Clinical experiences of 2 drugs regimen

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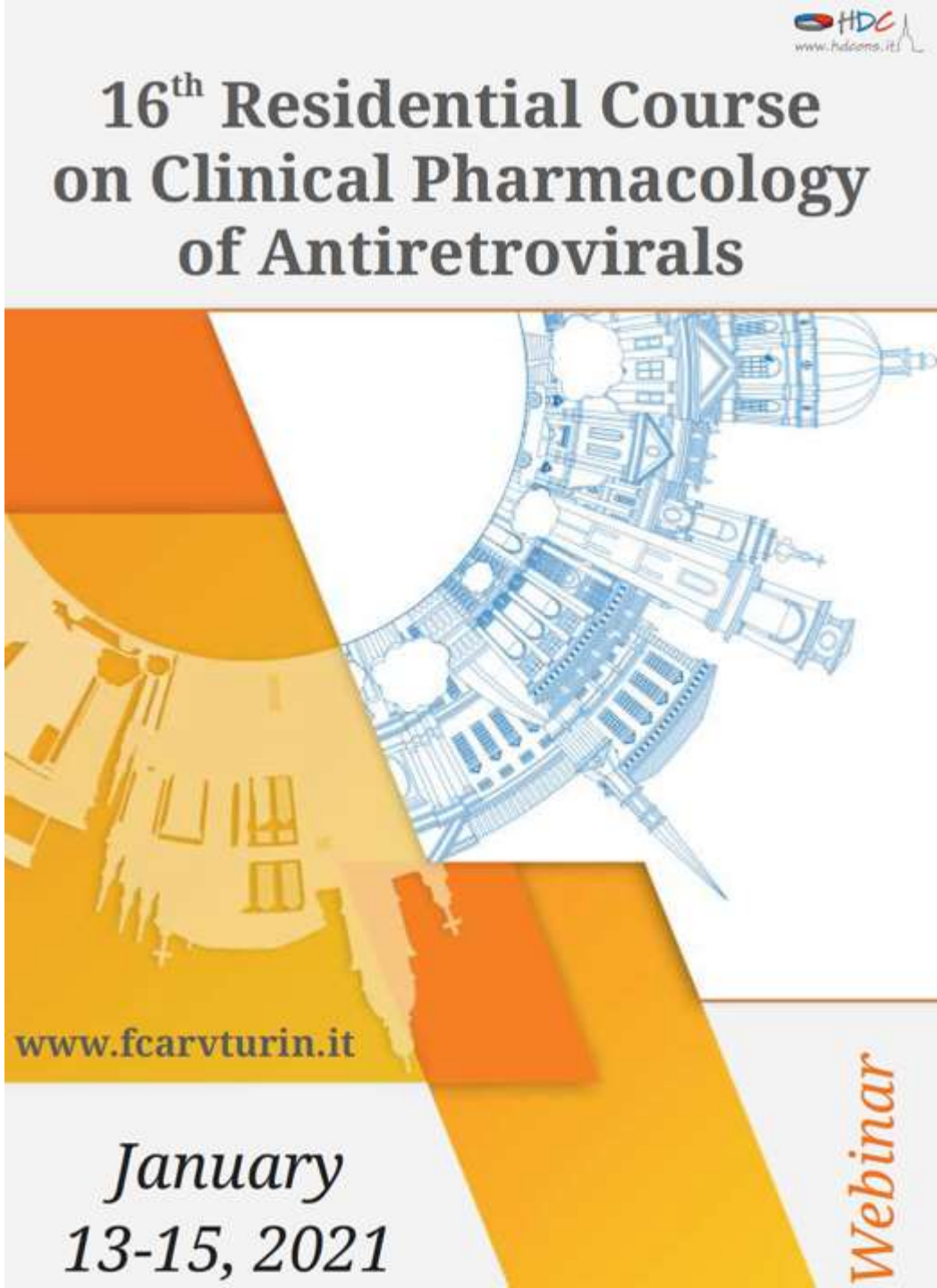


EACS Guidelines 2020

Regimen	Main requirements	Additional Guidance (footnotes)
Recommended regimens		
2 NRTIs + INSTI		
ABC/3TC + DTG or ABC/3TC/DTG	HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, cardiovascular risk) II (Weight increase (DTG))
TAF/FTC or TDF/FTC or TDF/3TC + DTG		III (Weight increase (DTG, TAF)) IV (TDF: prodrug types. Renal and bone toxicity TAF dosing)
TAF/FTC/BIC		II (Weight increase (BIC))
TAF/FTC or TDF/FTC or TDF/3TC + RAL qd or bid		IV (TDF: prodrug types. Renal and bone toxicity. TAF dosing) V (RAL: dosing)
1 NRTI + INSTI		
3TC + DTG or 3TC/DTG	HBsAg negative HIV-VL < 500,000 copies/mL	

EACS European AIDS Clinical Society

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV, Dec 2019

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- BIC/TAF/FTC **(AI)**
- DTG/ABC/3TC **(AI)—if HLA-B*5701 negative**
- DTG plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
- RAL plus (TAF or TDF)[a] plus (FTC or 3TC) (**BI** for TDF/[FTC or 3TC], **BII** for TAF/FTC)

INSTI plus 1 NRTI:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable but have some disadvantages when compared with the regimens listed above or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

INSTI plus 2 NRTIs:
Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- EVG/c/(TAF or TDF)[a]/FTC **(BI)**

Boosted PI plus 2 NRTIs:

- In general, boosted DRV is preferred over boosted ATV
- (DRV/c or DRV/r) plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
- (ATV/c or ATV/r) plus (TAF or TDF)[a] plus (FTC or 3TC) **(BI)**
- (DRV/c or DRV/r) plus ABC/3TC—**if HLA-B*5701 negative (BII)**

NNRTI plus 2 NRTIs:

- DOR/TDF[a]/3TC **(BI)** or DOR plus TAF[a]/FTC **(BIII)**
- EFV plus (TAF or TDF)[a] plus (FTC or 3TC)
  - EFV 600 mg plus TDF plus (FTC or 3TC) **(BI)**
  - EFV 400 mg/TDF/3TC **(BI)**
  - EFV 600 mg plus TAF/FTC **(BII)**
- RPV/(TAF or TDF)/FTC **(BI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3**

Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available
- DRV/r plus RAL twice a day **(CI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3**
- DRV/r once daily plus 3TC[a] **(CI)**

CROI 2020

CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS
Boston, Massachusetts
March 8-11, 2020

DTG+3TC
Real life experiences

- Long-term data on the efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multi-centre cohort of HIV-1-infected, virologically suppressed patients
  Baldin G et al. Int J Antimicrob Agents. 2019 Dec;54(6):728-734.
- Retrospective study on the outcome of two-drug regimens based on dolutegravir plus one reverse transcriptase inhibitor in virologically-suppresse d HIV-infecte d patients
  Galizzi N et al., J Antimicrob Chemother 2020. Epub ahead of print
- Efficacy and durability of 2-Drug vs 3-Drug INSTI-based regimens: data from real life
  Fabbiani M et al. CROI 2020; Boston. Poster 0488
- Effect of past virological failure on dolutegravir+lamivudine as maintenance regimen
  Gagliardini R et al. CROI 2020; Boston. Poster 0486
- Shall we dance? Extending TANGO's results to clinical practice
  Baldin G et al. CROI 2020; Boston. Poster 0492

Shall We Dance? Extending TANGO's Results to Clinical Practice

Borghetti A. et al, CID 2020

The estimated probabilities of remaining on 3TC + DTG were 86.6% (SD ± 5.9) at Week 48 and 79.5% (SD ± 7.5) at both Weeks 96 and 144 in the TG, and 85.8% (SD ± 3.5), 78.9% (SD ± 4.3). and 73.9% (SD ± 5.1) at Weeks 48, 96, and 144 in the non-TG (log-rank P = .654), respectively

Higher—albeit not statistically significant—number of VF was seen in the non-TG.

Caution should be advised when considering 3TC + DTG for selected patients those with previous VF or shorter time of viral suppression).

Table 1. Baseline Patients' Characteristics

	TANGO Group, n = 145	Non-TANGO Group, n = 412	*P* Value
Age, years, median (IQR)	49 (40–55)	53 (47–58)	<.001
Male sex, n (%)	111 (76.6)	281 (68.2)	.058
Ethnicity, n (%)			
Caucasians	129 (89.0)	384 (93.2)	.112
Sub-Saharan	4 (2.8)	14 (3.4)	
Central or South American	6 (4.1)	6 (1.5)	
Other/unknown	6 (4.1)	8 (1.9)	
Risk factor for HIV, n (%)			
Heterosexual	56 (38.6)	169 (41.0)	<.001
MSM	37 (25.5)	108 (26.2)	
IDU	15 (10.4)	86 (20.9)	
Other/unknown	37 (25.5)	49 (11.9)	
CDC stage C, n (%)	20 (13.8)	62 (15.0)	.854
Anti HCV–positive serostatus, n (%)	25 (17.2)	101 (24.5)	.076
Peak HIV RNA, $\log_{10}$ copies/mL, median (IQR)	4.95 (4.45–5.35)	4.89 (4.37–5.43)	.780
Nadir CD4+ cell count, cells/mm^3, median (IQR)	278 (140–395)	212 (93–309)	.001
Non-B HIV subtype, n (%)	5 (3.4)	13 (3.2)	.875
Years from HIV diagnosis, median (IQR)	9 (5–17)	18 (10–24)	<.001
Years of cumulative ARV exposure, median (IQR)	7 (3–12)	13 (8–19)	<.001
Months of virological suppression, median (IQR)	61.5 (31.5–103.1)	95.4 (51.5–126.9)	<.001
Time of virological suppression ≤6 months (%)	/	13 (3.2)	NA
Baseline CD4+ cell count, cells/mm3, median (IQR)	692 (453–912)	660 (500–876)	.826
Previous virological failure, n (%)	/	223 (54.1)	NA
Previous ARV regimen, n (%)			
2NRTI + bPI	22 (15.2)	55 (13.3)	<.001
2NRTI + NNRTI	90 (62.1)	55 (13.3)	
2NRTI + INI	33 (22.7)	57 (13.8)	
Dual/monotherapy	0 (0)	220 (53.4)	
Other	0 (0)	25 (6.2)	
M184V resistance mutation detection at last genotipic resistance test, n (%)	/	45 (10.9)	NA

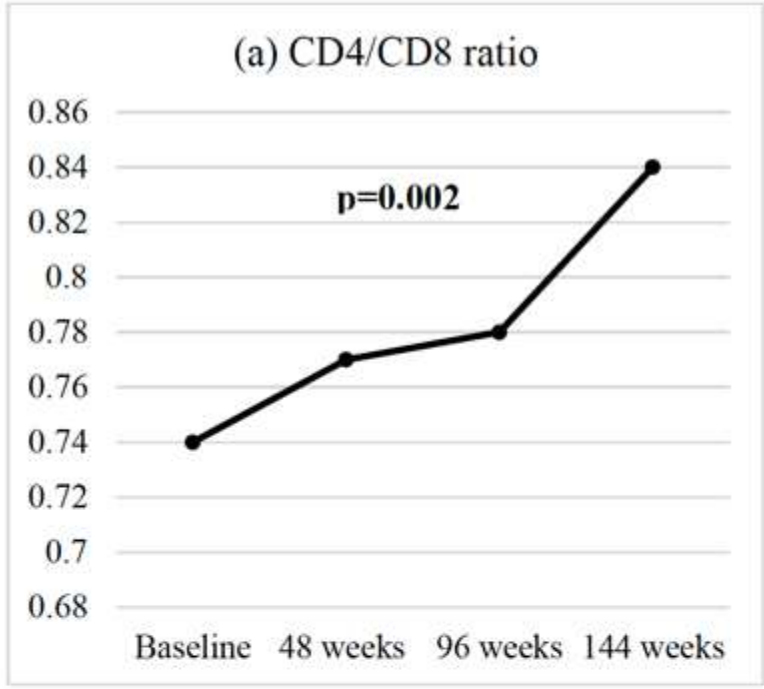
Long term data on the efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multicenter cohort of HIV1-infected, virologically suppressed patients.

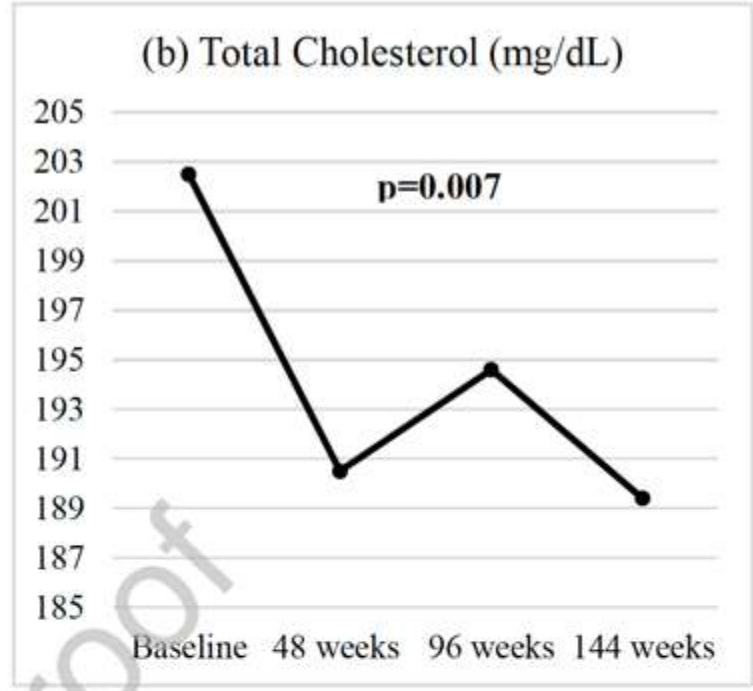
Gianmaria BALDIN et al., International Journal of Antimicrobial Agents 2019

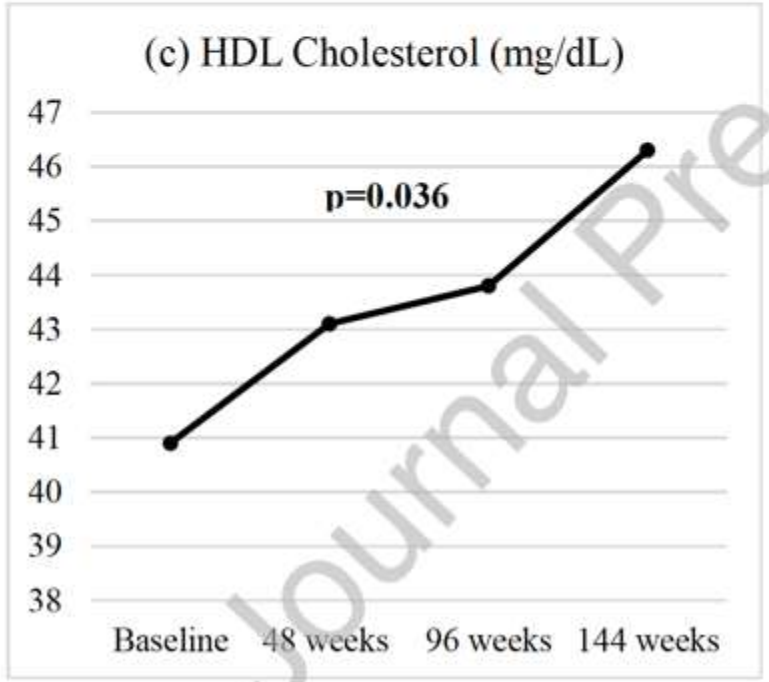
556 pts, FU 144 weeks

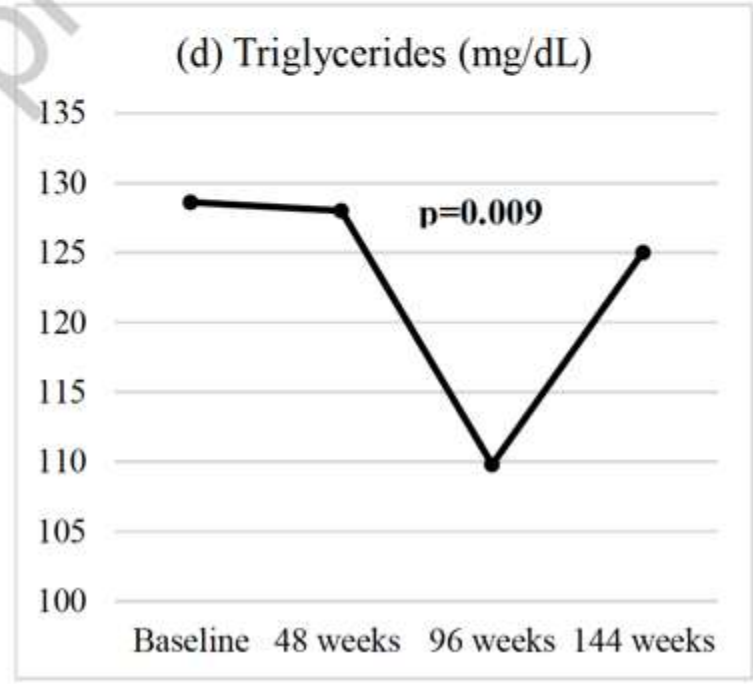
Highlights

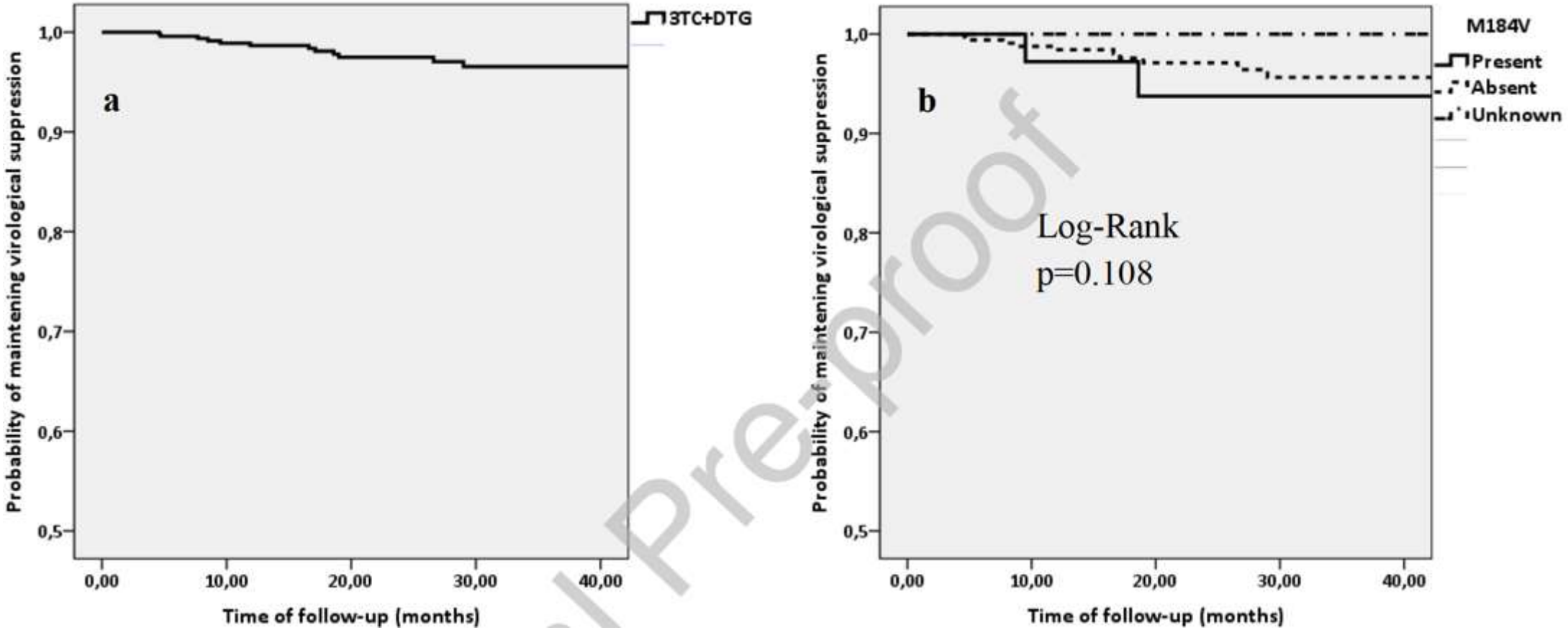
- 3TC+DTG in simplification showed high efficacy.
- The presence of M184V was significant in patients with shorter time of suppression.
- We registered a rate of discontinuation of 10.7 per 100 PYFU.
- The regimen led to an improvement in lipid profile.











The lone presence of the M184V resistance mutation is not a predictor of virological failure for this 3TC-containing dual regimen, probably because of the reduced replicative fitness caused to the virus by this mutation.

Mutation appears to be associated with virological failure in patients with a reduced time of virological suppression before switch to dual therapy[1]

1. Gagliardini R. et al., Open Forum Infect Dis. 2018

Long term data on the efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multicenter cohort of HIV1-infected, virologically suppressed patients.

Gianmaria BALDIN et al., International Journal of Antimicrobial Agents 2019

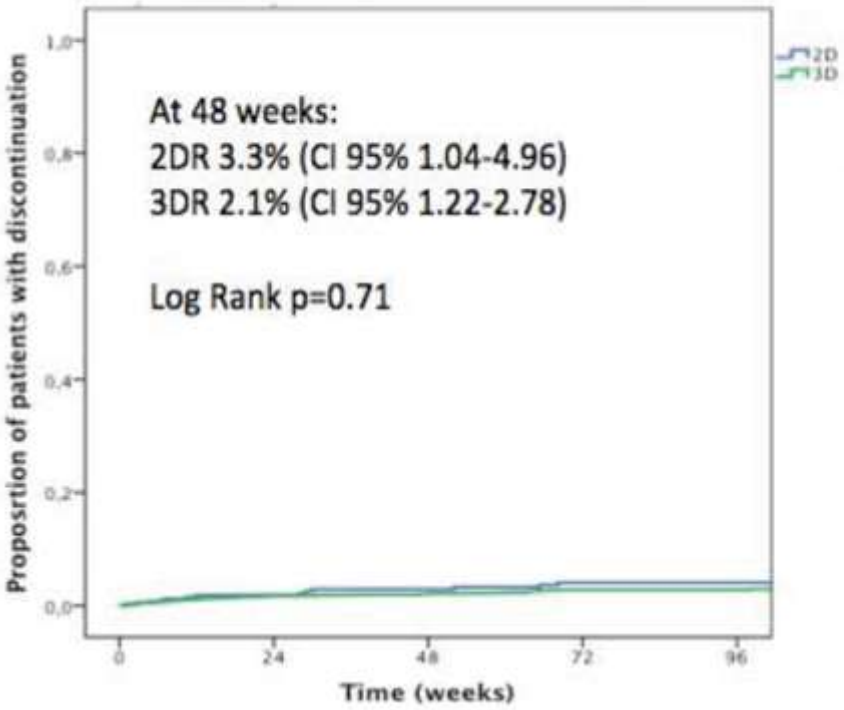
- 110 discontinuations (19.8% of the total population) during the first 60 weeks of follow-up
- Neuropsychological events: sleep disorders or a newly onset headache
- Correlation between treatment discontinuations due to neuropsychiatric disorders and co-infection with hepatitis C virus[1]

1. Munjal S, Crit Care Clin. 2017 Jul; 33(3): 681–712.

EFFICACY AND DURABILITY OF 2-DRUG VS 3-DRUG InSTI-BASED REGIMENS: DATA FROM REAL LIFE

Fabbiani M. et al, CROI 2020 Retrospective multicentre observational study in 8 italian clinical centres, 1666 tot pts

According to cART, overall

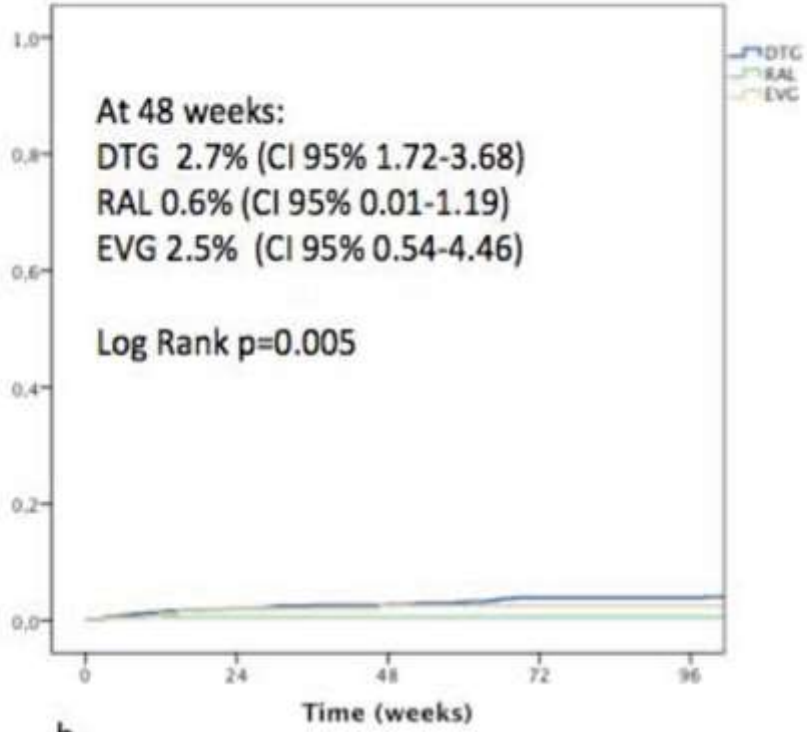


a

Number at risk

	W24	W 48	W 96
2DR	292	261	216
3DR	1168	1018	658

According to INSTI, overall

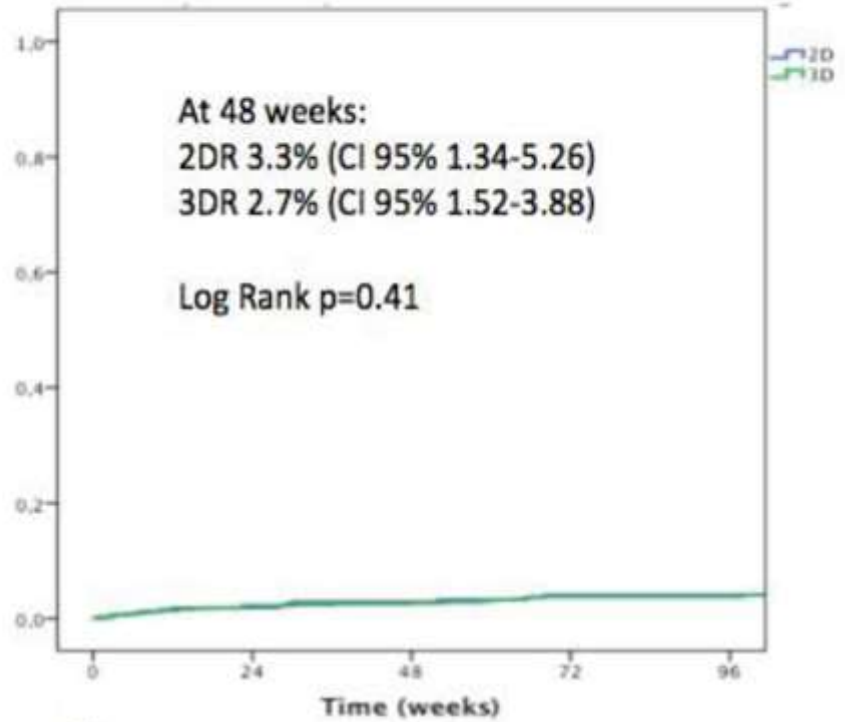


b

Number at risk

	W24	W 48	W 96
DTG	945	851	600
RAL	283	232	184
EVG	232	196	89

According to cART among DTG treated



c

Number at risk

	W24	W 48	W 96
2DR	292	261	216
3DR	653	590	384

Efficacy and safety of dolutegravir plus emtricitabine versus standard ART for the maintenance of HIV-1 suppression: 48-week results of the factorial, randomized, non-inferiority SIMPL'HIV trial

Delphine Sculier et al. and the Swiss HIV Cohort Study (SHCS), 2019

188 pts were randomly assigned either to switch to DTG + FTC dual therapy or to continue their cART

The combination demonstrated non-inferiority in efficacy and safety, as well as a **greater improvement in QoL** over time compared to standard regimens.

Table 5. Summary of patients' quality of life scores by treatment arm.

Outcome measure	Mean (±SD) change; *n*		Adjusted difference (95%CI)	*p*-Value
	DTG + FTC (*n* = 93)	cART (*n* = 94)		
Change in QoL between baseline and week 12 (PROQOL-HIV questionnaire)	+2.3 (±6.7); *n* = 79	+0.2 (±7.0); *n* = 79	+2.1 (+0.1; +4.1)	0.041
Change in QoL between baseline and week 48 (PROQOL-HIV questionnaire)	+2.9 (±6.7); *n* = 80	+0.3 (±8.6); *n* = 85	+2.6 (+0.4; +4.7)	0.023

cART, combined antiretroviral therapy; DTG, dolutegravir; FTC, emtricitabine; QoL, quality of life.

Clinical outcomes of two-drug regimens vs. three-drug regimens in antiretroviral treatment-experienced people living with HIV

Lauren Greenberg1 et al for the RESPOND study group, Oxford University Press for the Infectious Diseases Society of America, in press 2020

10,000 ART-experienced individuals (1088 on 2DRs) from across Europe and Australia

3DRs-third drugs† (n=8703, 88.9%)	
DTG	4081 (46.9%)
RPV	1726 (19.8%)
RAL	1228 (14.1%)
DRV/b	923 (10.6%)
NVP	388 (4.5%)
ATV or ATV/b	277 (3.2%)
ETV	80 (0.9%)

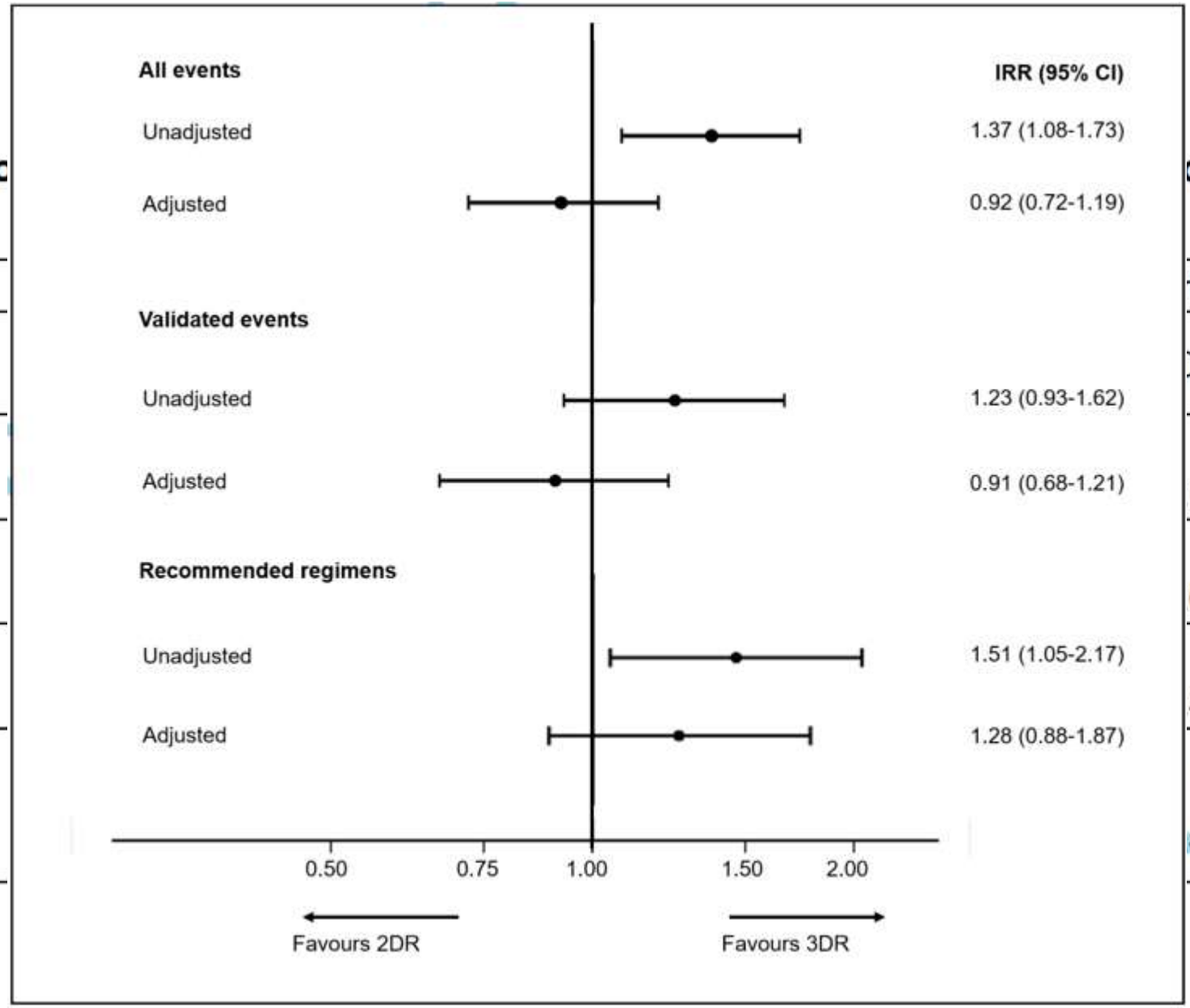
2DRs (n=1088, 11.1%)	
DTG + 3TC	248 (22.8%)
RAL + DRV/b	215 (19.8%)
DTG + DRV/b	200 (18.4%)
DTG + RPV	146 (13.4%)
3TC + DRV/b	107 (9.8%)
RAL + ETV	79 (7.3%)
RAL + NVP	36 (3.3%)
RPV + DRV/b	31 (2.9%)
3TC + ATV/b	26 (2.4%)

Primary outcome
Severe clinical event:
AIDS (cancer and non-cancer)
NADC
CVD (defined as invasive cardiovascular procedures, myocardial infarction, or stroke),
ESLD, ESRD, and death.

Individuals were followed until the first severe event of any type, last clinical visit, or 1st October 2018

Table 2. Comparison c … o and three drug regimens

		… riable*	
		…CI)	P
Death	Regimen Type	…12)	0.13
NADC	Regimen Type	…09)	0.17
CVD	Regimen Type	…41)	0.44
AIDS – non cancer	Regimen Type	…43)	0.47



Lauren Greenber et al for the Swiss Cohort, in press 2020

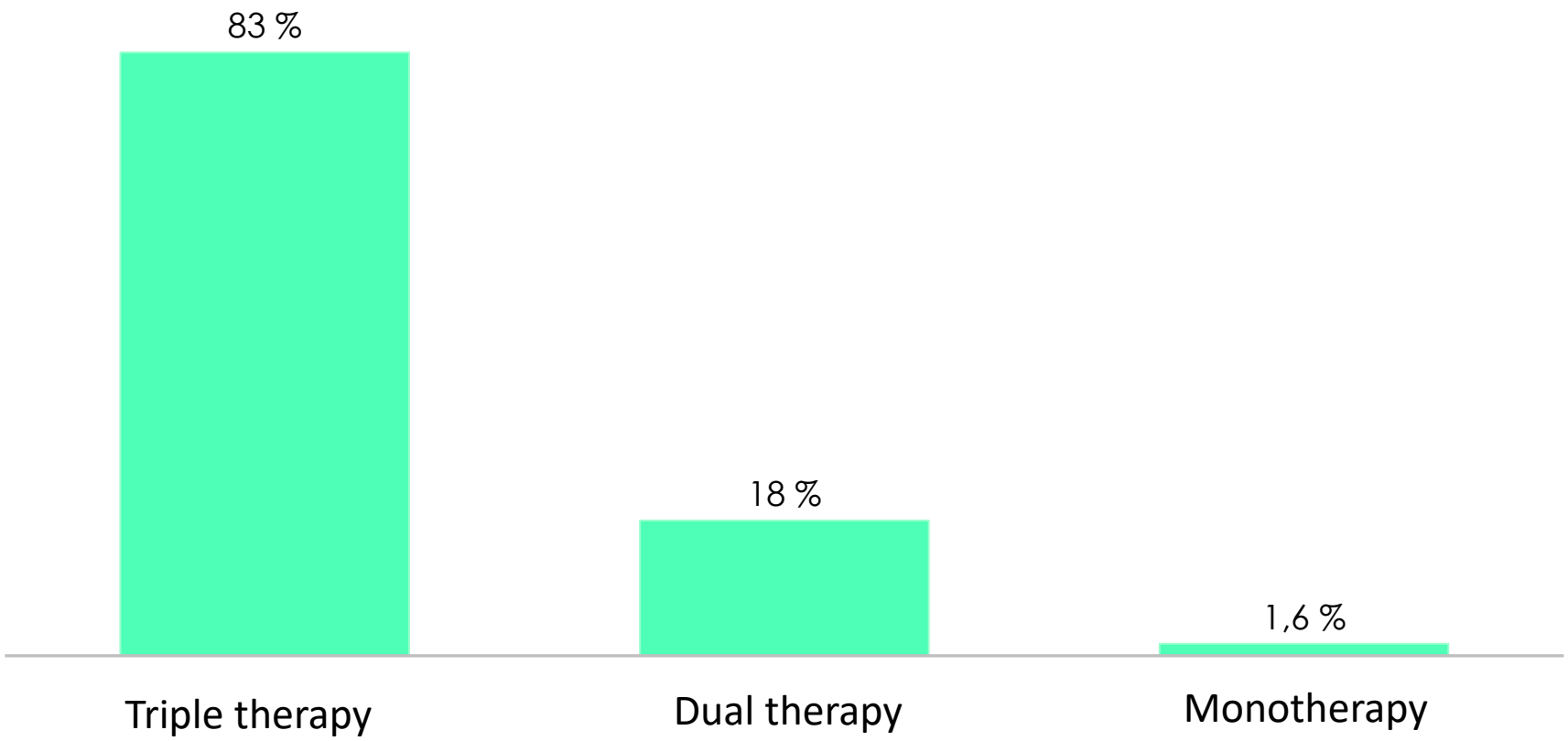
Study population characteristics

Switch to DTG+3TC

Demographic characteristics	Total population (n=122) Median [IQR]
Age (yrs)	49.5 [44.0-48.0]
Gender M (%)	88 %
BMI	25.0 [22.3-26.9]
Weight	73.0 [66.0-84.0]
Smokers	39.3% (48/122)
Heavy smokers > 10 cigarettes/die % (n)	66.7 % (32/48)
Light smokers < 10 cigarettes/die % (n)	33.3% (16/48)

Unpublished data

PRE-SWITCH ARV regimens



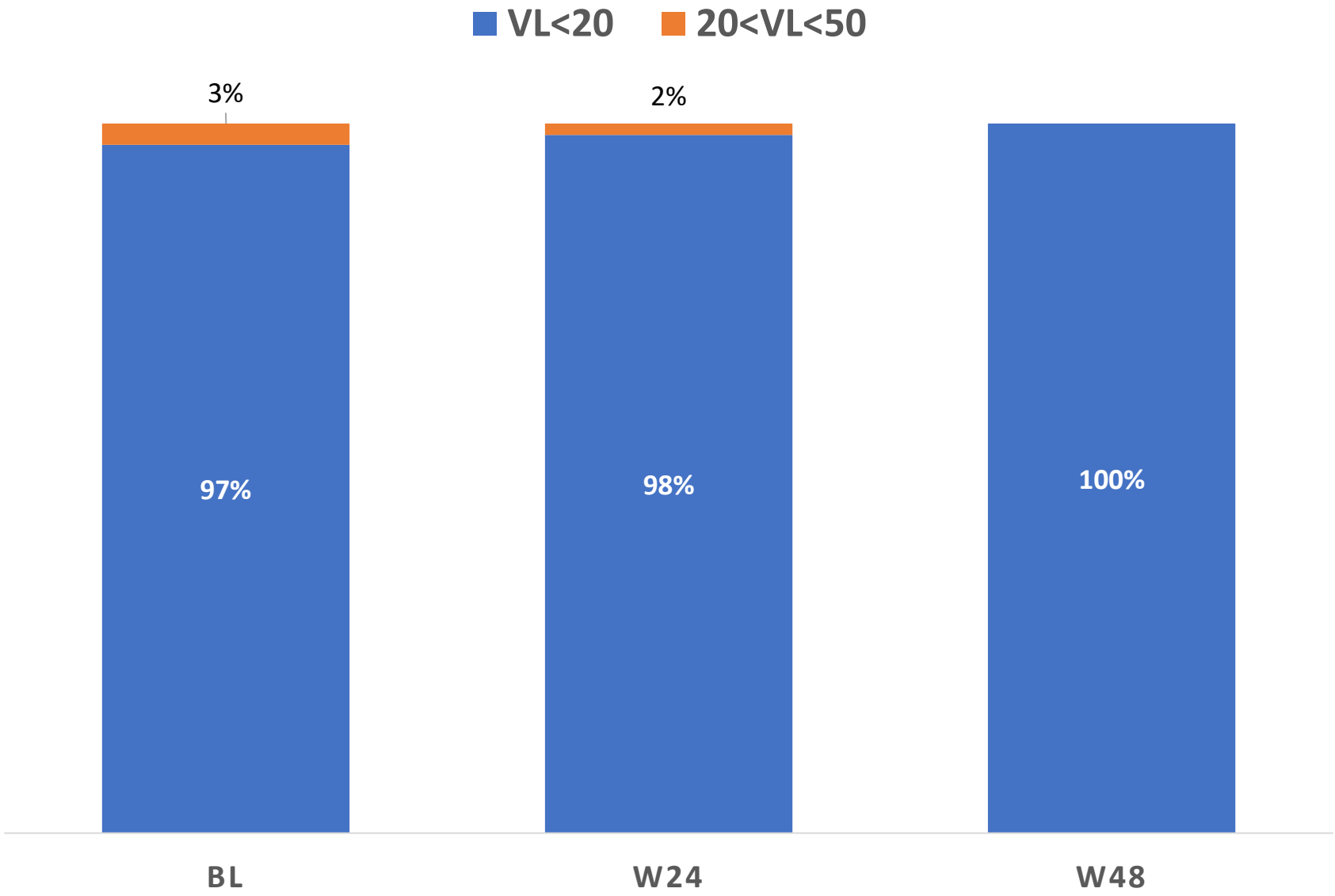
73% switch from DTG-sparing regimens
27% switch from DTG-including regimens

Study Population Immunovirological characteristics

	Median [IQR]
VL <20 cp/mL VL 20-50 cp/mL	97% (118) 3 % (4)
nadir $CD4^+$ cells/mm^3	327.5 [222.0-416.0]
$CD4^+$ T cells/mm^3	771.0 [586.0-1023.0]
$CD4^+/CD8^+$ ratio	1.1 [0.8-1.4]
Time of HIV exposure (yrs)	8.0 [4.8-14.0]
Time of ARV exposure (yrs)	6.5 [3.0-12.0]
HBV +	0/122
HCV +	5/122

RESULTS

- **Efficacy**

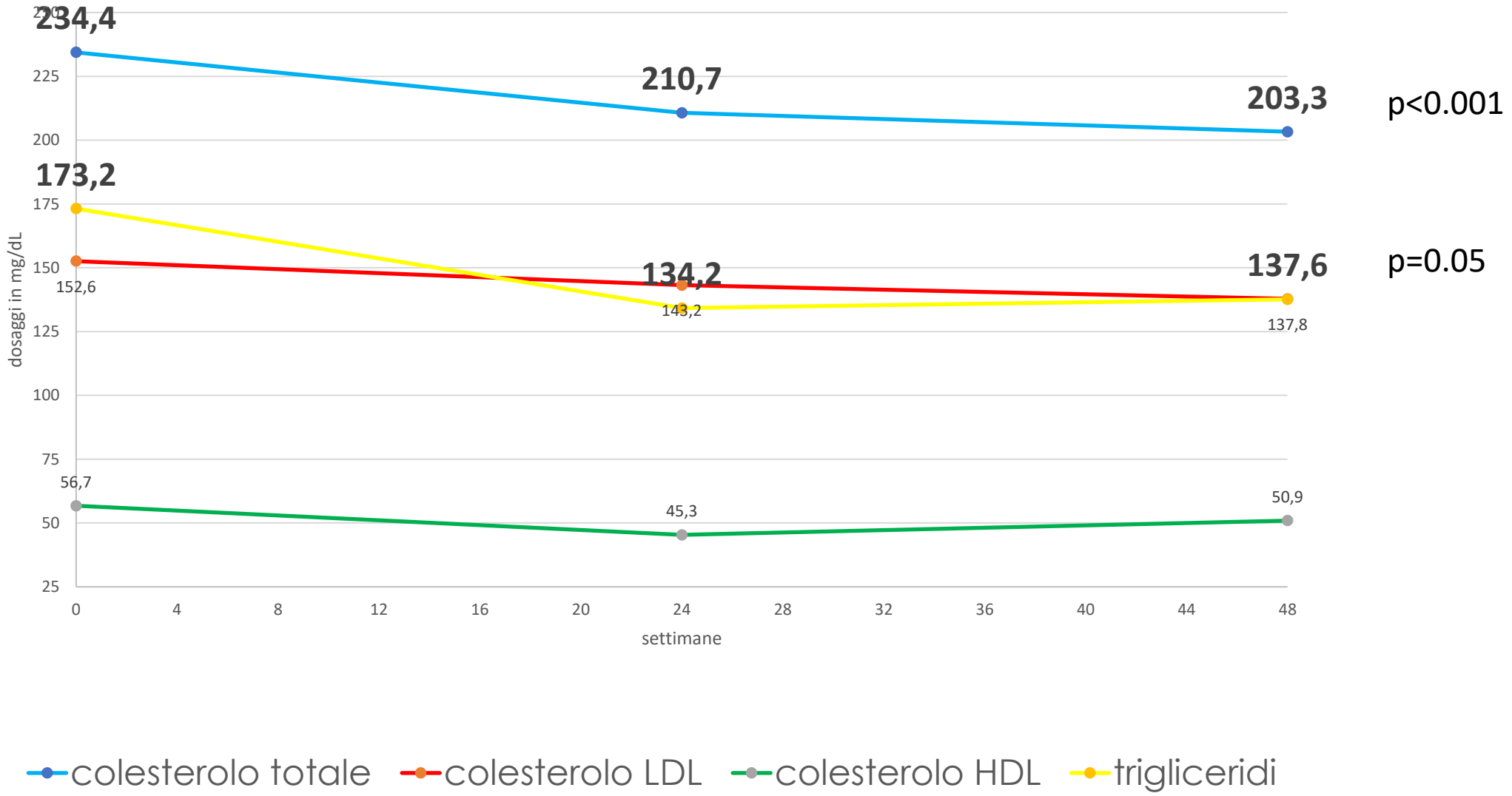


RESULTS

- **Tolerability**

Metabolic Parameters	**Baseline**	**Week 24**		**Week 48**	
	Median (IQR)	Median (IQR)	p	Median (IQR)	p
Creatinine	1.0 [0.8-1.2]	1.1 [-2.6-4.9]	0.005	1.1 [1.2-3.5]	**0.039**
Total cholesterol (mg/dL)	185.9 [178.5-193.5]	182.2 [173.0-191.3]	0.04	179.4 [170.5-188.3]	**0.029**
LDL cholesterol (mg/dL)	118.2 [111.8-124.6]	115.7 [107.0-124.4]	0.026	113.3 [101.5-126.4]	0.423
HDL cholesterol (mg/dL)	48.7 [45.1-52.2]	44.8 [41.1-48.4]	0.142	47.5 [44.6-50.3]	0.204
Triglycerides	121.0 [95.9-146.1]	111.7 [90.9-132.5]	0.146	114.0 [101.5-126-4]	0.851
Glicemia	88.3 [83.7-93.0]	79.6 [74.3-84.9]	0.914	89.9 [83.0-97.0]	0.202

FU Metabolic parameters of Pts with dislypidemia at BL (tot chol > 200 mg/dL)

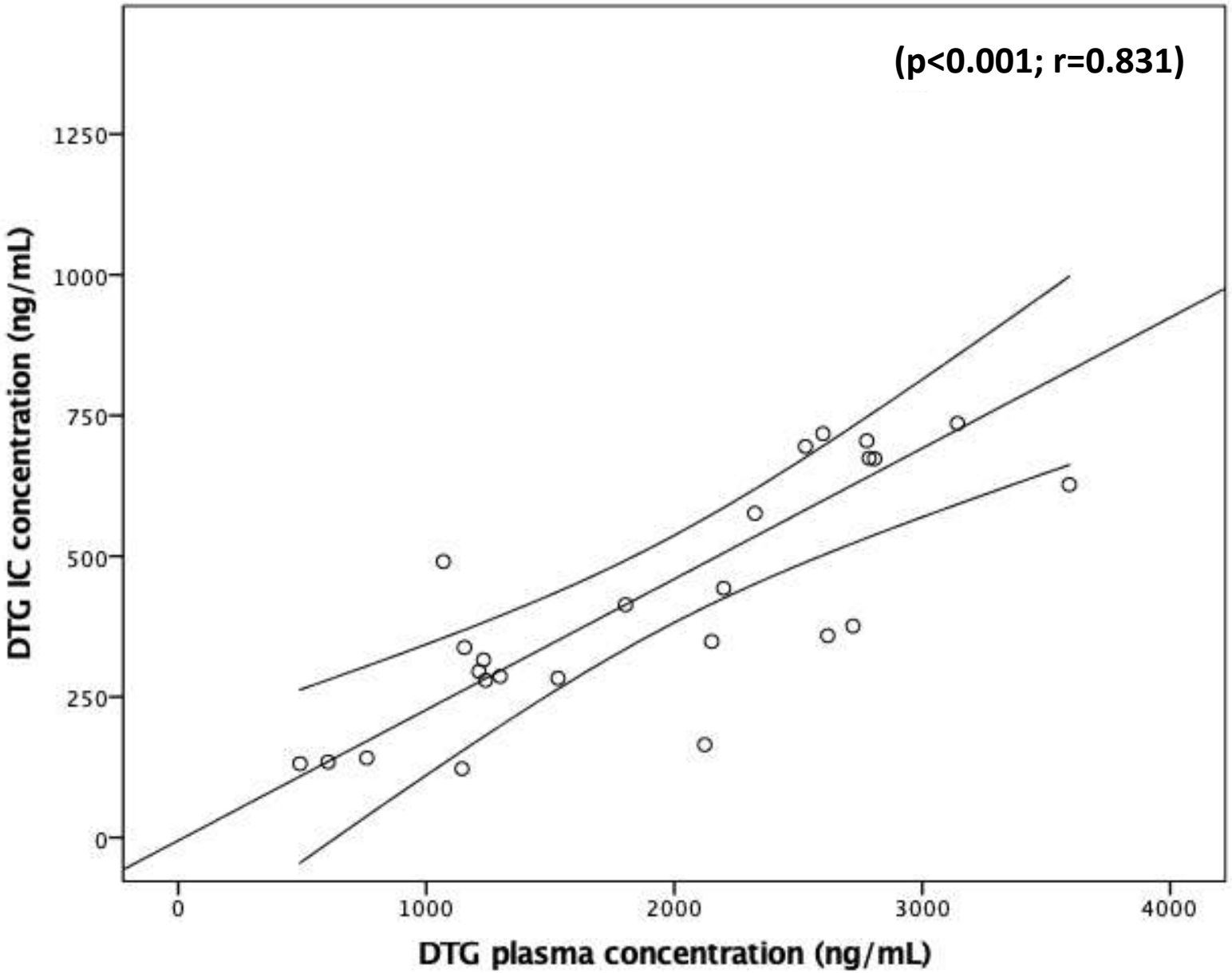


DTG plasma and IC C_{trough} analysis

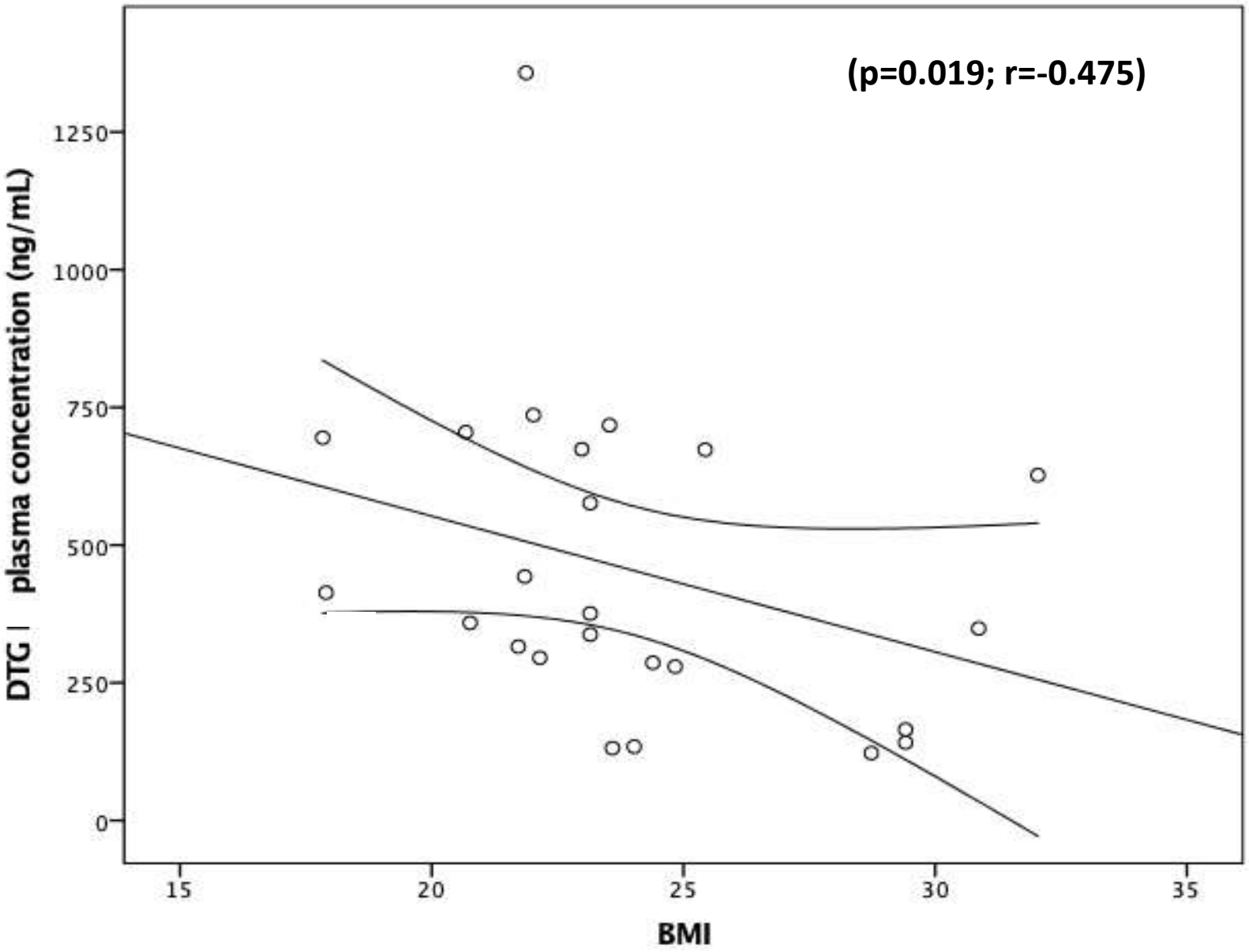
PK Parameters	DTG+3TC (26 pz)	DTG+bPI[1] (40 pz)	p
DTG IC (ng/mL)	449,37 [338,01-560,73]	323.04 [243.47-402.62]	**0.023**
DTG pls (ng/mL)	1956,4 [1604,9-2307,8]	2090.76 [1339.26-2842.26]	0.172
DTG IC/plasma Ratio	0.231 [0.196-0.265]	0.248 [0.186-0.309]	0.346

1. Ferrara et al. Unpublished data, ICAR 2019

PK Results


(p<0.001; r=0.831)
DTG IC concentration (ng/mL)
1250
1000
750
500
250
0
0
1000
2000
3000
4000
DTG plasma concentration (ng/mL)

PK Results_2



No correlation observed between DTG PK parameters and age
No difference between gender

Beyond the virological efficay?

The existence of ongoing HIV replication onART remains a highly controversial topic

Poor antiviral drug diffusion

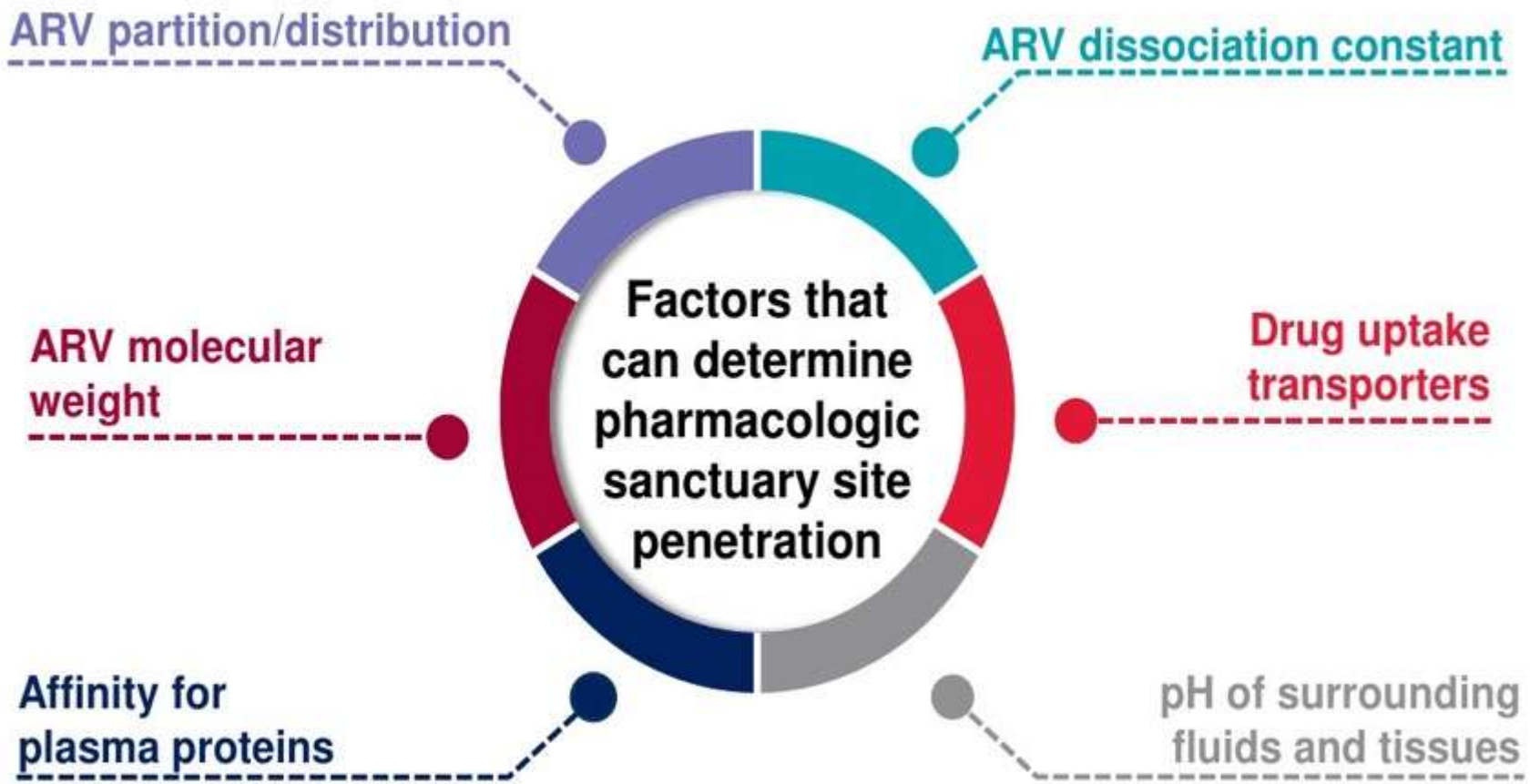
Favor residual replication

Viral persistence

Chronic state of inflammation

potentiates the risk on non-AIDS morbidity and mortality and virological rebound

Specific Properties of ARVs Determine the Extent of Sanctuary Site Penetration



[no notes on this page]

ARVs with more favourable physiochemical properties may be better able to penetrate sanctuary sites

Else LJ, et al. Antiviral Ther 2011;16:1149–67

Two-drug *vs.* three-drug combinations for HIV-1: Do we have enough data to make the switch?

S Moreno et al, HIV Medicine (2019)

Does the number of drugs impact on viral production and, consequently, on immune activation and associated comorbidities?

- CD8 T cell and memory B cell activation in subjects either under multi-ART or under PI monotherapy . After 96 weeks, a significant increase in the activation level of both lymphocyte populations was noticed in subjects being treated with monotherapy[1]

- PI monotherapy has also been associated with markers of inflammation (IL-6) and of monocyte activation(plasma levels of soluble CD14 and CD163)[2]

- The restoration of CD4+/CD8+ ratio was better achieved under multi therapy. Due to a decrease in CD8 T cell count under triple therapy contrasting with an increase in this count under double-ART[3]

1. Petrara MR et al. PLoS One 2017; 2. Torres B et al, AIDS Soc 2014; 3. Mussini C et al, BMC Med 2018;

Review

Differences in HIV Markers between Infected Individuals Treated with Different ART Regimens: Implications for the Persistence of Viral Reservoirs

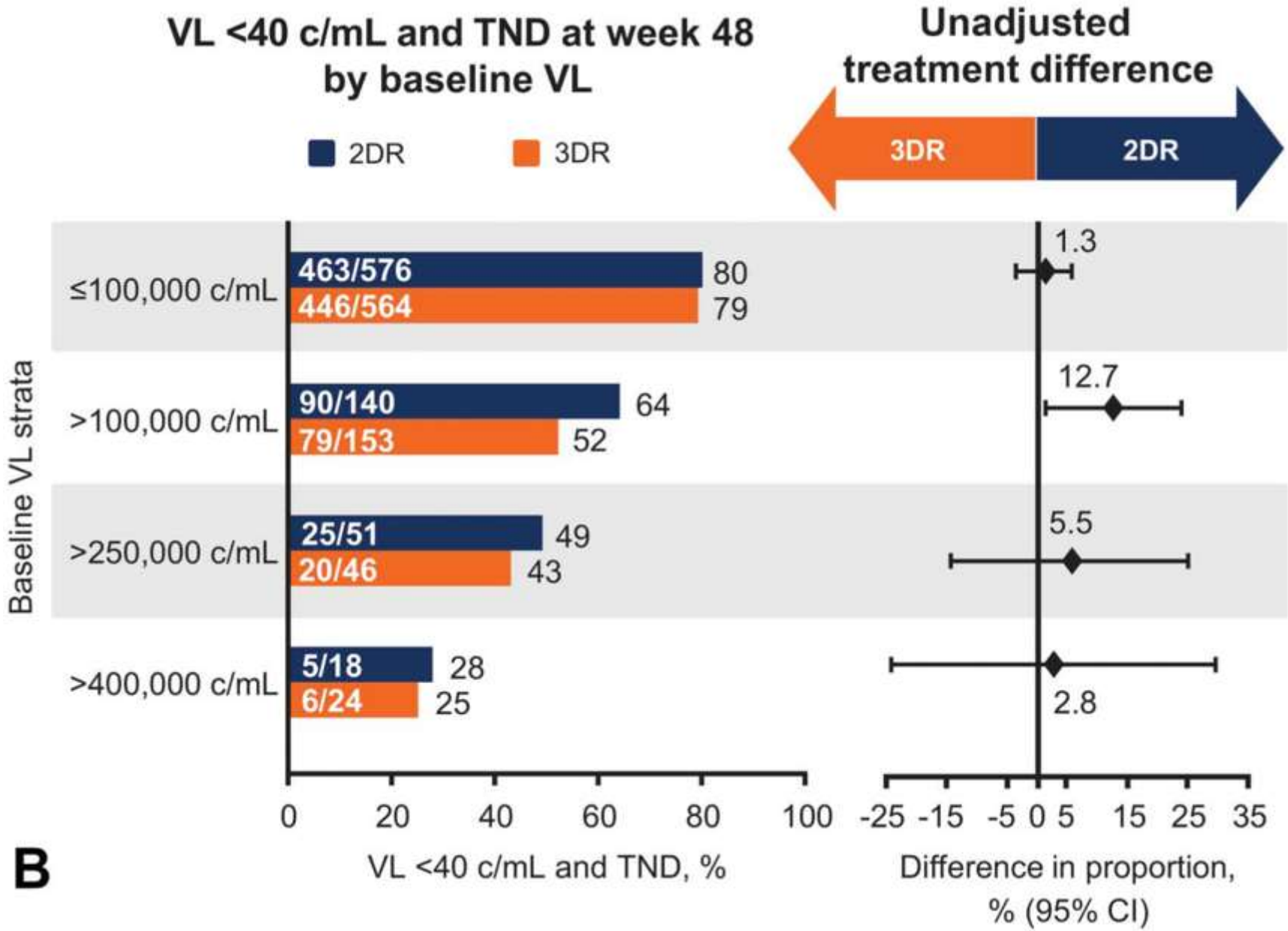
Darcis G et al, Viruses 2020, 12, 489

Impact of ART Intensification on Residual Viremia and Other HIV Reservoir Markers

- INSTI-based regimens were associated with significantly lower cumulative RV compared to both PI-based and NNRTI-based regimens[1]

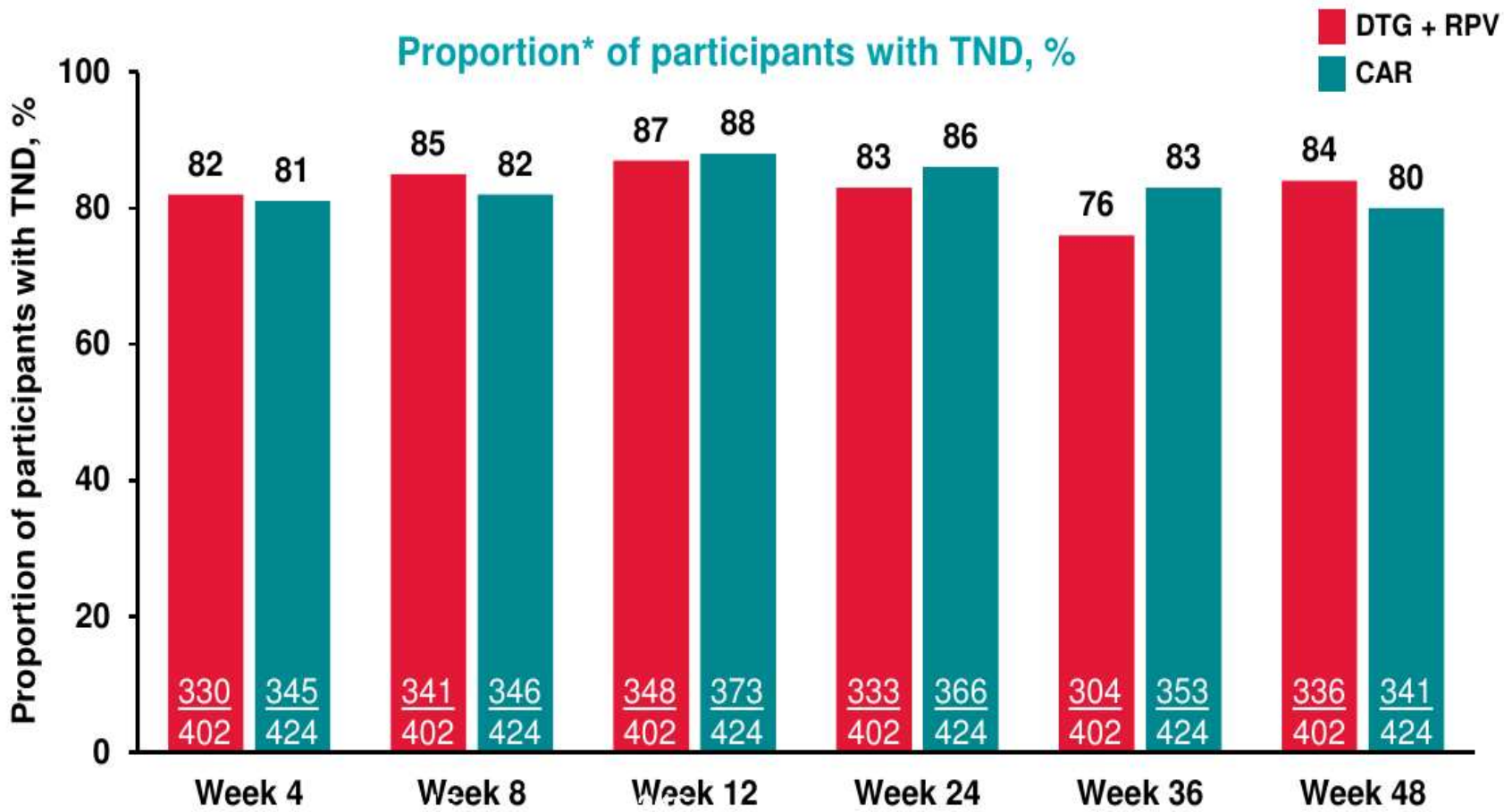
- Switching from a PI-based to a DTG-based regimen on blood and tissue HIV reservoirs might decrease RV in individuals who have a relatively high residual viral load[2]

1. Pascom et al, J. Int. AIDS Soc. 2019. 2. Morón-López et al. Clin. Infect. Dis. 2019



Eron J et al. J Acquir Immune Defic Syndr 2020

Rates of TND were similar for DTG + RPV and CAR in SWORD-1 & -2



[no notes on manual]

Similar proportions of participants with TND were observed at each visit in the DTG + RPV and CAR arms through Week 48 among participants with TND at baseline

The Abbottt RealTime HIV-1 assay measures quantitative HIV-1 RNA viral load from 40 c/mL to 10,000,000 c/mL and generates qualitative TD or TND for viral loads <40 c/mL

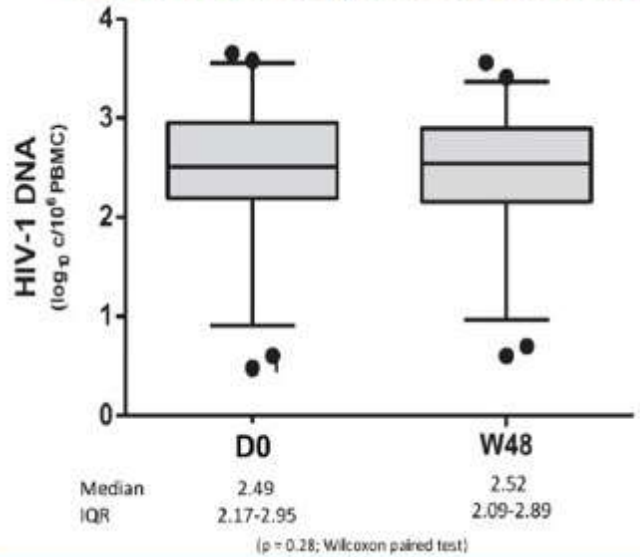
*Of four participants in the DTG + RPV arm with no Post-Baseline data, three had TND and one had TD at Baseline. Two with Baseline TND in CAR had no Post-Baseline VL. TND, target not detected

Underwood M, et al. HIV Glasgow 2018. Poster P311

DTG + 3TC: No Change in PBMC DNA or Residual Viremia on Switching to 2DR

- In the ANRS 167 LAMIDOL trial, patients virologically suppressed on a first-line 3DR with no previous change in regimen for virologic failure were switched from a 3DR* to a DTG + 3TC. This substudy analysed cellular reservoir size and residual viremia at Day 0 and up to Week 48.
- All total plasma DTG C_{min} values but one exceeded the *in vitro* protein-binding adjusted IC_{90} (64 ng/mL)

Total HIV-1 DNA at Day 0 and Week 48 of the DTG + 3TC dual-class therapy (Whiskers 2.5%–97.5%)



Description of the ultra-sensitive plasma viral load

Virology USpVL	D0 (n=101)	W24 (n=101)	W48 (n=99)
USpVL < LOD	38%	41%	49%
LOD < USpVL < LOQ	30%	30%	21%
USpVL > LOQ	32%	29%	30%

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In this substudy of the ANRS 167 LAMIDOL trial, there was no change in HIV-1 PBMC reservoir size or residual viremia on switching to DTG + 3TC in participants with no history of virologic failure and adequate plasma trough levels of DTG

LOD, limit of detection; LOQ, limit of quantification; USpVL, ultra-sensitive plasma viral load
*two NRTIs and a boosted PI, an NNRTI or an INI

Charpentier C, et al. CROI 2019. Poster 491

Conclusion

- Good virologic efficay, safety and tolerability

- Good options for therapeutic switch un selected patients

- Impact of the different regimens on immune dysfunction, such as immune activation, systemic inflammation, microbial translocation, mitochondrial dysfunction, and oxidative stress, is unclear

- Systematic follow-up of the viral blood reservoir, and when possible of viral tissue reservoirs, in studies of treatment and trials of new regimens would provide much needed information

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