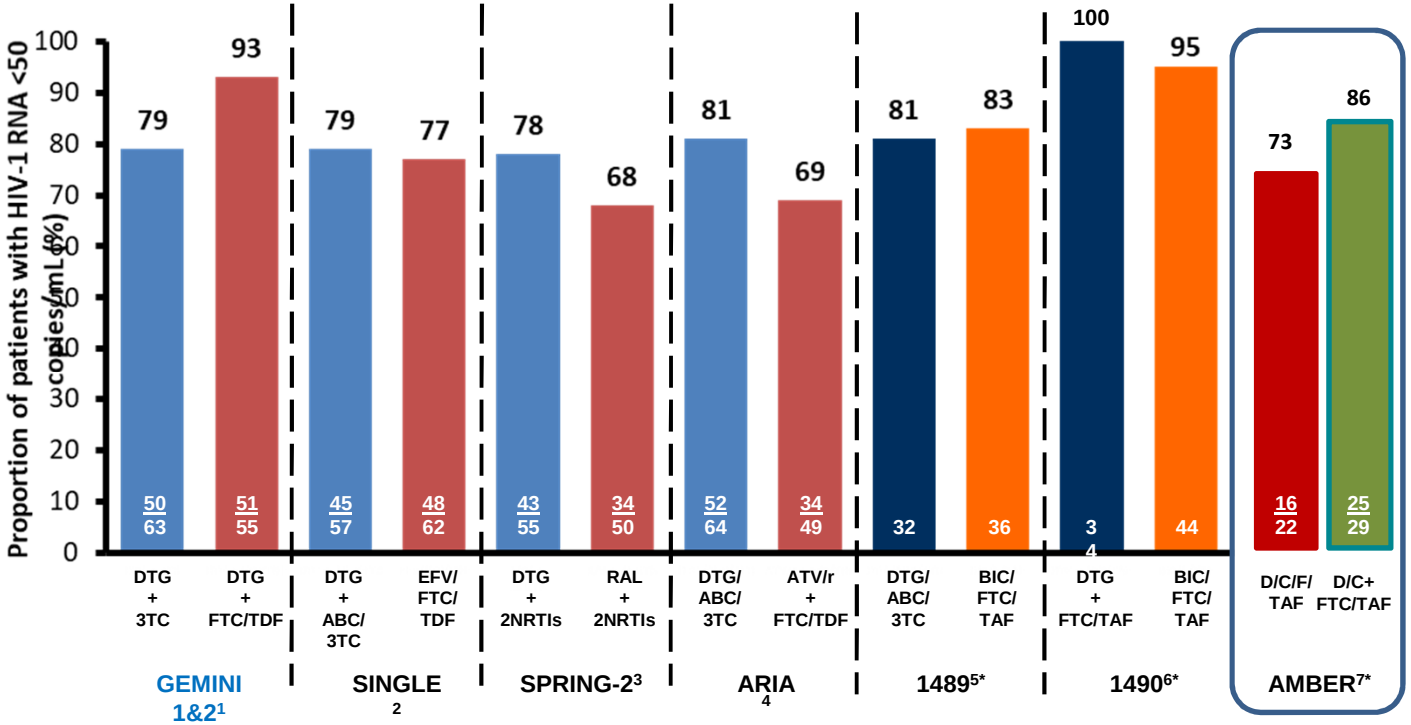
Risultati dai trial clinici

Baseline characteristics and Efficacy results- In Insti studies in HIV naive pts

		pVL (median)	VL>5 log	CD4 median	CD4<200	CD4<50	pVL<50c/mL at 48 w
STARMRK	RAL	5.1	55%	212	47%	10%	86.1 %
	EFV	5	51%	204	48%	11%	81.9 %
102	EVG/c	4.75	34%	391	12%		87.6 %
	EFV	4.78	33%	382	14%		84.1 %
103	EVG/c	4.88	43%	364	15%		89.5 %
	ATV/r	4.86	40%	375	11%		86.8 %
SINGLE	DTG	4.67	32%	335	14%		88 %
	EFV	4.70	31%	339	14%		81 %
SPRING-2	DTG	4.52	28%	359	13%		88 %
	RAL	4.58	28%	362	12%		85 %
FLAMINGO	DTG	4.49	25%	390	10%	2%	90 %
	DRV/r	4.48	25%	400	10%	2%	83 %
ACTG5257	RAL	4.7	32%	304	31%		80 % (96W)
	ATV/r	4.6	32%	309	29%		63 %
	DRV/r	4.6	28%	310	29%		73 %

Phase III Treatment-naïve Studies: Week 48 Snapshot Analysis

Week 48 snapshot analysis: Baseline CD4+ count ≤200 cells/mm3

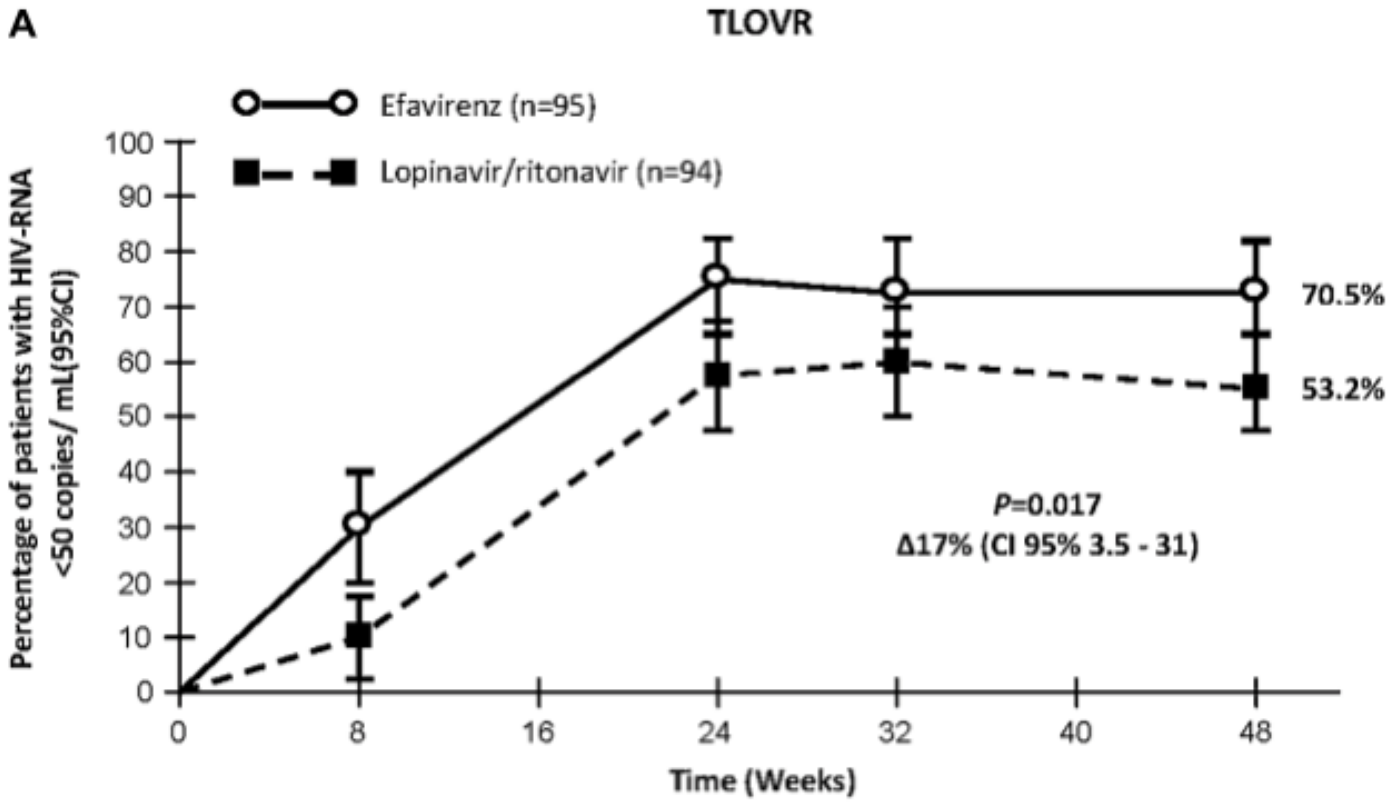


*Gilead-sponsored trials

1. Cahn P. et al., AIDS 2018, Oral Abstract TUAB0106LB; 2. Walmsley et al. N Engl J Med 2013;369:1807–18;
3. Raffi et al. Lancet 2013;381:735–43; 4. Orrell et al. Lancet 2017;4:e536–e546;
5. Gallant J, et al. Lancet 2017;390:2063–72; 6. Sax PE, et al. Lancet 2017;390:2073–82

Prospective, Randomized, Open Label Trial of Efavirenz vs Lopinavir/Ritonavir in HIV+ Treatment-Naive Subjects With $CD4^{+}<200$ cell/mm^3 in Mexico

Juan Sierra-Madero, MD, Angelina Villasis-Keever, MD, MSc,* Patricia Méndez, MD,†*
Juan Luis Mosqueda-Gómez, MD,‡ Indiana Torres-Escobar, MD, MPH,§
Fernanda Gutiérrez-Escolano, MD,¶ Irene Juárez-Kasusky, MD,‖ Martín Magana-Aquino, MD,#
*Carmen Ramos-Santos, MD,** Leticia Pérez-Saleme, MD,†† Sigfrido Rangel-Frausto, MD,‡‡*
Barbara Antuna-Puente, MD, Luis Enrique Soto-Ramírez, MD,* Vivian Lima, PhD,‡‡*
Franciso Belaunzarán-Zamudio, MD, MPH, Brenda Crabtree-Ramírez, MD,**
and Julio Montaner, MD, FRCPC, FCCP§§



Sierra-Madero JS, et al. J Acquir Immune Defic Syndr. 2010;53:582-8.

Journal of Antimicrobial Chemotherapy Advance Access published April 10, 2016

J Antimicrob Chemother
doi:10.1093/jac/dkw103

Journal of Antimicrobial Chemotherapy

Efficacy and safety of once-daily ritonavir-boosted atazanavir or darunavir in combination with a dual nucleos(t)ide analogue backbone in HIV-1-infected combined ART (cART)-naive patients with severe immunosuppression: a 48 week, non-comparative, randomized, multicentre trial (IMEA 040 DATA trial)

Laurence Slama[1]*, Roland Landman[2–4], Lambert Assoumou[5], Aida Benalycherif[3], Assia Samri[6], Véronique Joly[2], Gilles Pialoux[1], Nadia Valin[7], André Cabié[8], Claudine Duvivier[9], Sidonie Lambert-Niclot[10], Anne-Geneviève Marcelin[5,10], Gilles Peytavin[11], Dominique Costagliola[5] and Pierre-Marie Girard[4,7] on behalf of the IMEA 040 DATA Study Group†

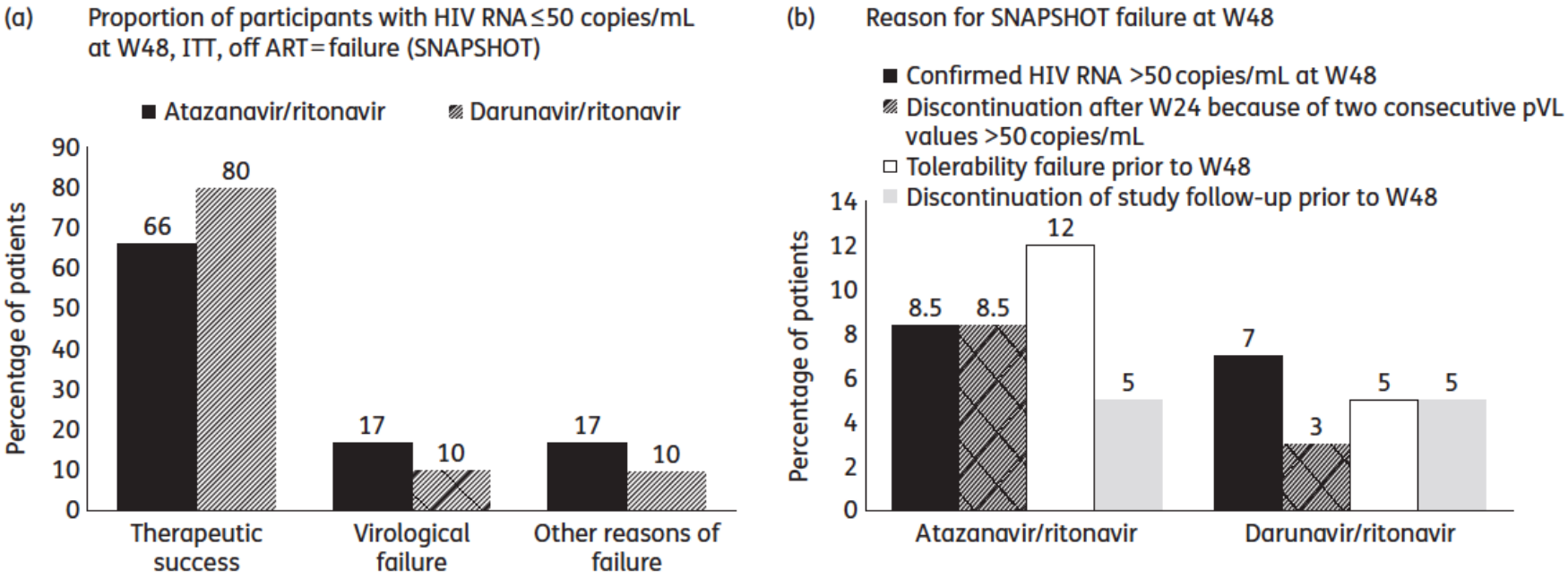


Figure 2. Proportion of participants with HIV RNA ≤50 copies/mL at W48, ITT, off ART = failure (SNAPSHOT) and reasons for failure at W48.

Table 2. Patients with virological failure in the atazanavir/ritonavir and darunavir/ritonavir groups

	Atazanavir/ritonavir-containing regimen			
Patient	pVL at baseline (copies/mL)	pVL at failure (copies/mL)	atazanavir plasma C_{min} >150 ng/mL (*n*/*N*)	Resistance mutations at failure
1	3170000	53 (W48)	4/4	PI: 36I, 62V, 63P
2	970000	114 (W48)	4/4	PI: non-amplifiable RT: 106I
3	2900000	630 (W31)	4/4	PI: 15V, 16E, 20R, 36I RT: 179I, 190A, 215L
4	573000	128 (W46)	5/5	PI: 33I, 62V, 63P, 77I RT: 65R
5	568382	122 (W39)	5/5	PI: NA
6	319000	53800 (W48)	2/2	PI: 63P, 77I RT: 184V
7	263000	1660 (W38)	2/2	PI: 10V, 11I, 63P, 69K, 71T RT: 184V
8	137500	23952 (W28)	3/4	PI: 46I/M, 62V, 71V, 77I, 88S/N RT: 184V
9	315072	215 (W48)	4/4	PI: 11I, 20I, 36I, 69K, 89M
10	81622	36345 (W48)	3/3	PI: 30N, 71V, 77I, 88D RT: 179D
	Darunavir/ritonavir-containing regimen			
Patient	pVL at baseline (copies/mL)	pVL at failure (copies/mL)	darunavir plasma C_{min} >1300 ng/mL (*n*/*N*)	Resistance mutations at time of failure
11	562008	111 (W48)	0/4	PI: 60E, 63P, 77I
12	4575322	142 (W48)	4/4	PI: 15V, 16E, 20R, 36I RT: 69S
13	860600	183 (W41)	0/4	RT: 215S
14	230000	378 (W48)	3/5	PI: 20I, 36I, 69K, 89M RT: 184V, 103N
15	197239	131 (W48)	5/6	PI: 20I, 36I, 69K, 89M RT: 101E
16	490000	90 (W36)	1/2	PI: 16E, 20I, 36I, 62V, 69K, 89M

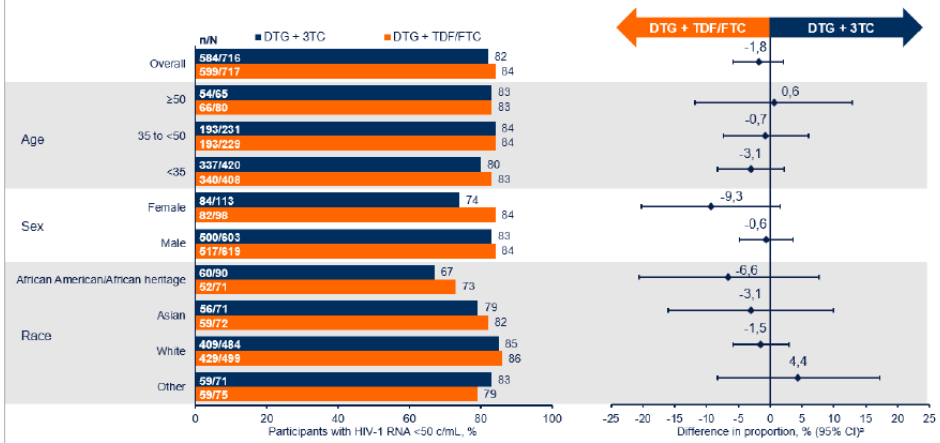
Nine of the 10 patients on atazanavir/ritonavir who experienced virological failure were receiving a tenofovir disoproxil fumarate/emtricitabine backbone and 9/10 were adherent to their ART, based on atazanavir C_{min} values >150 ng/mL (efficacy threshold) at all follow-up visits. All six patients in the darunavir group who experienced virological failure were receiving a tenofovir disoproxil fumarate/emtricitabine backbone, but two were non-adherent based on darunavir C_{min} values <1300 mL (efficacy threshold) at all follow-up visits.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR THE POOLED GEMINI-1 AND GEMINI-2 POPULATION

Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32 (18-72)	33 (18-70)
≥50 y, n (%)	65 (9)	80 (11)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
African American/African heritage	97 (14)	76 (11)
Asian	71 (10)	72 (10)
White	480 (67)	497 (69)
Other	68 (9)	72 (10)
Ethnicity, n (%)		
Hispanic or Latino	215 (30)	232 (32)
Not Hispanic or Latino	501 (70)	485 (68)
HIV-1 RNA, median (range), log_{10} c/mL	4.43 (1.59-6.27)	4.46 (2.11-6.37)
≤100,000	576 (80)	564 (79)
>100,000[a]	140 (20)	153 (21)
CD4+ cell count, median (range), cells/mm^3	427.0 (19-1399)	438.0 (19-1497)
>200	653 (91)	662 (92)
≤200	63 (9)	55 (8)

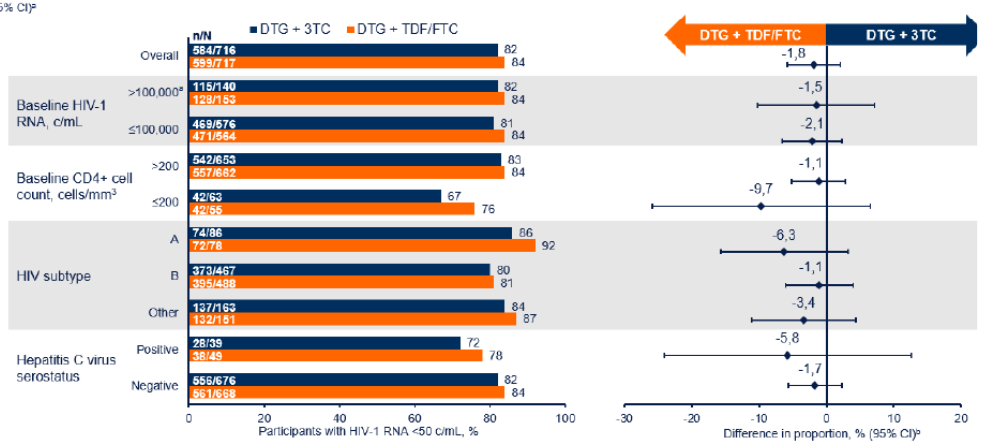
Cahn et al. IAS 2019; Mexico City, Mexico. Slides WEAB0404LB.

HIV-1 RNA <50 c/mL Was Comparable Across Demographic Subgroups at Week 144



[a]Adjusted difference (95% CI) for overall population (DTG + 3TC − DTG + TDF/FTC). Unadjusted difference for subgroups calculated by proportion on DTG + 3TC − proportion on DTG + TDF/FTC.

HIV-1 RNA <50 c/mL Was Comparable Across Baseline Disease Subgroups at Week 144

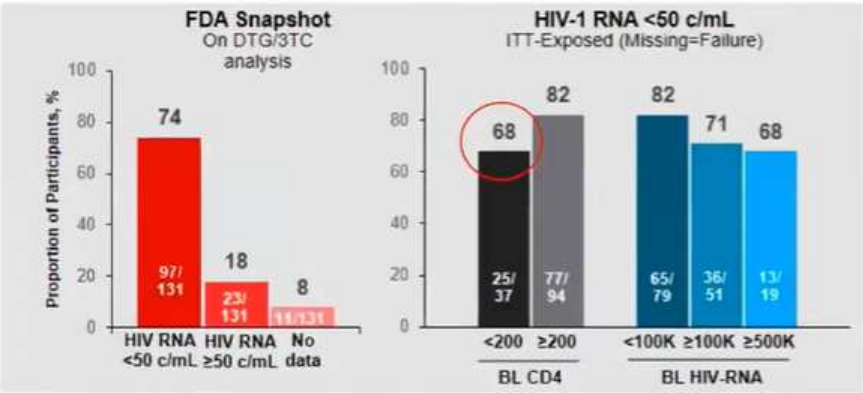


[a]Includes values for HIV-1 RNA >250,000 c/mL (DTG + 3TC, 41/51 [80%]; DTG + TDF/FTC, 37/46 [80%]), HIV-1 RNA >400,000 c/mL (DTG + 3TC, 15/18 [83%]; DTG + TDF/FTC, 19/24 [79%]), and HIV-1 RNA >500,000 c/mL (DTG + 3TC, 10/13 [77%]; DTG + TDF/FTC, 12/15 [80%]). [b]Adjusted difference for overall population (DTG + 3TC − DTG + TDF/FTC). Unadjusted difference for subgroups calculated by proportion on DTG + 3TC − proportion on DTG + TDF/FTC.

DTG/3TC as a First-Line Regimen: Test and Treat (within 14 Days) Strategy

Evaluation of efficacy and safety of DTG/3TC initiated within 14 days of diagnosis in ART-naïve adults where baseline laboratory results are not available (N=131)

Efficacy at Week 24



- 87% (97/111) achieved HIV-1 RNA <50 c/mL in the observed analysis
- No treatment-emergent resistance detected

Safety

- Grade 2-5 drug-related AEs (2%) and serious AEs (2%)
- 8 (6%) participants switched from DTG/3TC
  - 5 HBV, 1 M184V, 1 adverse event (rash), 1 withdrew
  - 7/8 switched to 3-drug regimen
- 15 (11%) participants discontinued the study
  - 9% loss to follow-up or withdrew consent
  - 2% investigator decision
- Absolute median increase in weight: +4.6 kg

DTG/3TC in a test and treat setting showed numerically lower viral suppression rates in participants with baseline CD4 <200 cells/mm^3 and VL ≥100,000 c/mL

Treatment modifications were necessary as a result of baseline HBV coinfection and NRTI resistance

Rolle CP, et al. HIV Drug Therapy 2020. Glasgow. P020

AE, adverse event; BL, baseline; ITT, intention to treat

What about using 4 drugs?

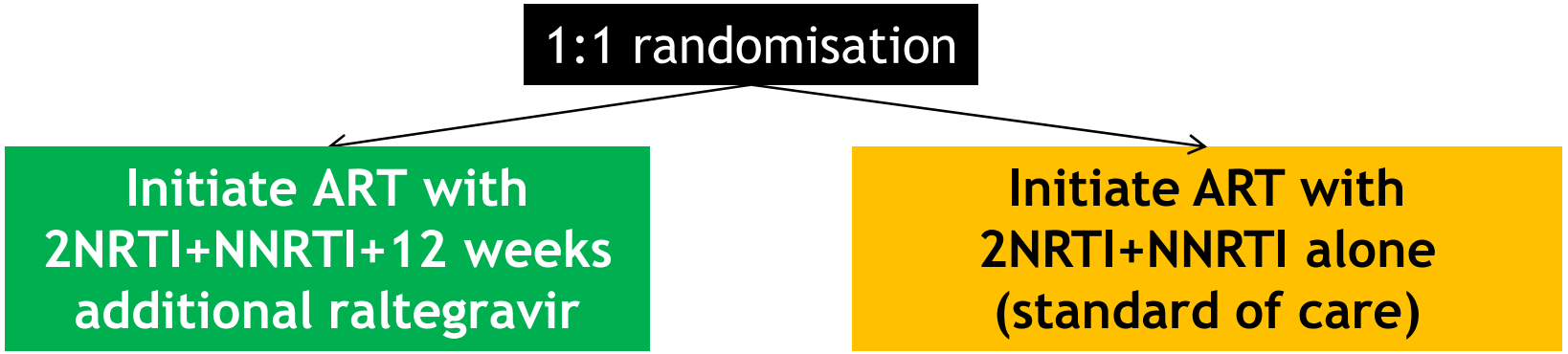
Adding Raltegravir…

12-week raltegravir-intensified quadruple therapy versus triple first-line ART reduces viral load more rapidly but does not reduce mortality in severely immunosuppressed African HIV-infected adults and older children: the REALITY trial

Cissy Kityo, Abraham Siika, Alexander J. Szubert, Jane Mallewa, Mutsa Bwakura-Dangarembizi, Sheila Kabahenda, Shalton Mwaringa, Sarah L. Pett, Anna Griffiths, Abbas Lugemwa, Simon Wachira, Godfrey Musoro, Chatu Rajapakse, Timothy Etyang, James Abach, Priscilla Wavamunno, Linda Nyondo-Mipando, Andrew Reid, Kusum Nathoo, James Hakim, Diana M. Gibb, A. Sarah Walker
and the REALITY trial team

Design

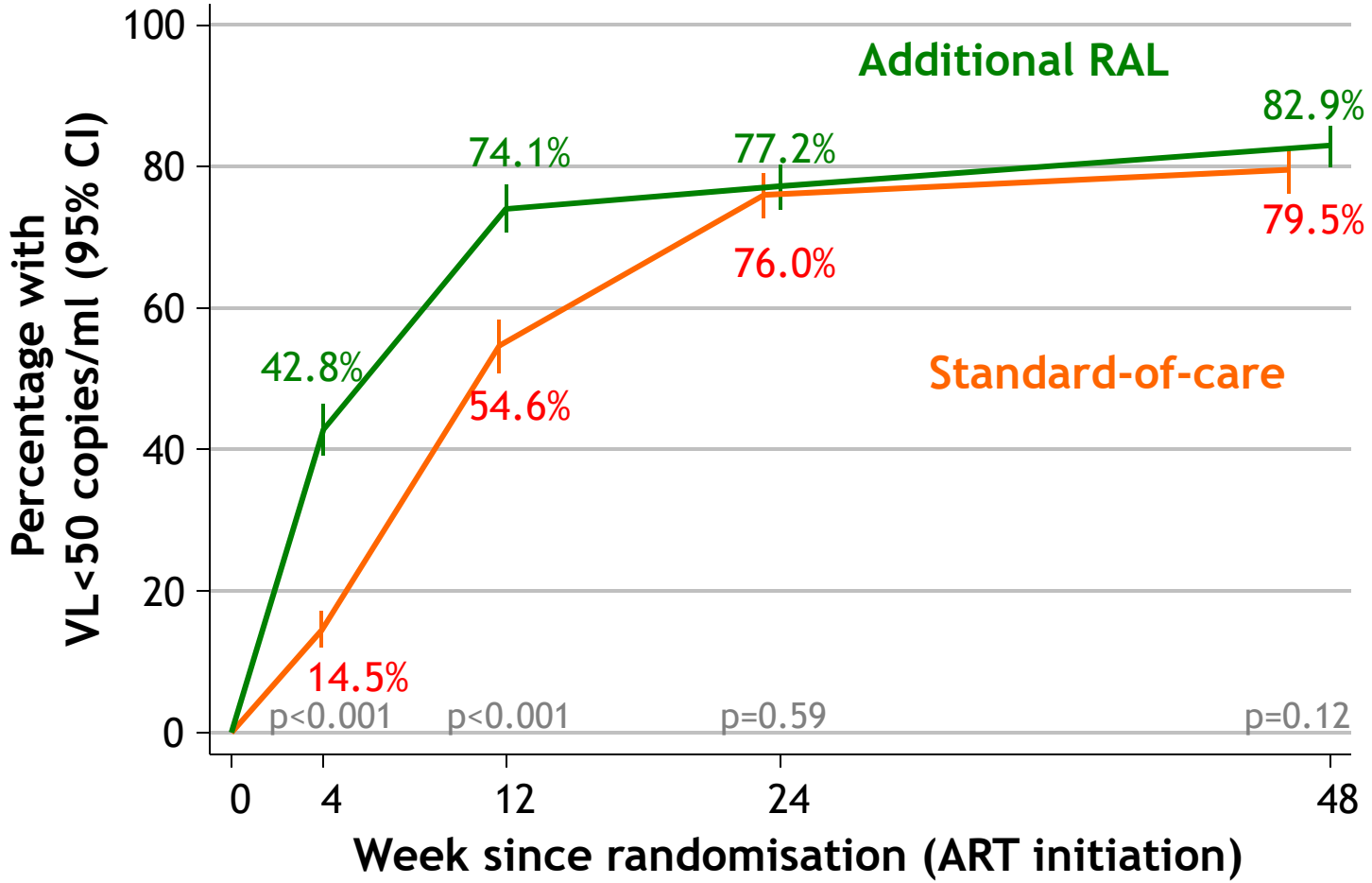
- ART-naïve HIV-infected adults, adolescents and children >5 years with CD4<100 cells/mm^3



- Follow-up to week 48
  - Safety bloods at screening, weeks 4 and 48; FBC & CD4 at weeks 0, 12, 24, 36, 48; Viral loads retrospectively at weeks 0, 4, 12, 24, 48
- Two other factorial randomisations investigated
  - 12 weeks enhanced prophylaxis (**FRAB0101LB**)
  - 12 weeks supplementary food
- **Primary endpoint: 24-week mortality**

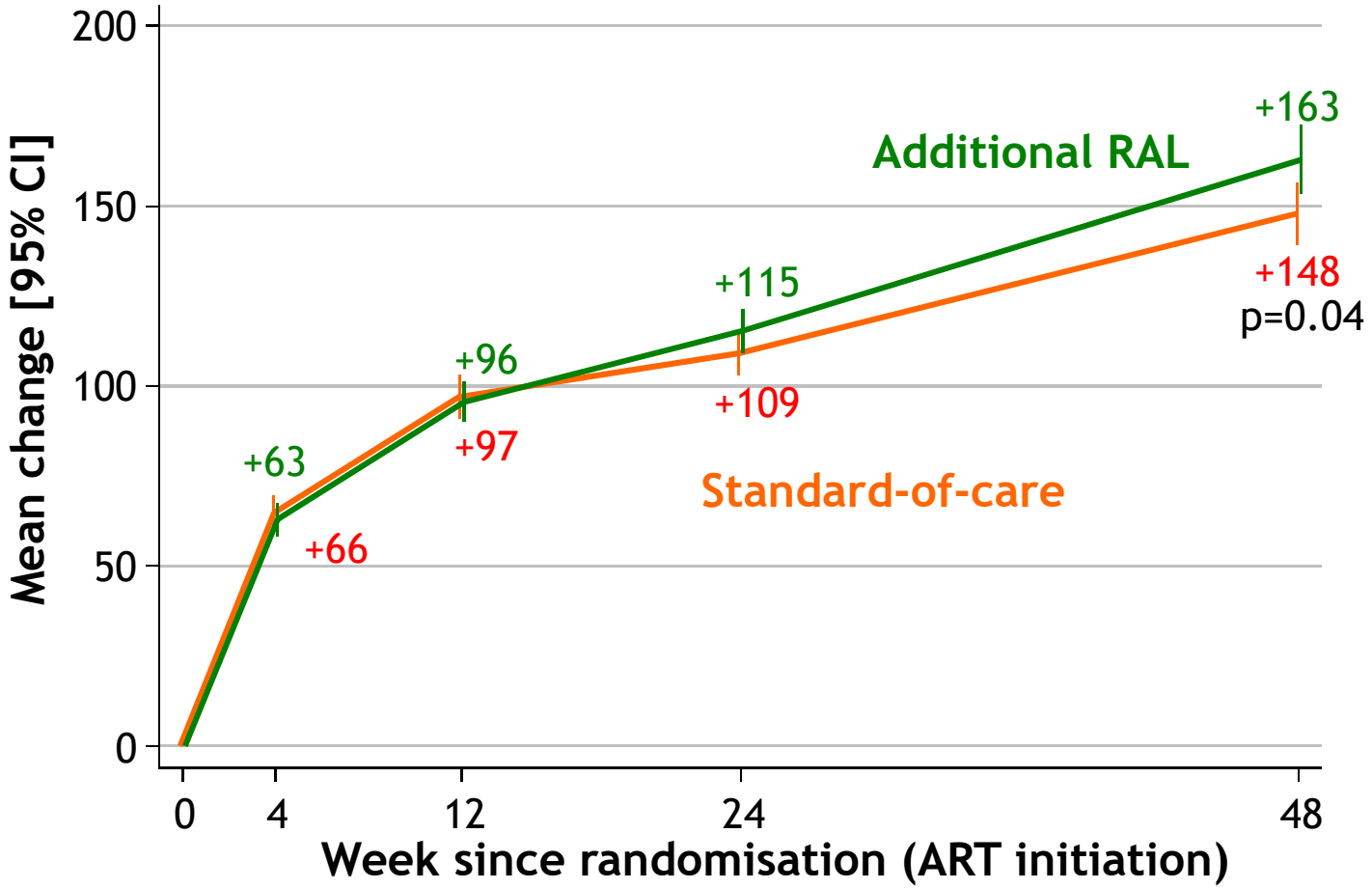
N Engl J Med. 2017 Jul 20;377(3):233-245.

Results: VL<50 copies/ml



- >99% compliance with randomised strategy
- 98% and 99% of time to 48 weeks spent on allocated ART as at randomisation or having made within class substitutions only

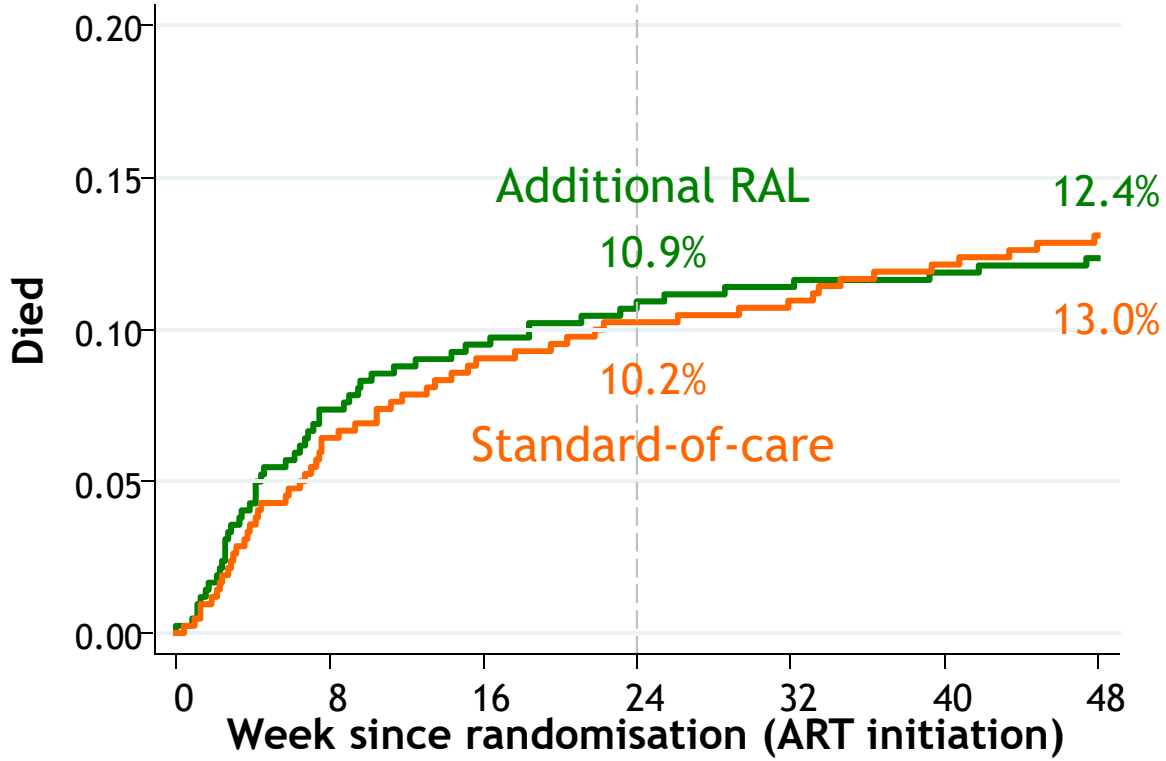
Results: change in CD4



- No evidence of difference in CD4 reconstitution overall (GEE p=0.30)

Results: all cause mortality

- Mortality at 24 weeks: 10.9% RAL vs 10.2% standard-of-care



Number at risk (deaths)

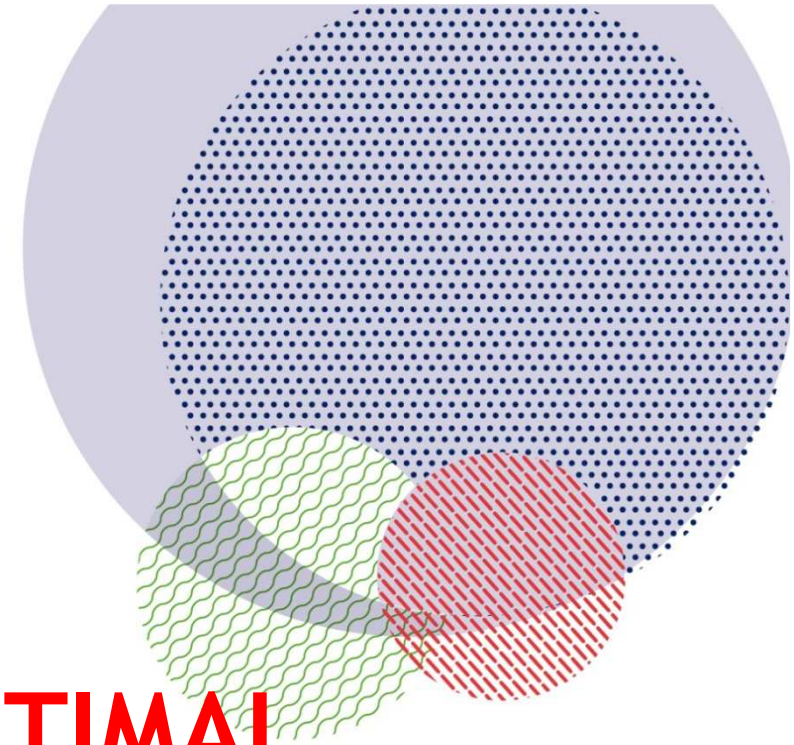
Standard-of-care	903	(57)	830	(23)	801	(10)	789	(7)	776	(10)	760	(8)	669
Additional RAL	902	(65)	825	(20)	801	(11)	786	(6)	775	(3)	766	(5)	657

w24: **HR=1.09**
(95% CI 0.82-1.46)
p=0.54

w48: **HR=0.98**
(95% CI 0.75-1.27)
p=0.86

- 56 (3.1%) lost to follow-up at 48 weeks
- No interactions with other randomisations (p>0.7)

Adding Maraviroc…



ANRS 146 OPTIMAL

Optimized Phase III Trial of Immuno-stimulation with Maraviroc, a CCR5 antagonist, combined with Anti Retroviral Therapy (cART) in advanced, Late diagnosed HIV-1 infected patients with an AIDS-defining event and/or CD4 counts ≤ 200 cells/mm^3

Yves Lévy, Jean-Daniel Lelièvre, Lambert Assoumou, Esther Aznar, Federico Pulido, Giuseppe Tambussi, Manuel Crespo, Agnès Meybeck, Jean-Michel Molina, Fanny Cardon, Constance Delaugerre, Rémi Lancar, Lydie Béniguel, Dominique Costagliola and the OPTIMAL trial team

Design

- HIV-1 infected patients with an AIDS-defining event and/or CD4 counts ≤ 200 cells/mm^3; Naïve from any antiretroviral

1:1 randomisation, double-blind,
stratification on the country and
treatment initiation regimen (PI vs non-PI)

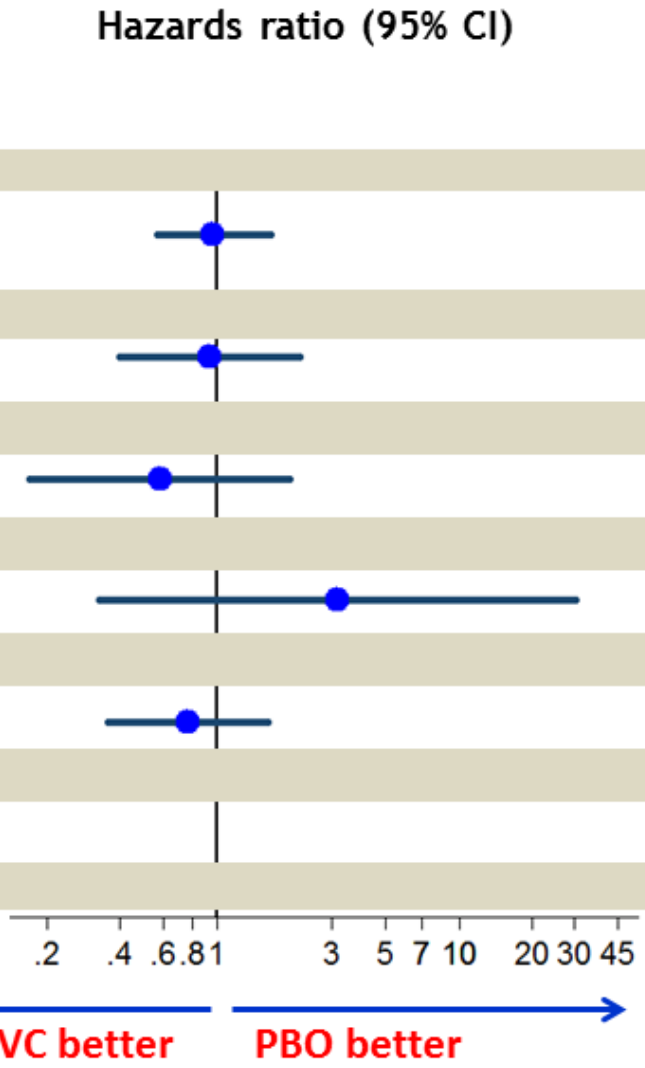
ARV according to the recommended regimen in most commonly used guidelines + **MARAVIROC**	ARV according to the recommended regimen in most commonly used guidelines + **Placebo**

- International: France, Spain and Italy,
- Follow-up to week 72
- FPFV: September 2011; LPLV: March 2016

- **Primary endpoint: Occurrence of a severe morbidity (AIDS, other HIV related diseases, serious non-AIDS events, IRIS and death)**

Primary endpoint and its components:
Incidence of the first event

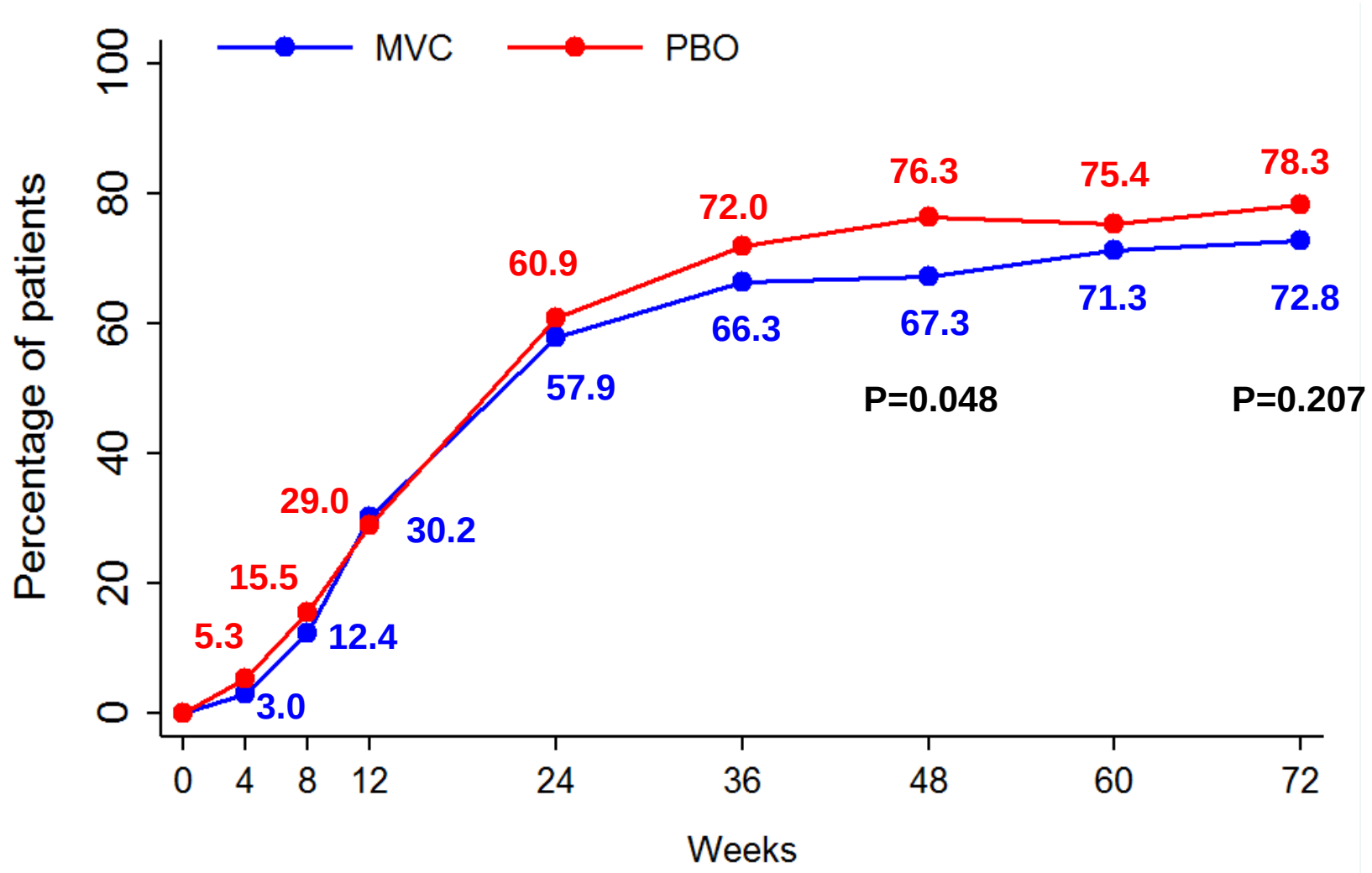
	MVC (N=202) Incidence (per 100 person-yr)	PBO (N=207) Incidence (per 100 person-yr)	HR
Primary composite endpoint	26 (11.13)	27 (11.22)	0.97
New ADE	10 (4.04)	11 (4.24)	0.94
Non B or C event	4 (1.59)	7 (2.65)	0.59
Serious non-AIDS event	3 (1.19)	1 (0.37)	3.15
IRIS (French)	12 (4.89)	16 (6.33)	0.76
Death*	0 (0.00)	4 (1.48)	



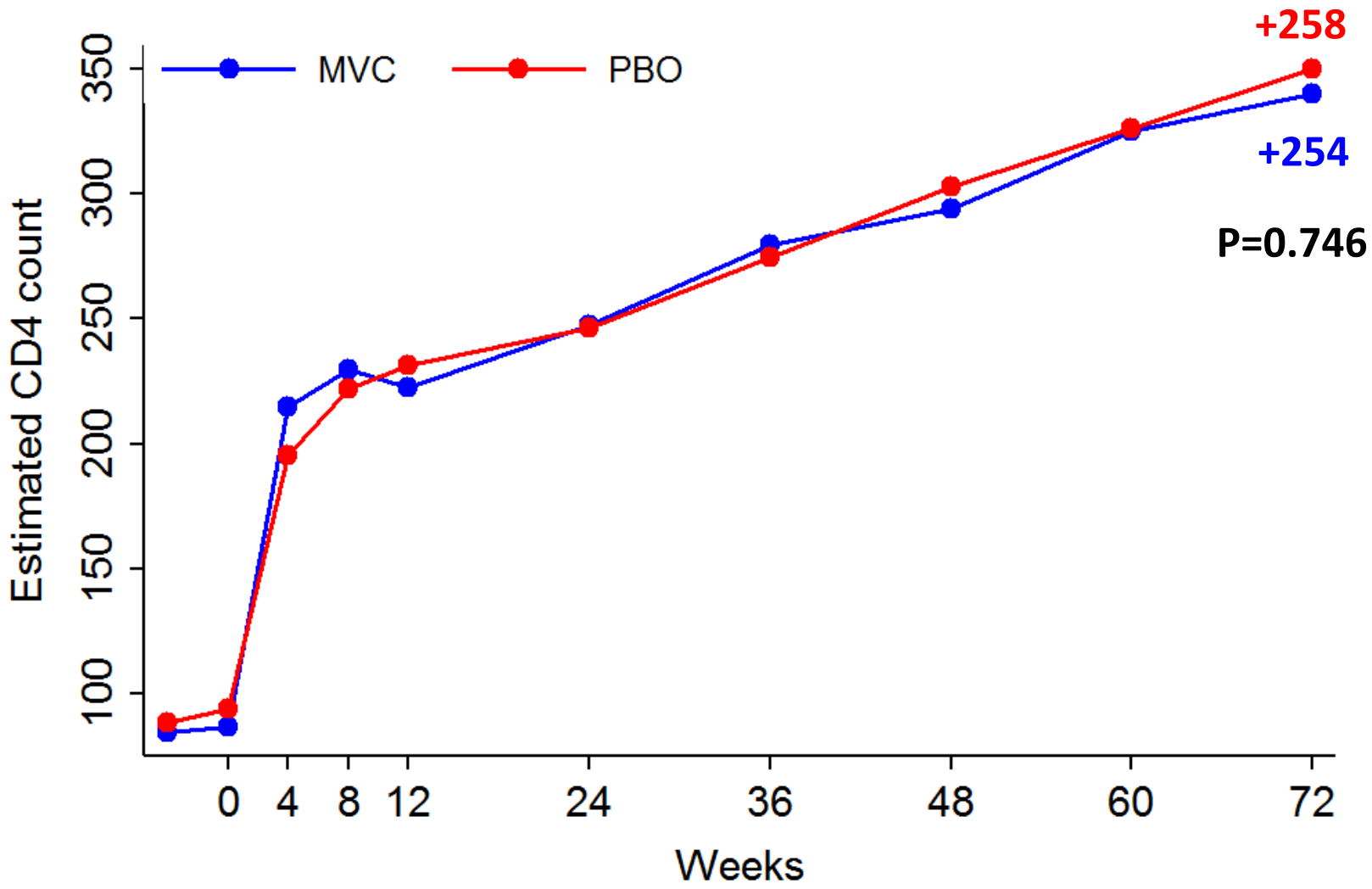
* *No death in MVC group: Cox model does not apply*

Cox regression model adjusted for stratification factors

Virological success
(HIV RNA< 50 c/mL, Snapshot method)



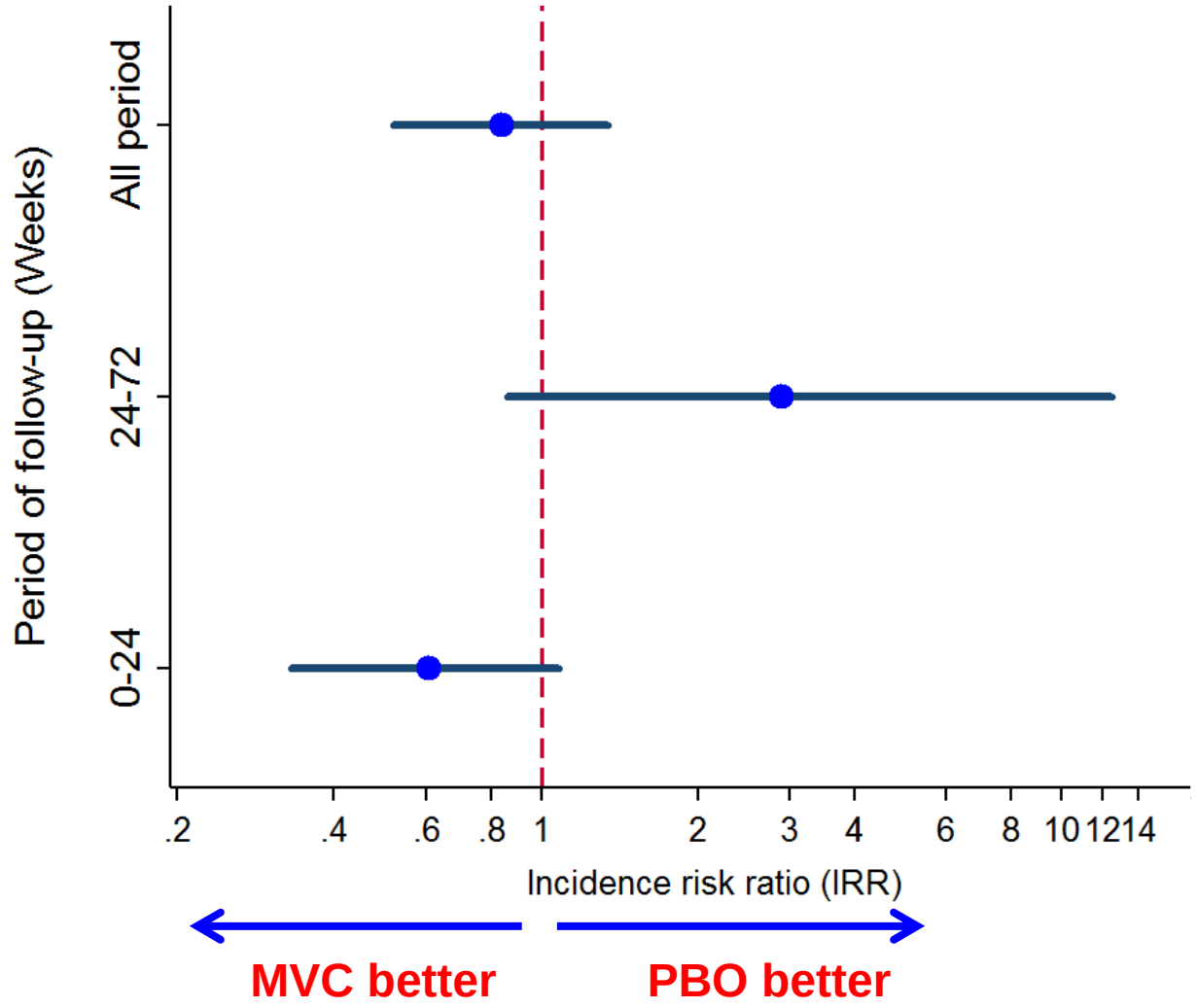
Evolution of CD4 T cell count



ANRS

Linear mixed model

Modifying effect on the incidence of events according to period (post hoc analysis)



Nb of events (Nb of pts)	
MVC	PBO
31 (26)	39 (27)
11 (10)	4 (3)
20 (17)	35 (26)

Interaction between group and period: **p=0.016**

ANRS

Poisson regression model

Risultati dalla pratica clinica

HIV Drug Therapy GLASGOW 2020

P046

BICSTaR

Please see Poster #P053 for BICSTaR patient-reported outcome data

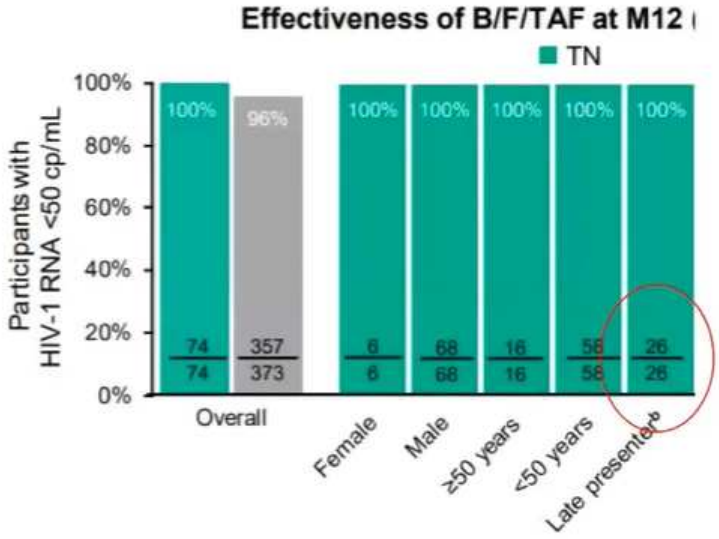
Starting or switching to bictegravir/emtricitabine/ tenofovir alafenamide (B/F/TAF) in clinical practice: Pooled 12-month results from the global BICSTaR study

CD Spinner[1], A Stoehr[2], A Wong[3], J de Wet[4], J Zeggagh[5], L Hocqueloux[6], B van Welzen[7], M Heinzkill[8], S Sahali[9], A Torres Cornejo[10], H Ramroth[11], R Haubrich[12], D Thorpe[13], CJ Kim[14]

BICSTaR – HIV Therapy @ Glasgow 2020

Baseline Characteristics

		TN, n=84
Demographics	Male, n (%)	76 (91)
	Age, years, median (Q1–Q3)	38 (29–48)
	Age ≥50 years, n (%)	20 (24)
	White, n (%)	71 (85)
Ongoing comorbidities	None, n (%)	41 (49)
	1–2, n (%)	25 (30)
	≥3, n (%)	18 (21)
	Neuropsychiatric disorder[a], n (%)	16 (19)
	Hyperlipidaemia, n (%)	7 (8)
	Hypertension, n (%)	5 (6)
HIV-related characteristics	HIV-1 RNA, log_{10} cp/mL, median (Q1, Q3)	4.77 (3.94, 5.18)
	<50 cp/mL, n (%)	0 (0)
	>100,000 cp/mL, n (%)	30/82 (37)
	CD4 count[b], cells/µL, median (Q1, Q3)	427 (244, 581)
	CD4 <200 cells/µL, %	21
	CD4 <350 cells/µL, %	38
	CD4/CD8 ratio, median (Q1, Q3)	0.4 (0.3, 0.6)
	≥1 major mutation[c], n (%)	7 (9)
	PI / NNRTI / NRTI / INSTI, n (%)	2 (2) / 5 (6) / 1 (1) / 0



How good is what we are doing?

Efficacy and safety of dolutegravir-based regimens in advanced HIV-infected naïve patients: results from a multicenter cohort study

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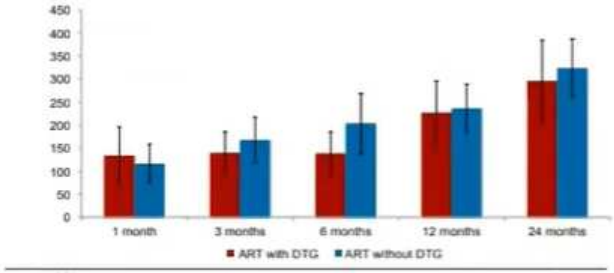
Rationale

Multicenter cohort of advanced naïve HIV-1 infected patients starting first-line antiretroviral regimens (ART) between 01/01/2014 and 30/12/2017 in 9 clinical centers.
All patients presenting for care with a CD4 count below 350 cells/mm3 (late presenter) or presenting with an AIDS-defining event, regardless of the CD4 cell (AIDS-presenter), starting their first ART were retrospectively included.

The integrase strand transfer inhibitors (INSTIs), raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG) and bictegravir (BIC), are recommended for first-line antiretroviral therapy in combination with two nucleos(t)ide reverse transcriptase inhibitors (NRTI). DTG is a second generation unboosted-integrase inhibitor, given once daily with limited cross resistance and a high barrier to resistance. However, limited data are available about efficacy and safety of first-line DTG use in late presenter HIV-1 infected patients in clinical practice.

The aims of the study were to compare frequency of IRIS defining events and to assess viro immunological efficacy and tolerability of DTG-including regimens vs regimens without DTG in ART-naïve late and AIDS presenters HIV-1 infected patients.

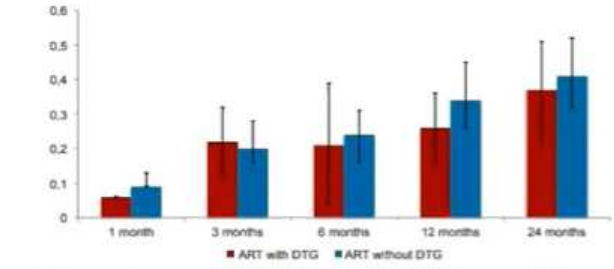
Figure 4. Mean CD4 change from baseline



with DTG	123	139	122	106	53
without DTG	40	42	47	47	37

P<0.005 for all comparisons intragroup

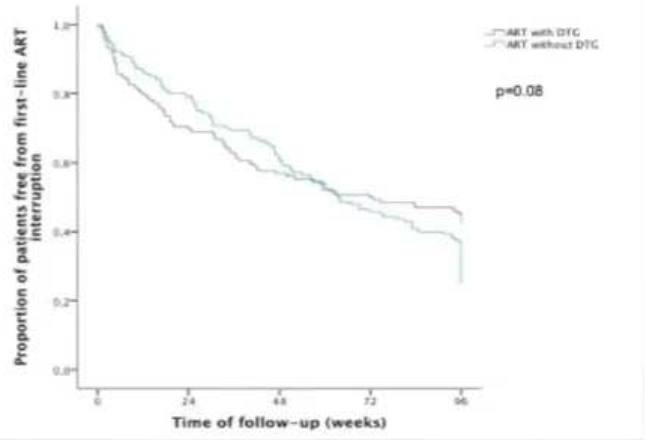
Figure 5. Mean CD4/CD8 ratio change from baseline



with DTG	84	101	88	73	42
without DTG	31	33	36	37	31

P<0.005 for all comparisons intragroup

Figure 2. Estimated probability of remaining free from first-line ART-interruption



IRIS was reported in 13/272 (5%) AIDS-presenters: 5/132 (4%) among patients on treatment with regimens including DTG and 8/140 (6%) among those treated with regimens without DTG.

Univariate analysis showed no association between the development of IRIS and baseline HIV-1 RNA >100,000 copies/mL or HIV-1 RNA >500,000 copies/mL, DTG-including reminens, two different NRTIs backbones use (TDF or TAF/FTC vs ABC/3TC), HBV or HCV coinfection.

Overall, 10 patients died within 24 months after first-line cART initiation, of these 5 patients were on DTG regimens.

Although preliminary, our results confirm the high potency, good tolerability and safety of DTG-containing regimens as first-line treatment of advanced-naive patients. Patients treated with DTG exhibited a frequency of IRIS which was comparable to those who did not receive DTG.

PRADAR Study

C. Mussini et al. PLOS ONE https://doi.org/10.1371/journal.pone.0222650
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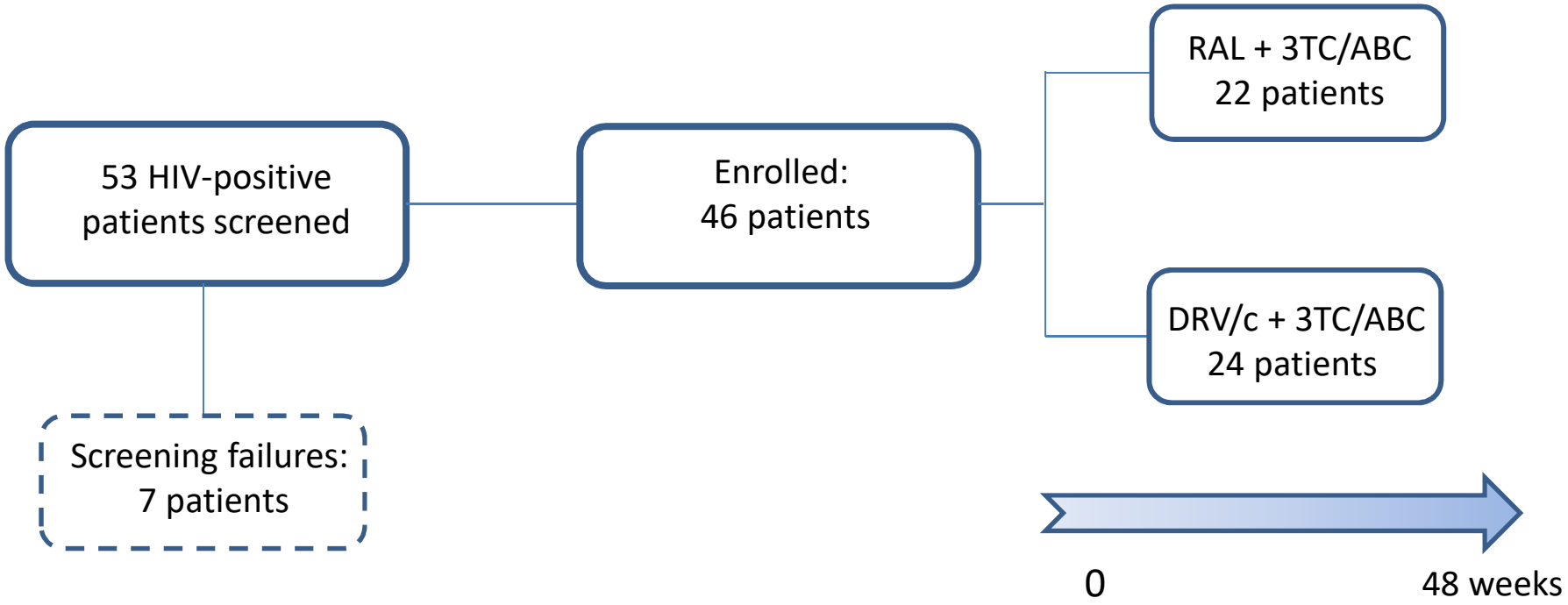


Patients' disposition.
53 patients were screened: 46 patients were randomly allocated into 2 groups (22 with RAL and 24 with DRV/c) and 7 patients were excluded (4 because of HIV-RNA >500,000 copies/mL and 3 for HLAB5701 positivity).

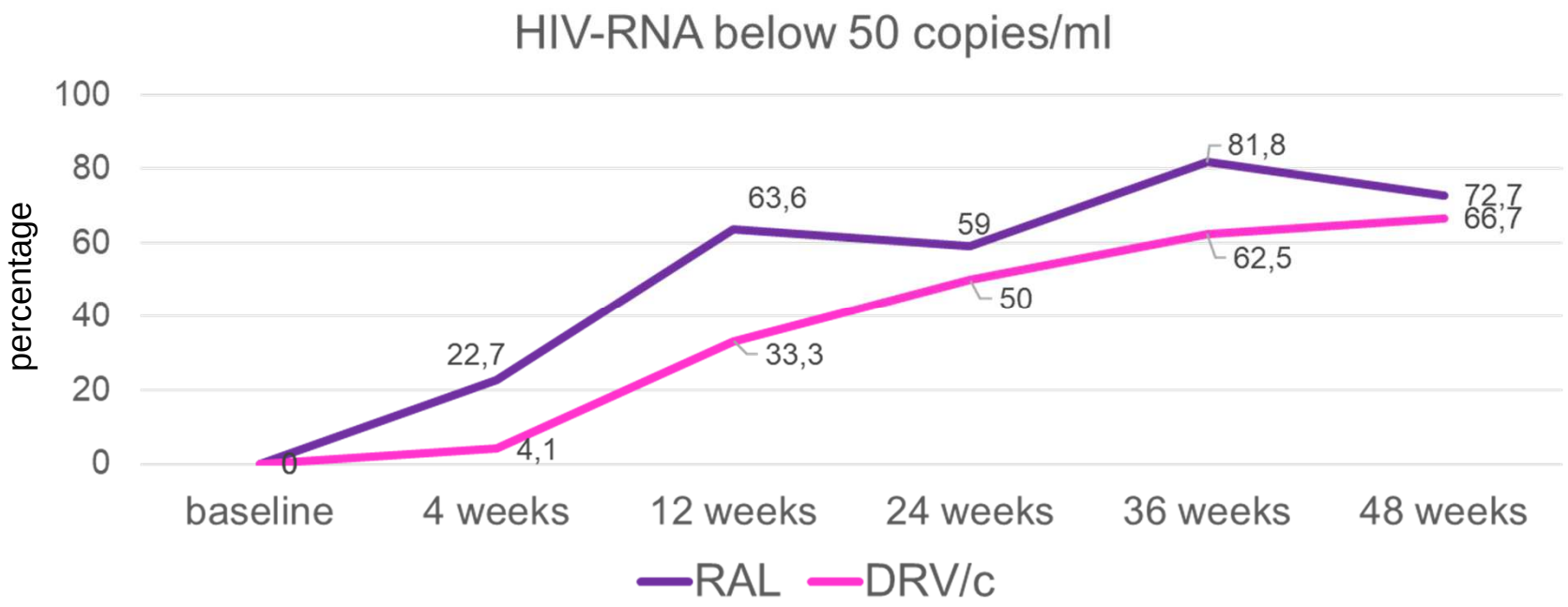
Baseline characteristics

Variable	RAL	DRV/c
Gender (male/female; number)	19/3	19/5
Age (years; median & IQR)	41 (13)	35 (16)
Risk factor for HIV (number)		
MSM	9	12
Heterosexual contacts	11	10
IVDU	1	1
Other	1	0
unknown	0	1
CDC stage (number)		
A	10	15
B	5	3
C	7	6
HIV RNA (copies/ml; median & IQR)	89731 (99356)	112250 (204238)
CD4 (cells/mcL; median & IQR)	108 (145)	117 (141)
CD8 (cells/mcL; median & IQR)	701 (672)	817 (461)

Opportunistic infections

Opportunistic infections and pathologies were oro-esophageal candidiasis (5 in RAL and 6 in DRV/r); Pneumocystis pneumonia (1 in RAL and 3 in DRV/r) and neuro-toxoplasmosis (one in each group). Kaposi Sarcoma, cryptococcal meningitis, lymphoma and wasting syndrome (one each) were diagnosed only in the raltegravir group, while Cytomegalovirus disseminated disease (2 cases) only in the darunavir/r group. Some patients presented more than an opportunism.

ITT analysis



Key messages

- In pazienti con bassa conta dei CD4+ il regime a 2 farmaci con DTG+3TC sembra presentare una minore efficacia.

- Nella pratica clinica, in questo gruppo di PLWHIV, l'utilizzo di terapie a 3 farmaci con DTG o BIC garantisce efficacia e sicurezza come prima linea terapeutica.

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