Semplificazione a duplice terapia

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IRCCS-Fondazione Gemelli

- Dalla loro introduzione in commercio, gli inibitori dell’integrasi hanno trovato ampio utilizzo grazie alla loro potenza e al loro profilo di tollerabilità.

- Attualmente rappresentano la prima scelta nella terapia del paziente naive.

- Sempre più attenzione si sta ponendo nel loro ruolo nelle terapie di deintensificazione, in particolare nel loro utilizzo in contesto di regimi dual.

- Le linee-guida sulla deintensificazione
- Dati di letteratura
- La nostra esperienza

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Devono quindi essere accuratamente valutati, bilanciati e discussi i potenziali rischi e i benefici di *schemi personalizzati di trattamento, modulati sulla base delle preferenze e delle esigenze cliniche del singolo paziente*.

Le principali ragioni che possono portare alla scelta dell'ottimizzazione sono:

- Intolleranza al regime in atto (effetti indesiderati, documentata tossicità);
- Regime in atto che possa aggravare comorbosità presenti;
- Prevenzione di tossicità a lungo termine (*pre-emptive switch*);
- Regime in atto non più raccomandato;
- Interazioni con altri farmaci, inclusa necessità di cura di altre infezioni (TB, HBV, HCV, ecc.);
- Necessità di migliorare l'aderenza del paziente alla terapia.

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e Tropicali

Da 3 farmaci a DRV/r o DRV/c + RAL (b)	Riduzione/Prevenzione tossicità da NRTI.		Limitati dati sull'efficacia, soprattutto a lungo termine. Sviluppo resistenza a InSTI (incluso DTG) in caso di fallimento.	
Da 3 farmaci a DTG + RPV (c)	Riduzione/Prevenzione tossicità da NRTI.	Risparmio tossicità IP	Limitati dati sull'efficacia, soprattutto a lungo termine. Possibile resistenza a NNRTI e InSTI in caso di fallimento.	
Da 3 farmaci a DTG + 3TC (d)	Riduzione/Prevenzione tossicità da NRTI.	Risparmio tossicità IP	Limitati dati sull'efficacia, soprattutto a lungo termine. Possibile sviluppo resistenza a InSTI (incluso DTG) e a 3TC in caso di fallimento.	

EACS Guidelines 2017

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Indications

1. **Documented toxicity** caused by one or more of the antiretrovirals included in the regimen. Examples of these reactive switches: lipoatrophy (d4T, AZT), central nervous system adverse events (EFV), diarrhoea (PI/r) and jaundice (ATV), proximal renal tubulopathy and low bone mineral density (TDF), see Adverse Effects of ARVs and Drug Classes.
2. **Prevention of long-term toxicity.** Example of this proactive switch: prevention of lipoatrophy in persons receiving d4T or AZT and prevention of proximal renal tubulopathy with TDF, see Adverse Effects of ARVs and Drug Classes.
3. **Avoid serious drug-drug interactions**
4. **Planned pregnancy**
5. **Ageing and/or co-morbidity** with a possible negative impact of drug(s) in current regimen, e.g. on CVD risk, metabolic parameters.
6. **Simplification:** to reduce pill burden, adjust food restrictions and improve adherence.
7. **Starting of HCV treatment in case of drug-drug interaction,** see Drug-drug Interactions between DAAs and ARVs.

Class-sparing strategies

Dual therapy:

DTG + RPV

3TC + (DRV/r or DRV/c) or

3TC + (ATV/r or ATV/c)

In clinical trials these strategies have not been associated with more virological rebounds than triple therapy.

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

Strategies with Some Supporting Evidence

Other switching strategies in patients with viral suppression have some evidence to support their use. These strategies cannot yet be recommended under most circumstances, or at all, until further evidence is available. If used, patients should be closely monitored to assure viral suppression is maintained. Some of these strategies are listed below.

Boosted Darunavir plus Raltegravir

The efficacy of this combination in patients with lower viral load levels was established in ART-naive patients. At 96 weeks, DRV/r plus RAL was noninferior to DRV/r plus TDF/FTC, but was inferior in patients with low pre-treatment CD4 T lymphocyte counts (<200 cells/mm^3) and high viral loads (>100,000 copies/mL).[20] The efficacy of switching to DRV/r plus RAL in virologically suppressed patients with no resistance to either DRV or RAL has not been explored.

Dolutegravir plus Lamivudine or Emtricitabine

The Lamidol trial evaluated a regimen of DTG and 3TC as a maintenance strategy in virologically suppressed patients who have no evidence of NRTI, INSTI, or PI resistance.[21] At 24 weeks, 103 of the 104 participants remained virologically suppressed. In a small (20-patient), single-arm study of DTG plus 3TC for ART-naive patients, 90% of patients achieved and maintained viral suppression at 48 weeks.[22] However, there is currently insufficient evidence to support use of this regimen, given that Lamidol was a single-arm trial and

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

Dolutegravir plus Rilpivirine

Two Phase 3 trials enrolled 1,024 participants with viral suppression for at least 1 year and no history of virologic failure.[18] Participants were randomized to stay on their combination ART regimen or to switch to a regimen of once-daily DTG plus RPV. Virologic suppression was maintained in 95 to 96% of the participants in both arms at 48 weeks. DTG plus RPV can be a reasonable option when the use of NRTIs is not desirable and when resistance to either DTG or RPV is not expected **(AI)**.

Switching from a PI/r to the INI, raltegravir, in virologically suppressed individuals has been evaluated in three randomised controlled trials. Two studies have shown that previous history of NRTI resistance mutations increases the risk of subsequent virological failure on switching compared with continuing on a PI/r [25,26]. This association was not seen in a third trial [6]. However, it is not surprising that switching from an ARV with a high genetic barrier to one with a low genetic barrier to resistance may potentially increase the risk of virological failure if the activity of the NRTI backbone has been compromised by previous NRTI resistance. One randomised controlled trial assessed switching from PI to elvitegravir/c in people with viral suppression (excluding individuals with a history of virological failure or resistance to tenofovir-DF or emtricitabine), finding suppression is maintained and regimen is well tolerated [27].

6.3.2.3.3 Switch from NNRTI

Switching from an NNRTI to an alternative third agent (elvitegravir/c or raltegravir [28,29]) in virologically suppressed patients has been assessed. Raltegravir was assessed for patient preference and was found to be acceptable. NNRTI switch to elvitegravir/c maintained viral suppression and was well tolerated. If switching from an NNRTI, consideration must be given to previous treatment history and potential pharmacokinetic interactions. The latter is discussed in more detail in Section 6.2.4.

- Le linee-guida sulla deintensificazione
- Dati di letteratura
- La nostra esperienza

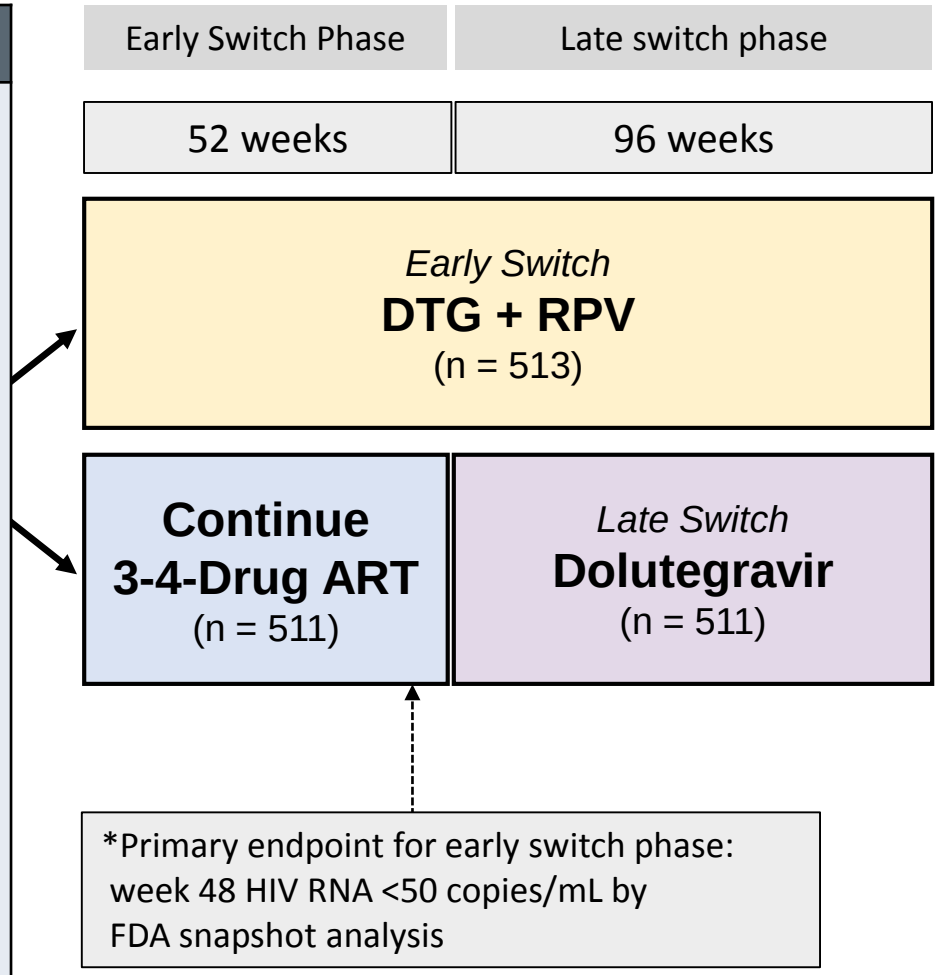
Dolutegravir plus Rilpivirine as Maintenance Dual Therapy
SWORD-1 and SWORD-2: Design

Study Design: SWORD-1 and Sword-2

- **Background**: Identical randomized, multinational, open-label, industry-sponsored, parallel-group, non-inferiority studies of dolutegravir plus rilpivirine to maintain virologic suppression

- **Inclusion Criteria:**
  - Age ≥18 years of age
  - On stable 3-4 drug ART ≥6 months
  - No history of virologic failure
  - No resistance to DTG or RPV
  - 1st or 2nd regimen
  - HIV RNA <50 copies/mL in prior 12 months
  - HIV RNA <50 copies/mL at screening
  - No HBV co-infection

- Regimen (Once daily)
  - Dolutegravir 50 mg + Rilpivirine 25 mg



Source: Llibre JM et al. Lancet 2018

Dolutegravir plus Rilpivirine as Maintenance Dual Therapy
SWORD-1 and SWORD-2: Baseline Characteristics

Baseline Characteristic	DTG + RPV (n=513)	3 or 4-Drug ART (n=511)
Age (mean)	43	43
Age >50 years	147 (29%)	142 (28%)
Female	120 (23%)	108 (21%)
Race, non-white	92 (18%)	111 (22%)
CD4 count (median)	611	638
Baseline PI	133 (26%)	136 (27%)
Baseline NNRTI	275 (54%)	278 (54%)
Baseline INSTI	105 (20%)	97 (19%)
Baseline TDF	374 (73%)	359 (70%)
ART duration (median)	51 months	53 months

Dolutegravir plus Rilpivirine as Maintenance Dual Therapy
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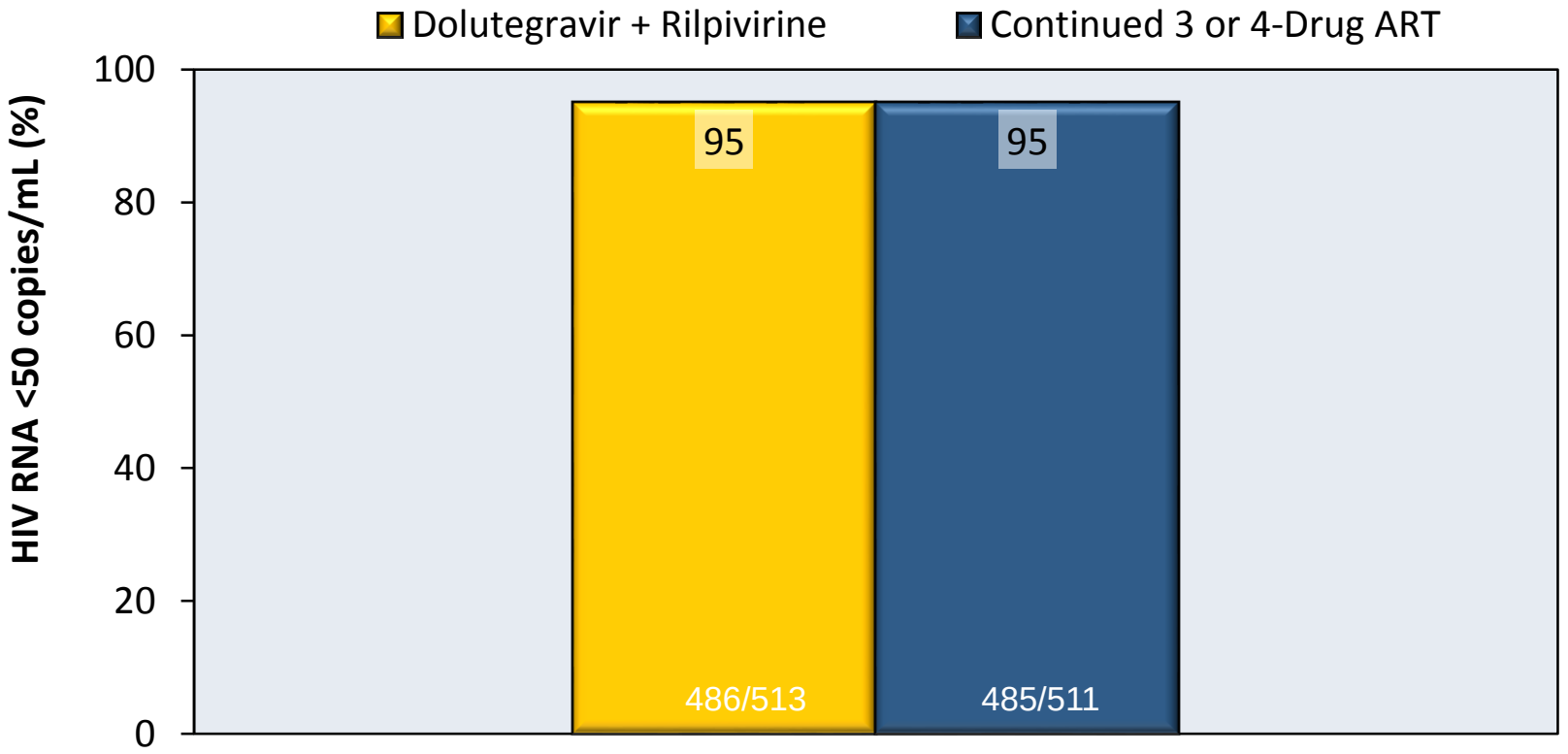
Dolutegravir plus Rilpivirine as Maintenance Dual Therapy
SWORD-1 and SWORD-2: Pooled Results at Week 48

Week 48 Virologic Response (by FDA Snapshot Analysis)



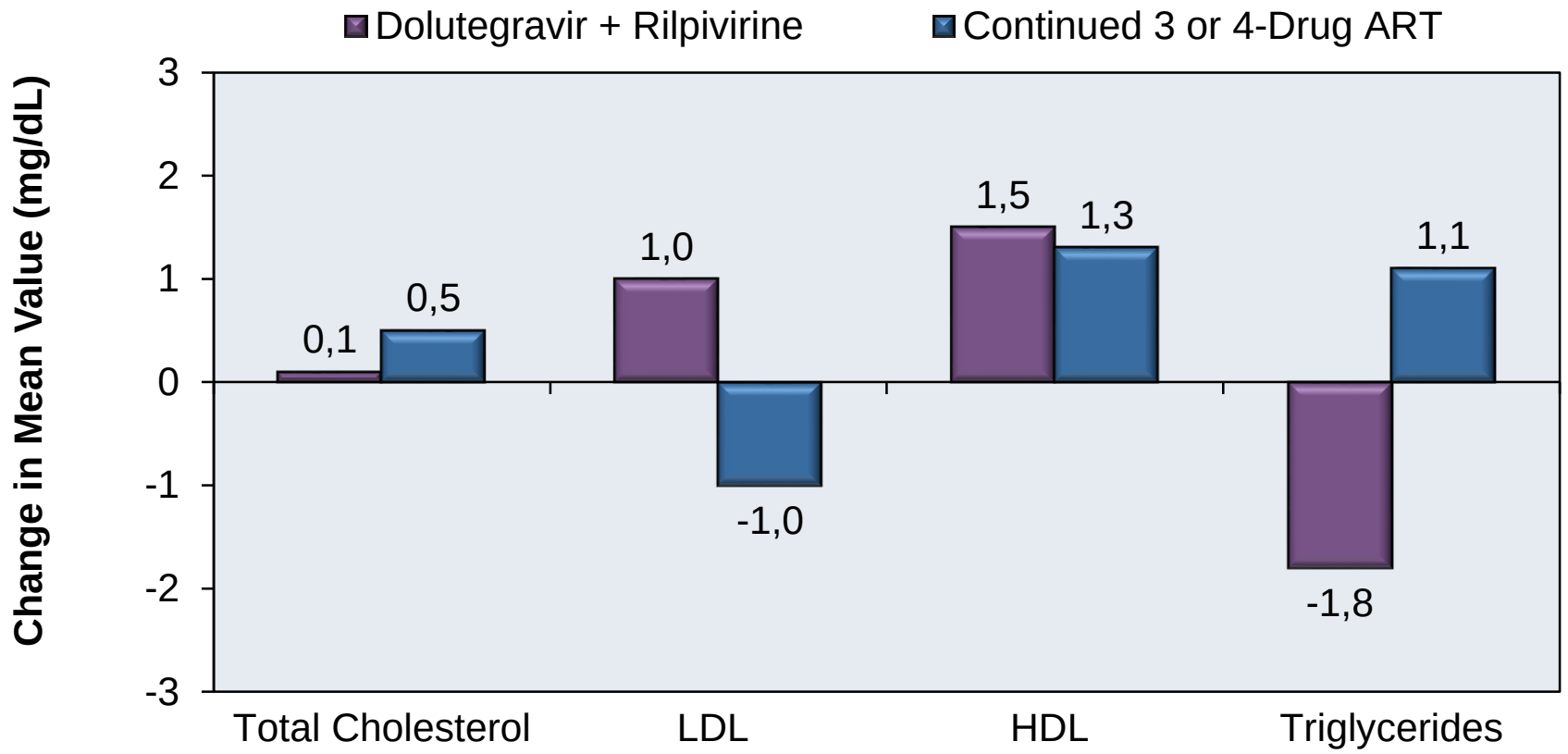
- Confirmed virologic withdrawal: 2 (<1%) in each arm
- One NNRTI resistance mutation (K101K/E) detected in DTG + RPV arm
- No integrase resistance occurred

Dolutegravir plus Rilpivirine as Maintenance Dual Therapy
SWORD-1 and SWORD-2: Pooled Results at Week 48

SWORD 1&2 Pooled Results: 48-Week Adverse Events (AE)		
	DTG + RPV (n = 513)	**3 or 4-Drug ART** (n = 511)
Any AE	395 (77%)	364 (71%)
Any serious AE	27 (5%)	21 (4%)
Grade 1-2 drug-related AE	89 (17%)	8 (2%)
Grade 3-4 drug-related AE	8 (2%)	1 (<1%)
AE leading to study withdrawal	21 (4%)	3 (<1%)
CNS AE leading to study withdrawal	9 (2%)	1 (<1%)

Dolutegravir plus Rilpivirine as Maintenance Dual Therapy
SWORD-1 and SWORD-2: Pooled Results at Week 48

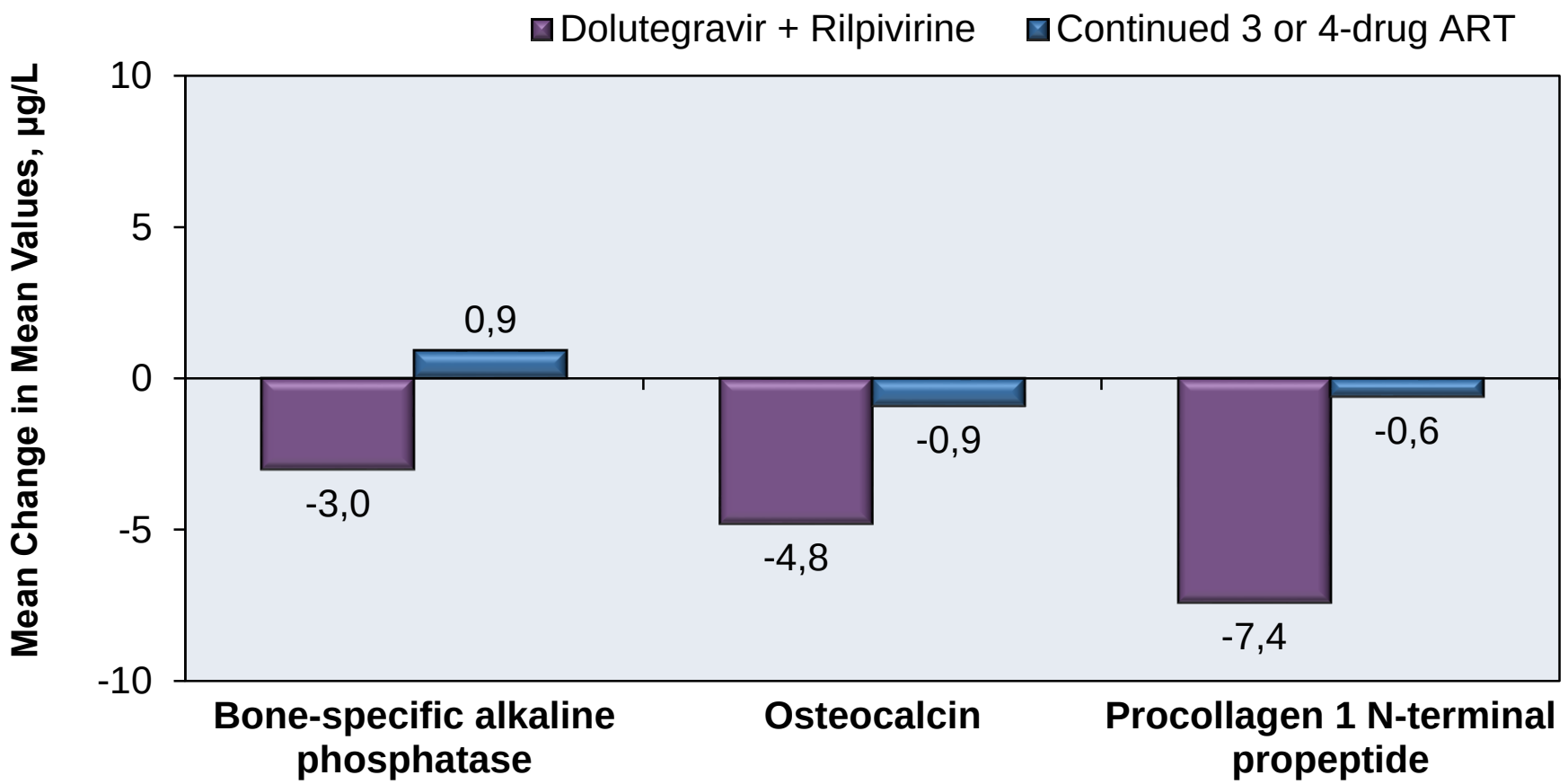
Week 48: Change in Plasma Lipids from Baseline



Dolutegravir plus Rilpivirine as Maintenance Dual Therapy

SWORD-1 and SWORD-2: Pooled Results at Week 48

Week 48: Change in Bone Biomarkers from Baseline



PROS VS CONS

PROS :

-Alta efficacia e non inferiorità della dual vs CAR

-Ottimi dati di tollerabilità sul metabolismo lipidico ed sull'osso della dual vs CAR

CONS :

-Bassa Barriera genetica dello schema dual vs CAR (se fallimento probabili mutazioni per RPV)

-Maggiori eventi avversi sul SNC della dual vs CAR

ACCEPTED MANUSCRIPT

Dolutegravir plus lamivudine maintain HIV-1 suppression through week 48 in a pilot randomized trial

Babafemi O Taiwo ✉, Vincent C Marconi, Baiba Berzins, Carlee B Moser, Amesika N Nyaku, Carl J Fichtenbaum, Constance A Benson, Timothy Wilkin, Susan L Koletar, Jonathan Colasanti ... Show more

Clinical Infectious Diseases, cix1131, https://doi.org/10.1093/cid/cix1131

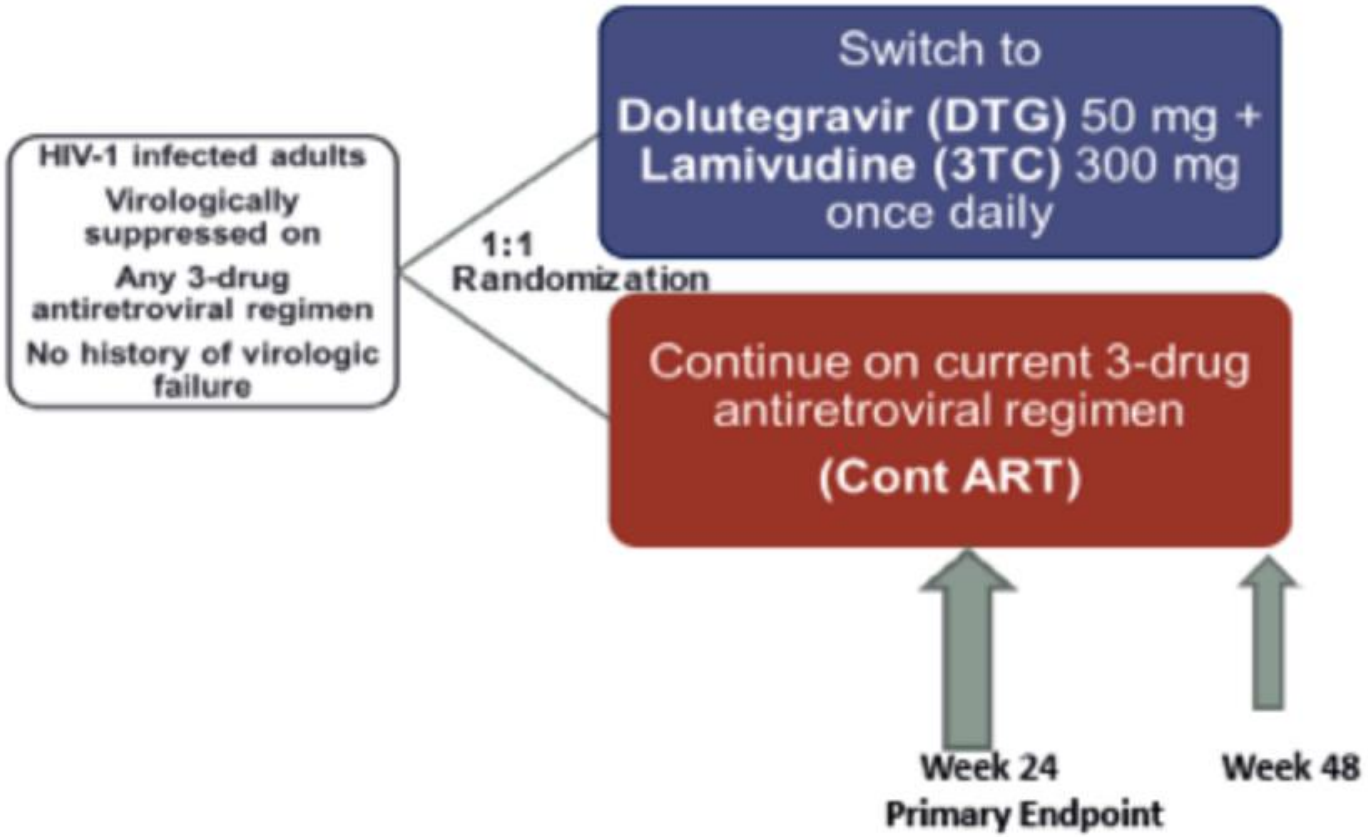
Discussion

In this randomized pilot clinical trial, switching to the two-agent regimen of DTG +3TC was non-inferior at 24 weeks to continuation of standard three-drug maintenance therapy. This was supported by the FDA snapshot analyses at weeks 24 and 48.

The regimen of DTG + 3TC has several advantages over other virologically effective two-drug combinations. Specifically, boosted PI + 3TC regimens [3-5] have a greater risk of drug interactions and metabolic complications while DTG + rilpivirine [1] is limited by food requirement and the need to avoid acid-reducing therapies. Long acting cabotegravir plus rilpivirine [2] must be administered intramuscularly, hence may be unappealing to some patients. Of note, DTG+3TC and these other two-agent regimens are contraindicated in individuals with chronic hepatitis B infection.

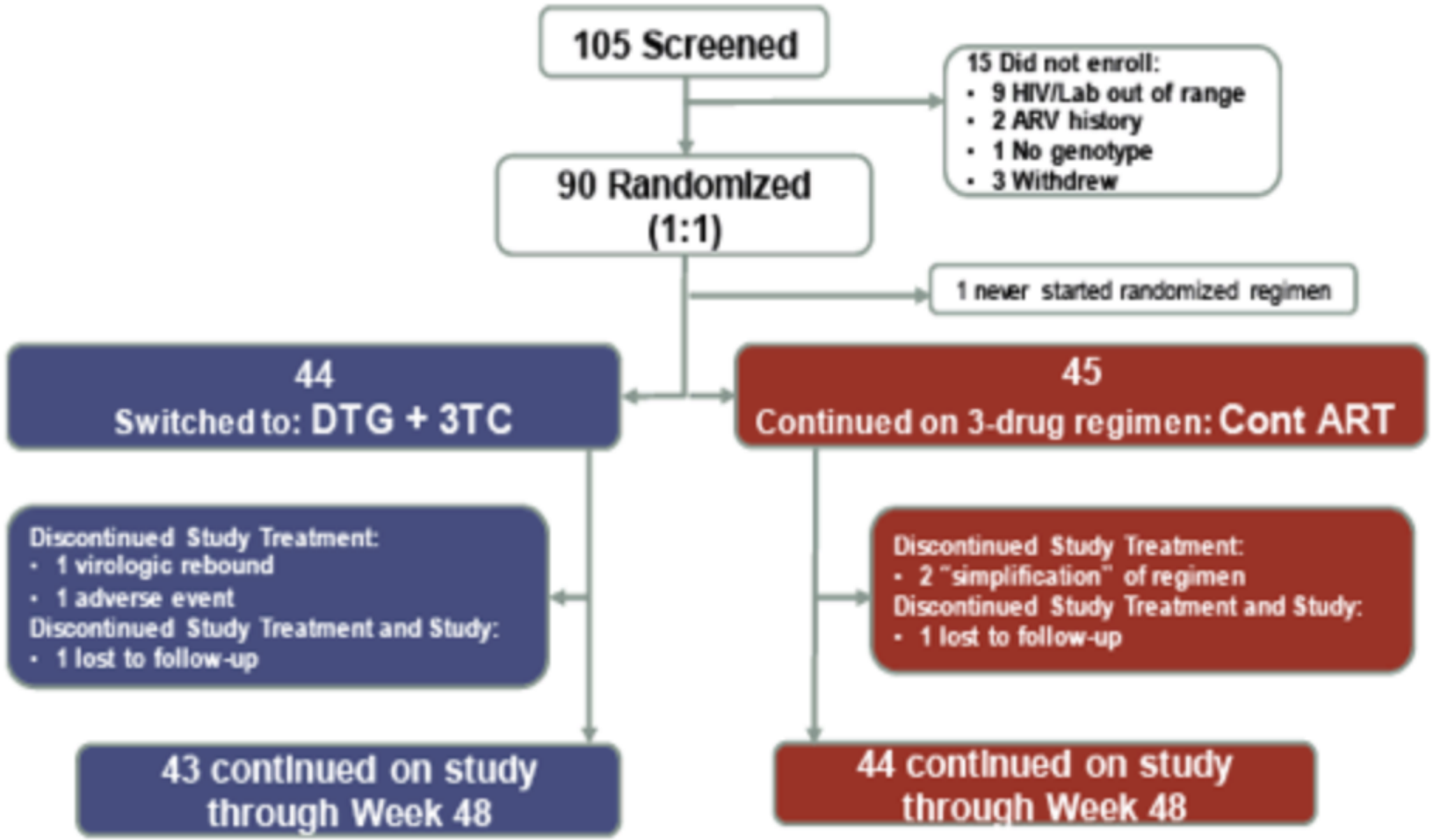
Study Design

Open-label, randomized, multicenter Investigator-Initiated clinical trial



Taiwo CID 2018

Participant Disposition to Week 48



Taiwo CID 2018

Baseline Characteristics

		DTG + 3TC (N=44)	Cont. ART (N=45)	TOTAL (N=89)
Age (years)	Median (Q1, Q3)	46 (37,55)	50 (41,53)	47 (38,54)
Sex	Male	89%	87%	88%
Race	White	52%	64%	60%
	Black	43%	33%	38%
Ethnicity	Hispanic	18%	11%	15%
CD4 Count	Cells/mm^3	694 (533,1034)	646 (380,819)	680(498,927) p=0.047
Nadir	Median (Q1, Q3)	333 (184, 408)	228 (91, 341)	278(109, 387)p=0.027
Time on ART	Years, Median	5.28 (3.81,7.49)	6.03 (3.72,7.44)	5.70 (3.72, 7.48)
Current ART	EFV, RPV, NVP	12 (27%)	15 (33%)	27 (30%)
	DRV/r, ATV/r	14 (32%)	15 (33%)	29 (33%)
	DTG, RAL, ELV/c	18 (41%)	15 (33%)	33 (37%)
Current NRTI	TDF/FTC	35 (80%)	41 (91%)	76 (86%)
	ABC/3TC	8 (18%)	4 (9%)	12 (14%)

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Virologic Outcome at Week 48 (FDA Snapshot)

	DTG + 3TC N= 44 (%)	Cont ART N= 45 (%)	Total N=89 (%)
HIV-1 RNA < 50 cpm [95% CI]	40 (90.9%) [77%,96%]	40 (88.9%) [75%,96%]	80 (89.9%) diff. 2.0% [-12.6%,16.5%]
HIV-1 RNA (VL) ≥ 50 cpm (%)	1 (2.3%)	1 (2.2%)	2 (2.2%)
VL ≥ 50 cpm	0	1	1
D/C study treatment due to lack of efficacy	0	0	0
D/C study treatment due to AE and last VL >50	0	0	0
D/C study treatment for other reasons while last VL ≥ 50	1	0	1
No virologic data in window	3 (6.8%)	4 (8.9%)	7 (7.9%)
D/C study treatment due to AE	0	0	0
D/C study treatment for other reasons	2	3	5
On study but missing data in window	1	1	2

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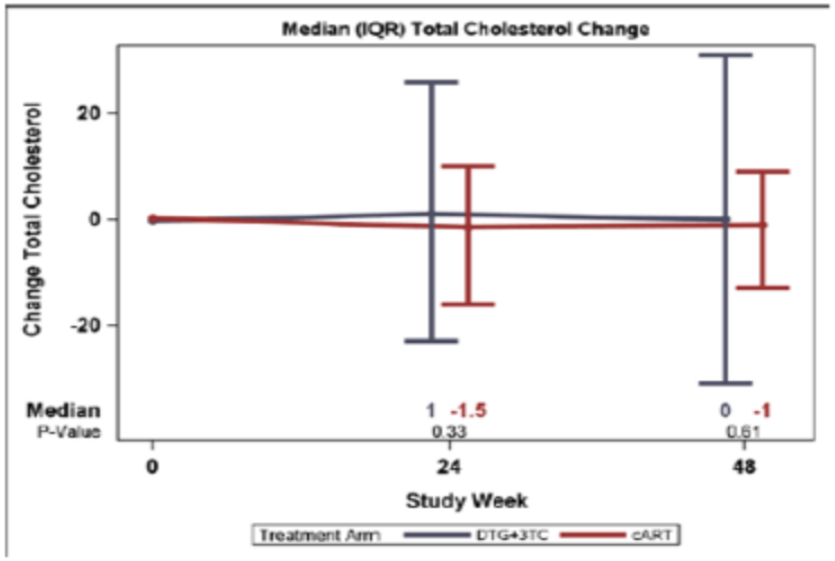
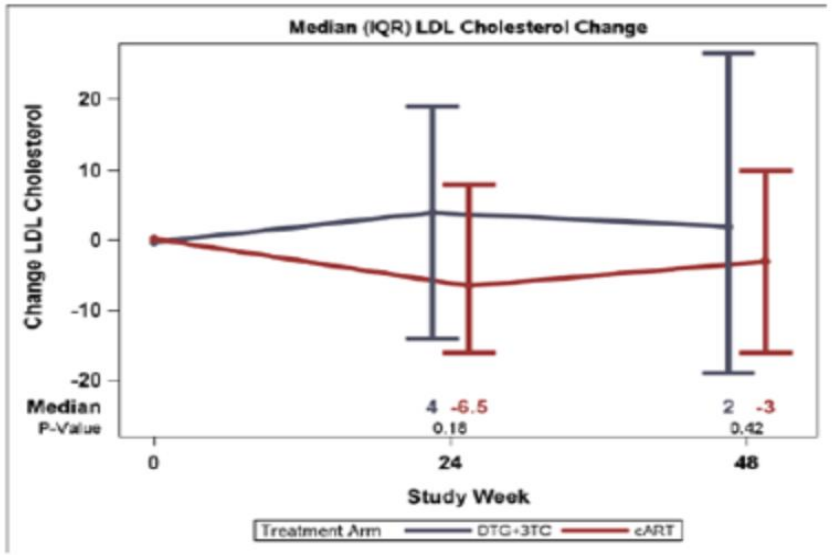
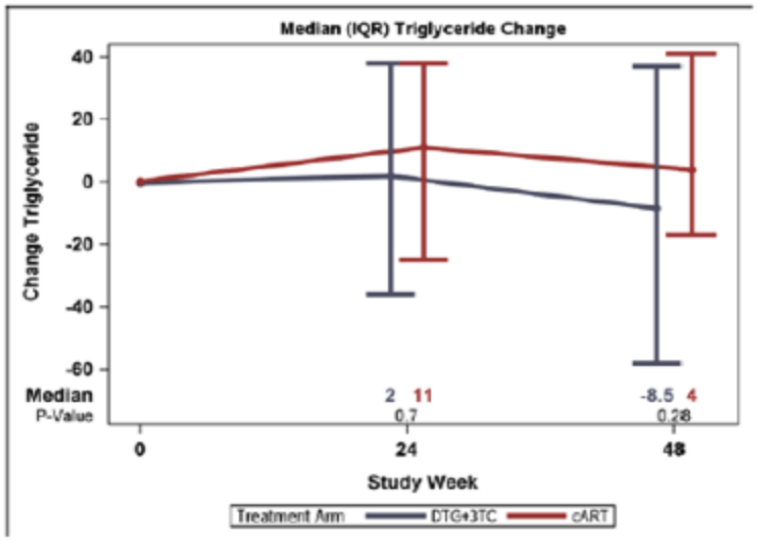
Lipid Changes: baseline to Week 24 and 48







Taiwo CID 2018

PROS VS CONS

PROS :

-Alta efficacia della dual vs CAR

-Ottimi dati di tollerabilità sul metabolismo lipidico della dual vs CAR

-Ruolo della 184????

CONS :

-Bassa numerosità del campione

-Follow up molto breve vs le dual Lamivudina PI/r

-Ruolo della 184????

- Le linee-guida sulla deintensificazione
- Estratti di letteratura
- La nostra esperienza

Dolutegravir plus rilpivirine as a switch option in cART-experienced subjects: 96-weeks data

Capetti et al., The Annals of Pharmacotherapy, in press.

Table 1. Baseline characteristics of the study population

Demographic parameters	
Age, median [IQR]	52 [44 – 61]
Sex, % M:F	68.3 : 31.7
Ethnicity, % Caucasian : African : Hispanic : Asian	89.7 : 5.5 : 3.4 : 1.4
Risk factor, % IVDU : HS : MSM : VI : TI	31.1 : 32.4 : 35.2 : 0.7 : 0.7
Reasons for switching, n (%)	
Simplification	75 (51.7%)
Toxicity	53 (36.5%)
Drug-drug interactions with anti-HCV therapy	10 (6.9%)
Persistent low-level viremia	4 (3.0%)
Non-adherence	3 (2.1%)
Viral failure	2 (1.4%)
Immunologic parameters	
Nadir CD4+ T-cells/mmc, median [IQR]; %, median [IQR]	263 [147 - 403]; 19.5 [16 - 26]
Baseline CD4+ T-cells/mmc, median [IQR]; %, median [IQR]	683 [494 - 896]; 32 [24.9 – 35.9]
Virologic parameters	
Zenith HIV RNA, log_{10} copies/mL, median [IQR]	5.11 [4.89 – 5.43]
Subjects with baseline HIV RNA ≥ 50 copies/mL, n (%)	21 (14.5)
N. of drug classes affected by resistance, n (%): 1 : 2 : 3	20 (13.8) : 32 (22.1) : 19 (13.1)
Overall resistance to NRTI, n (%)	67(46.2)
NRTI alone, n (%); NNRTI alone, n (%)	52 (35.9); 1 (0.7)
NRTI + NNRTI, n (%), NRTI + RPV, n (%)	15 (10.3); 6 (4.1)
PI	75 (51.7)
INSTI	1 (0.7)*
Treatment parameters	
At least one virologic failure, n (%)	118 (81.4)
N. of drugs in the previous regimen , n (%): 2 : 3 : ≥ 4	46 (31.7) : 93 (64.2) : 6 (4.1)
Subjects coming from BID, non-STR OD, STR OD therapy, n (%)	63 (43.4) : 70 (48.3) : 12 (8.3)
Patients taking drug X as part of the previous regimen, n	
NRTIs	Tenofovir 53; Emtricitabine 52; Lamivudine 47, Abacavir 28; Zidovudine 9
NNRTIs	Rilpivirine 29; Etravirine 19; Efavirenz 18; Nevirapine 15
PIs	Darunavir/r(c) 39; Atazanavir/r(c) 27; Atazanavir 3; Lopinavir 2
INSTIs, EI	Raltegravir 50; Elvitegravir/c 4; Maraviroc 6

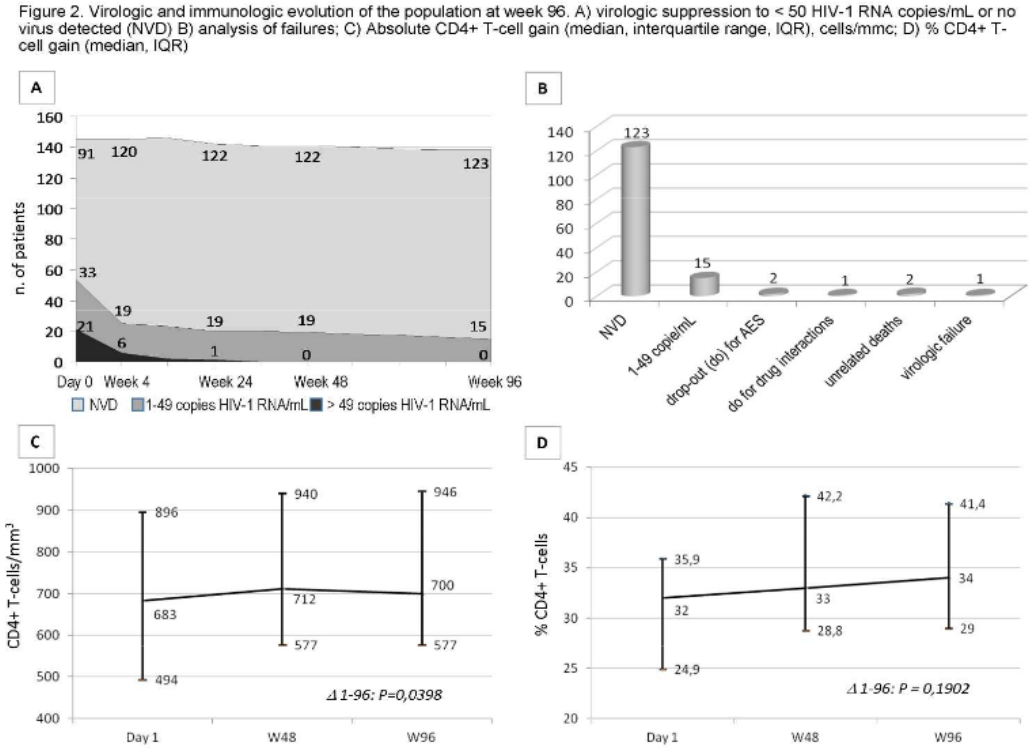


Figure 2. Virologic and immunologic evolution of the population at week 96. A) virologic suppression to < 50 HIV-1 RNA copies/mL or no virus detected (NVD) B) analysis of failures; C) Absolute CD4+ T-cell gain (median, interquartile range, IQR), cells/mmc; D) % CD4+ T-cell gain (median, IQR)

Figure 2. Virologic and immunologic evolution of the population at week 96. A) virologic suppression to < 50 HIV-1 RNA copies/mL or no virus detected (NVD) B) analysis of failures; C) Absolute CD4+ T-cell gain (median, interquartile range, IQR), cells/mmc; D) % CD4+ T-cell gain (median, IQR)

254x190mm (300 x 300 DPI)

Efficacia e tollerabilità di un regime dual con lamivudina/dolutegravir in pazienti HIV+ virologicamente soppressi: dati dalla pratica clinica. L'Esperienza del database ODOACRE

206 HIV-infected patients from 5 Italian clinical centers starting lamivudine plus dolutegravir were retrospectively evaluated. Criteria for eligibility were:

- patient's informed consent to data collection,
- adult age (≥18 years-old),
- being on stable cART with viral suppression (HIV-RNA<50 copies/mL) at the moment of switch (baseline).

Primary objective was to **evaluate the proportion of patients free from virological failure** (VF, defined by a single HIV-1 RNA≥1,000 copies/mL or by two consecutive HIV-1 RNA≥50 copies/mL) **and from treatment discontinuation** (=discontinuation of any agent of the regimen, TD) for any cause.

Patients not experiencing VF or TD were censored at their last available follow-up, at the moment of death or loss to follow-up (more than 6 months since previous study visit).

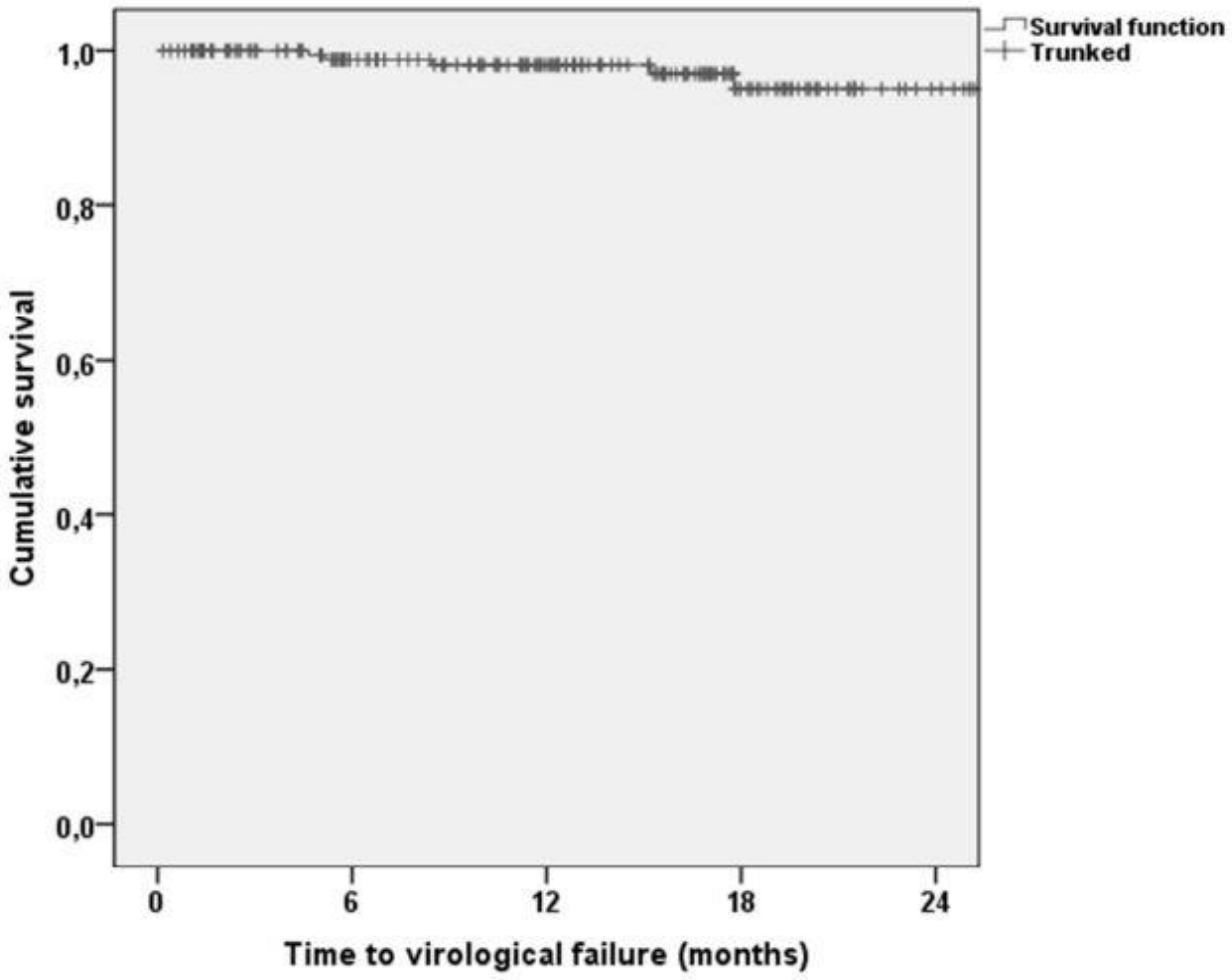
Caratteristiche al baseline-1

Variables	N (%)
Age*	51 (43-56)
Male sex	150 (72.8)
HIV risk factor	
Heterosexual	78 (37.9)
MSM	76 (36.9)
IDU	20 (9.7)
Other	32 (15.5)
Years since HIV diagnosis*	14 (8-20)
Years on antiretroviral therapy*	12 (5-17)
CDC stage C	52 (25.2)
Anti-HCV positive serostatus	29 (14.1)
Nadir CD4 count (cells/µL)*	199 (61-283)
Zenith HIV-RNA (log_{10} copies/mL)*	4.98 (4.42-5.40)
Current CD4 count (cells/µL)*	640 (490-860)

Caratteristiche al baseline-2

Variables	N: (%)
Therapy before switch	
2NRTIs+PI	50 (24.3)
2NRTIs+NNRTI	20 (9.7)
2NRTIs+INI	33 (16.0)
Less drug regimen	100 (48.5)
Lamivudine plus bPI	83 (40.2)
Reasons for switching	
Simplification	67 (32.5)
Dyslipidemia	64 (31.1)
Renal toxicity	15 (7.3)
Bone toxicity	10 (4.9)
Neurological toxicity	3 (1.5)
Other toxicity	20 (9.7)
Drug-drug interaction	7 (3.4)
Other/unspecified	20 (9.7)

1a



Virological failure

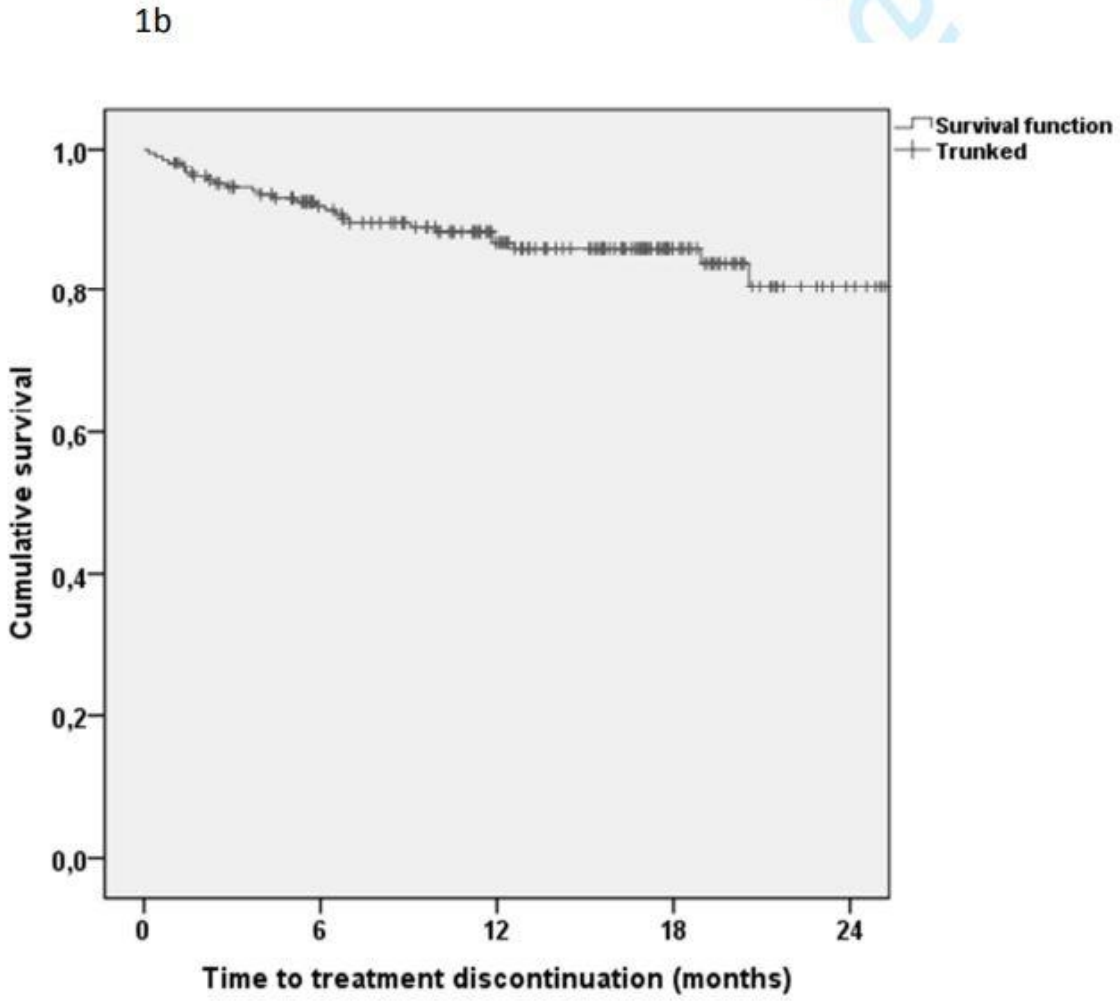
- 5 pts over 216.5 person-years of follow-up (PYFU);
- overall incidence of 2.3 VF per 100 PYFU;
- estimated probabilities of maintaining virological were:
  - 98.2% (95% CI, 96.0%-100%) at 48 ws;
  - 95.1% (95%CI 90.4%-99.8%) at 96 ws.

An increased rate of VF was found in patients with a **zenith HIV-1 RNA≥5x10^5 copies/mL** (7.8 VF per 100 PYFU)**(log-rank p-value=0.049)**.

Estimated probabilities of remaining free from VF in this group of patient were:

- 95.2% (95%CI, 86.2%-100.0%) at 48 ws;
- 86.6% (95%CI 68.4%-100.0%) at 96 ws;

Treatment discontinuation

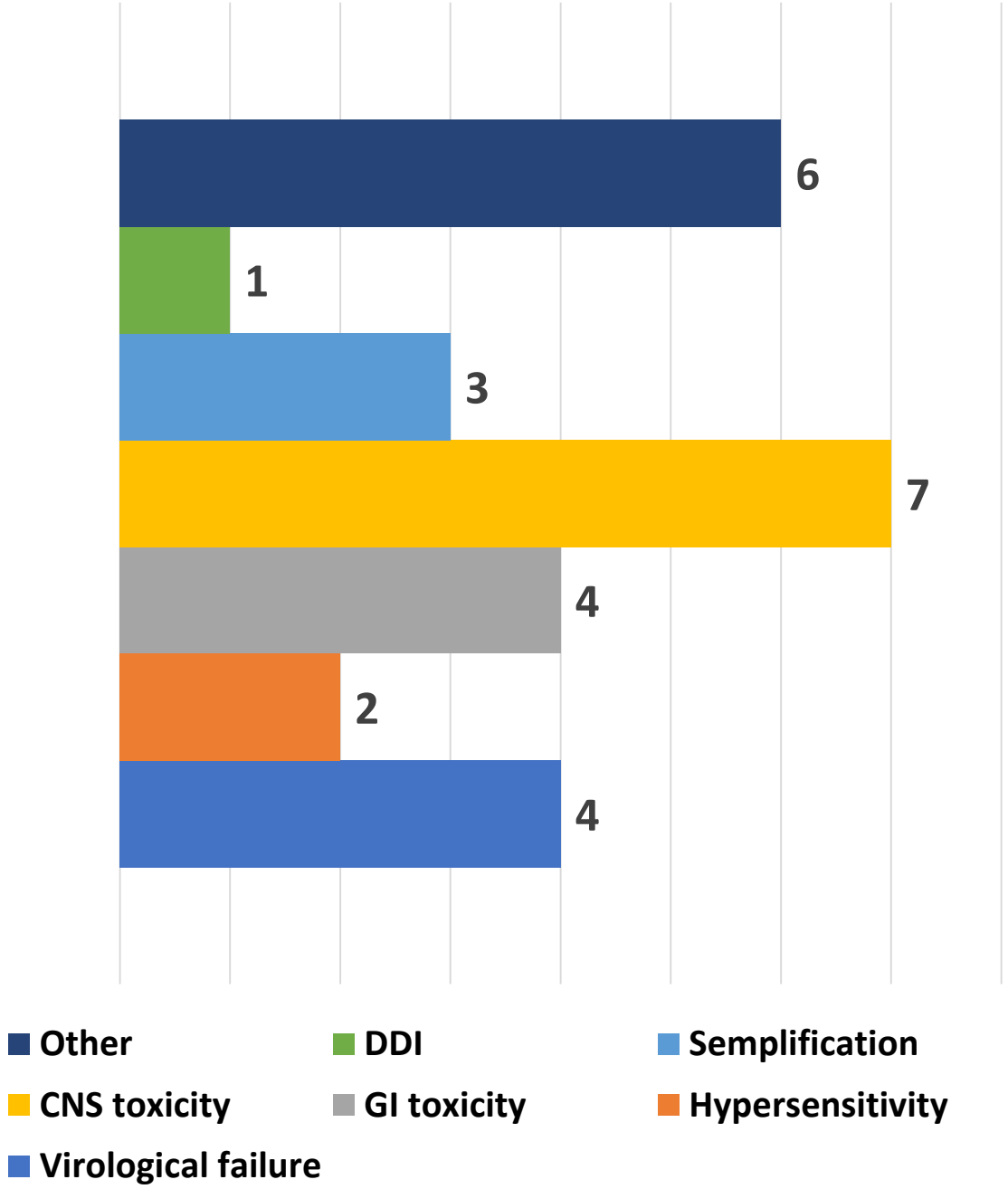


- 27 pts over 217.7 person-years of follow-up (PYFU);
- overall incidence of 12.4 TD per 100 PYFU;
- estimated probabilities of continuing the regimen were:
  - 86.7% (95% CI, 81.6%-91.8%) at 48 ws;
  - 80.5% (95%CI 71.5%-89.5%) at 96 ws.
- Median time to TD was 132 days (IQR 43-272).

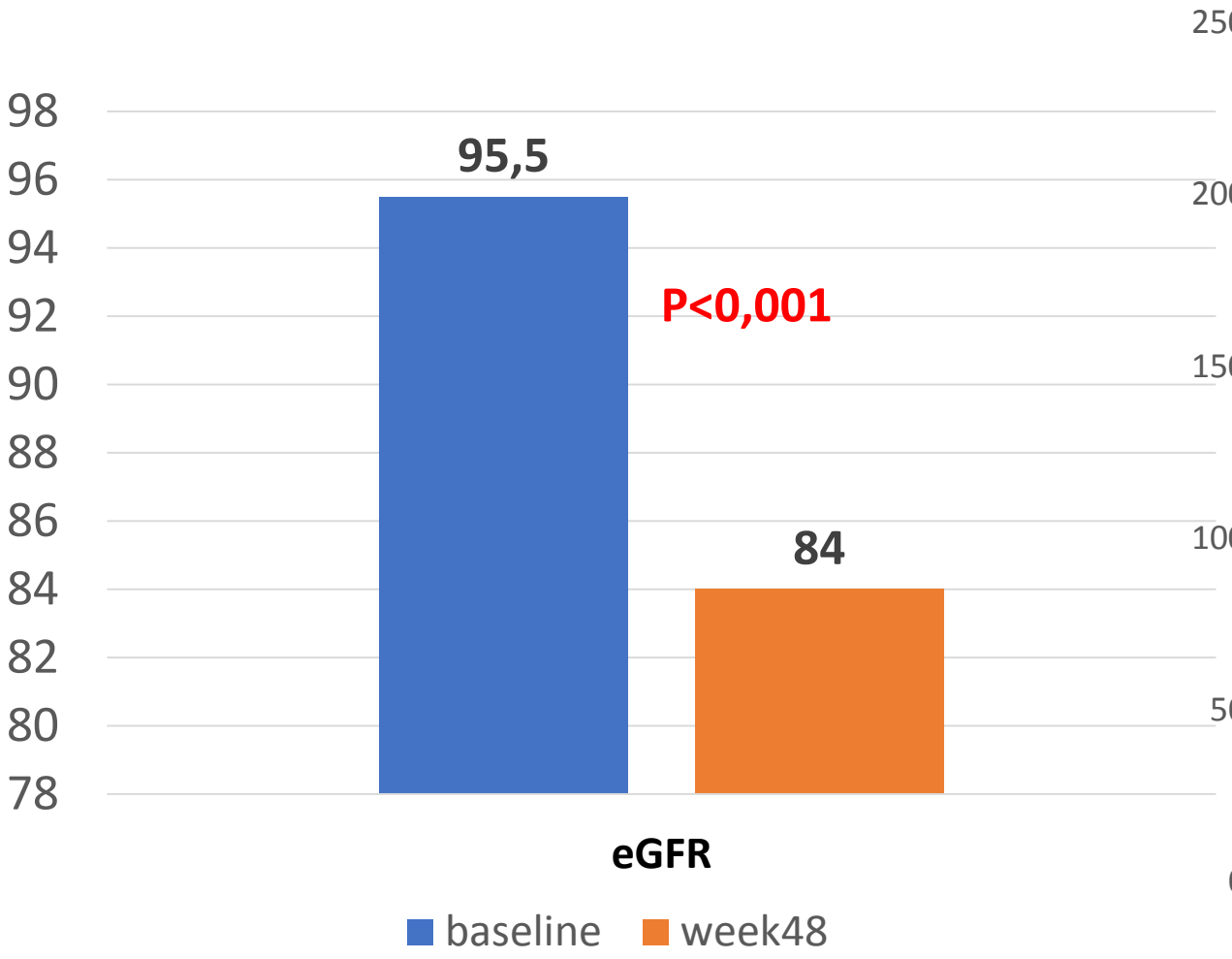
	aHR (95% CI)	p
HBsAg-pos	24.19 (3.45-169.87)	0.001
time since HIV diagnosis (per 1 year more)	1.11 (1.02-1.20)	0.013
belonging to one particular clinical center	10.49 (1.65-66.83)	0.013

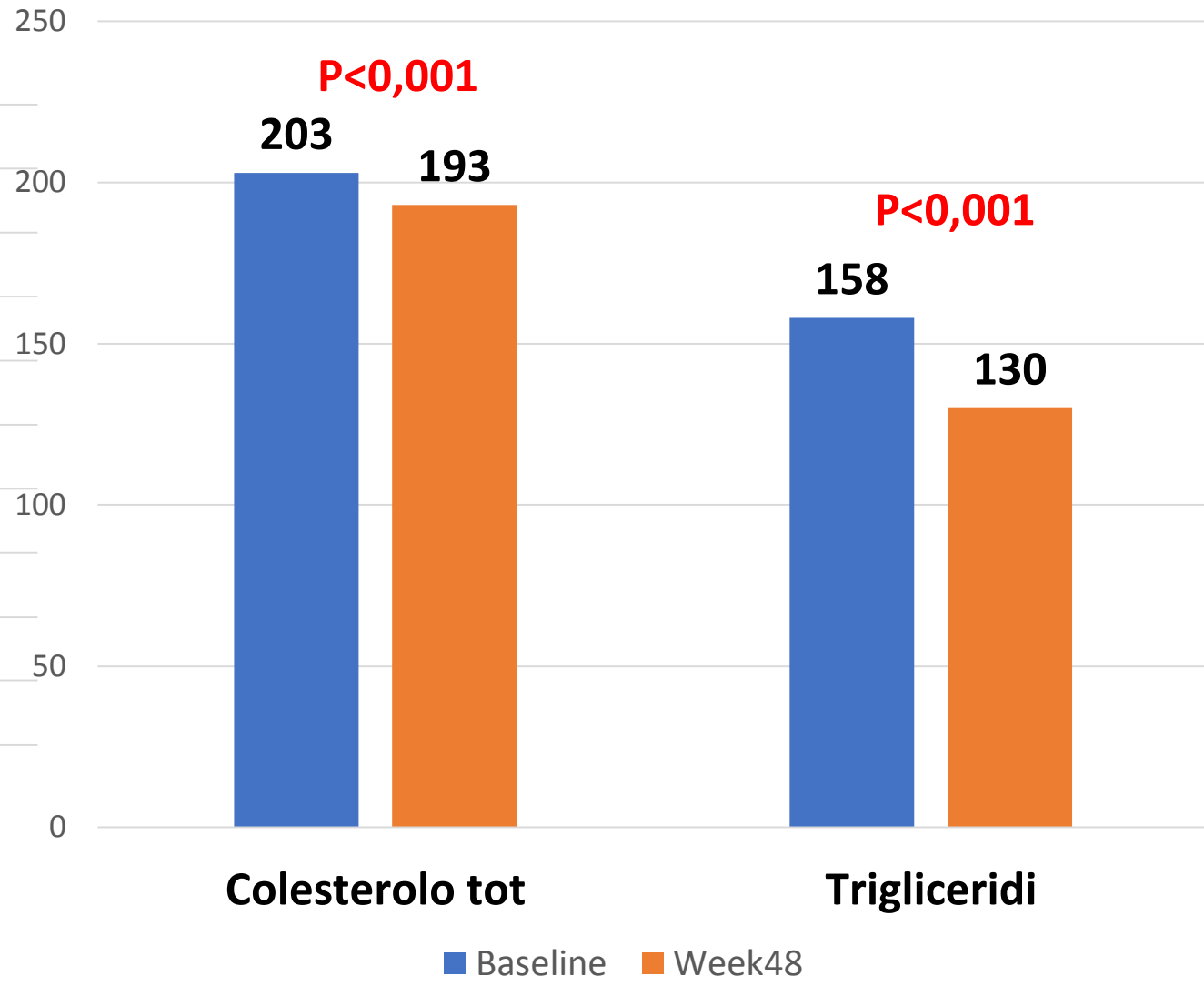
- **Reasons for TD were represented by:**

- virological failure (4 of 206, 1.9%),
- hypersensitivity reaction (2 cases, 1.0%),
- gastrointestinal toxicity (4 cases, 1.9%),
- neuropsychological events (7 cases, 3.4%: 2 cases of insomnia, 1 case of nightmares, 1 of hallucinations, 1 mood disturbances and 1 case with both depressed mood and headache),
- further simplification to a single tablet regimen (3 cases, 1.5%),
- drug-drug interactions (1 case, 0.5%)
- other causes (6 cases, 2.9%: 2 cases of death, 1 pregnancy, 3 unspecified reasons).



Mean Changes: baseline to Week 48 for creatinine and lipids





Conclusions

- Lamivudine plus dolutegravir **was effective in mantaining viral suppression** in a large percentage of a multicenter cohort of highly experienced, HIV-positive patients with undetectable HIV-RNA at the time of switch.
- Our analysis on metabolic outcome at 48 weeks confirmed **the improvement in the blood lipid profile** after switching to lamivudine plus dolutegravir.
- As expected, an apparent decline in renal function was observed after switching to this dual regimen, consistent with the inhibition of the renal protein organic cation transporter 2 (OCT2) by dolutegravir, but **no TD occurred due to impaired renal function.**

A comparison between two dolutegravir-based 2-drug regimens as switch strategies in a multicenter cohort of HIV-1 infected patients.

Background

- The association of dolutegravir (DTG) with low-toxicity transcriptase inhibitors in a less-drug regimen appears promising in terms of efficacy and tolerability.
- While randomized controlled trials comparing DTG plus RPV with standard triple therapy showed the non-inferiority of the 2-drug regimen and ongoing trials are exploring the efficacy of DTG plus lamivudine as first-line and maintenance therapy, little is still known about the efficacy and tolerability of DTG-based 2-drug regimens in clinical practice.
- In our multicenter cohort, we tried to investigate and compare the efficacy and safety of DTG plus 3TC versus DTG plus RPV.

Methods

- A cohort of HIV-positive patients with viral suppression (HIV-RNA <50 cp/ml) switching to 3TC+DTG (3TC group) or RPV+DTG (RPV group) from seven Italian centers was evaluated.

- Main outcomes were time to virological failure (VF) and time to treatment discontinuation (TD).

- 416 patients were analyzed, 229 in the 3TC group and 187 in the RPV group.

Patients' characteristics at baseline 1

Variables	Overall n=416 (%)	3TC-DTG n=229 (%)	RPV-DTG n=187 (%)	P
Males [n (%)]	298 (71.6)	172 (75.1)	126 (67.4)	0.101
Age (years) [median (IQR)]	52.3 (45.9 – 57.1)	51.0 (43.7 – 57.0))	52.9 (48.0 – 57.6)	0.121
Risk factor [n (%)]				**<0.001***
MSM	155 (37.3)	90 (39.3)	65 (34.8)	
Heterosexual	149 (35.8)	81 (35.4)	68 (36.4)	
IDU	72 (17.3)	24 (10.5)	48 (25.7)	
Others	40 (9.6)	34 (14.8)	6 (3.2)	
HCV Ab positive [n (%)]	86 (20.8)	35 (15.4)	51 (27.4)	**0.003***
HBsAg positive [n (%)]	5 (1.2)	3 (1.3)	2 (1.1)	1.000
Time from HIV diagnosis (years) [median (IQR)]	16.4 (9.1 – 22.3)	14.9 (8.2 – 20.1)	19.0 (10.6 – 27.7)	**<0.001***
CDC stage C [n (%)]	120 (28.8)	59 (25.8)	61 (32.6)	0.129
Zenith HIV-RNA (log10 copies/ml) [median (IQR)]	4.99 (4.57 – 5.39)	4.97 (4.42 – 5.42)	5.00 (4.75 – 5.32)	0.148
Peak HIV-RNA > 500.000 copies/ml [n (%)]	55 (13.9)	28 (13.0)	27 (15.0)	0.559
Nadir CD4+ (cell/mm3) [median (IQR)]	194.0 (73.0 – 286.0)	200.0 (61.0 – 286.0)	189.0 (98.0 – 286.7)	0.987
Years on cART [median (IQR)]	14.0 (6.9 – 18.1)	11.6 (5.5 – 17.4)	16.5 (8.9 – 19.3)	**<0.001***
Previous virological failure [n (%)]	184 (44.3)	88 (38.6)	96 (51.3)	**0.010***
Time on virological suppression, (months) [median (IQR)]	80.4 (38.6 – 110.0)	77.8 (36.0 – 102.7)	85.1 (43.5 – 122.6)	**0.018***
CD4+ at baseline (cell/mm3) [median (IQR)]	670.0 (500.0 – 899.0)	653.0 (500.0 – 862.0)	693.5 (517.0 – 992.0)	0.106

Patients' characteristics at baseline 2

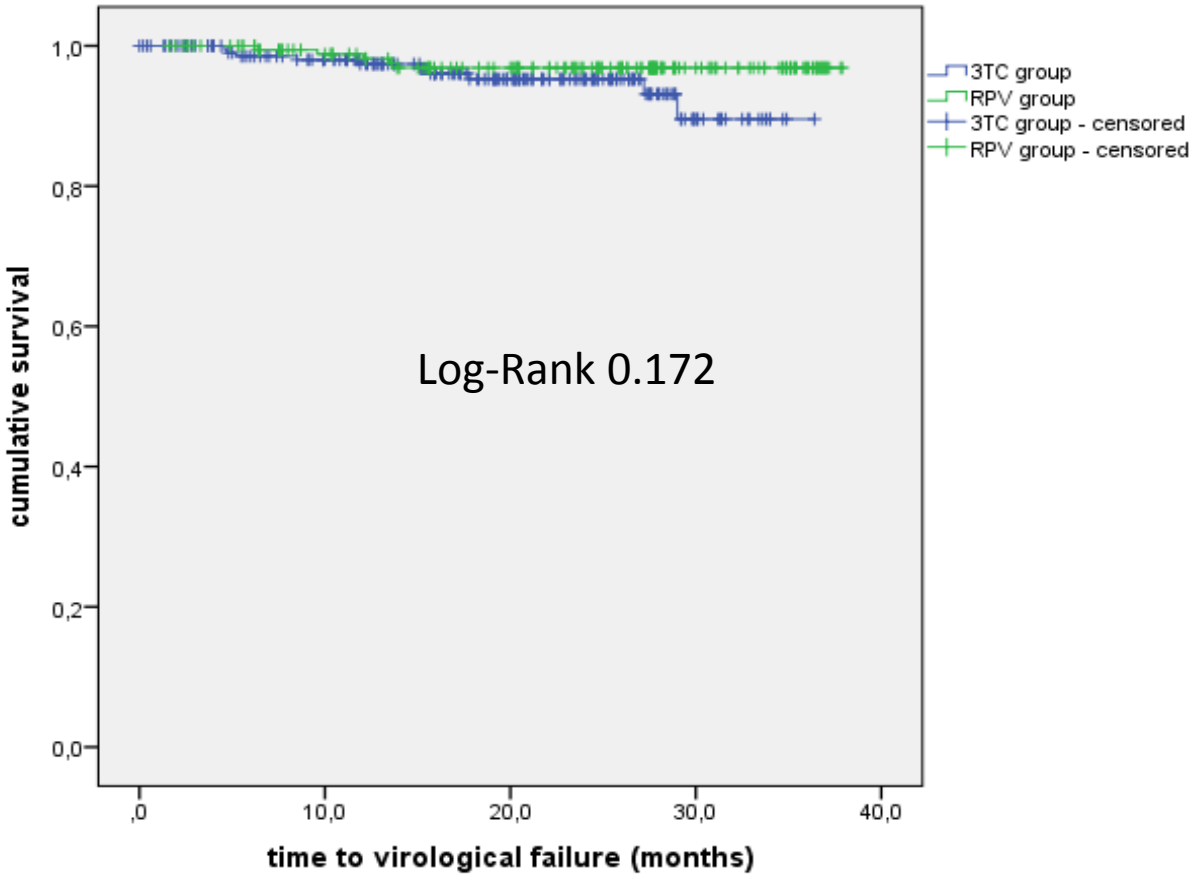
Variables	Overall n=416 (%)	3TC-DTG n=229 (%)	RPV-DTG n=187 (%)	P
Previous ART regimen: 2NRTIs + bPI 2NRTIs + NNRTI 2NRTIs + INI Dual regimen Other	 60 (14.4) 102 (24.5) 56 (13.5) 182 (43.8) 16 (3.8)	 25 (10.9) 57 (24.9) 38 (16.6) 106 (46.3) 3 (1.3)	 35 (18.7) 45 (24.1) 18 (9.6) 76 (40.6) 13 (7.0)	**0.002***
Discontinuation of previous regimen for dyslipidemia [n (%)]	108 (26.0)	73 (31.9)	35 (18.7)	**0.002***
Discontinuation of previous regimen for toxicities [n (%)]	103 (24.8)	67 (29.3)	36 (19.3)	**0.022***
Discontinuation of previous regimen for simplification [n (%)]	167 (40.1)	77 (33.6)	90 (48.1)	**0.003***
Discontinuation of previous regimen for drug-drug interaction [n (%)]	27 (6.6)	8 (3.5)	19 (10.2)	**0.008***

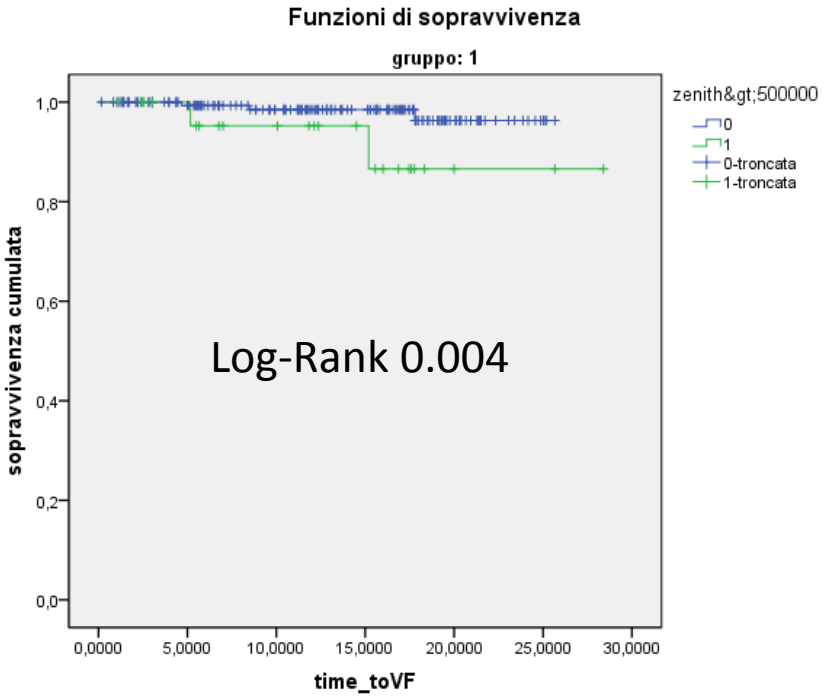
Virological failure

Time to VF was not statistically different between groups

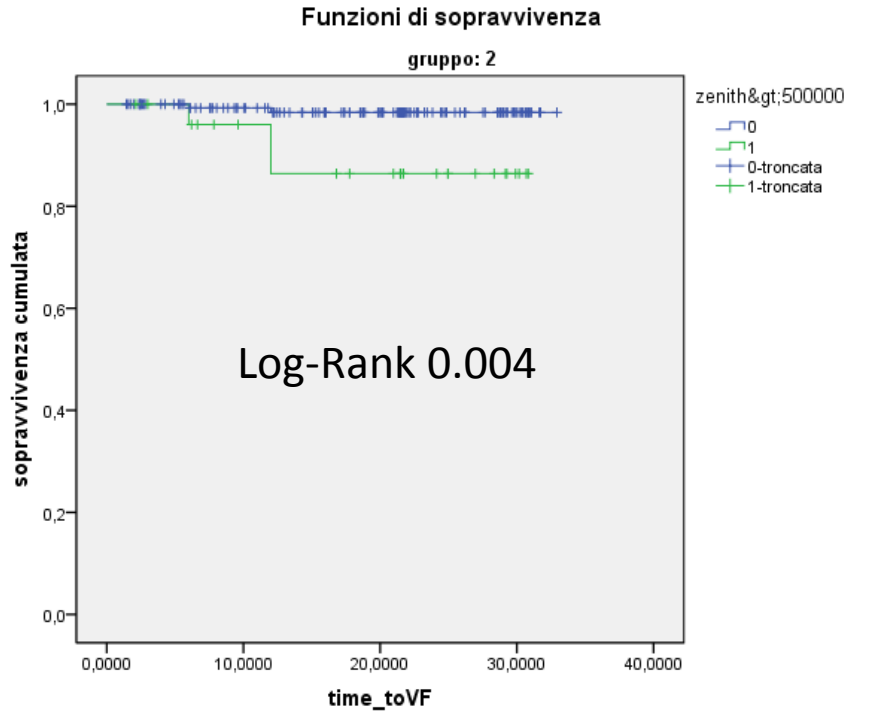
The estimated probability of remaining free from VF at week 48 was 97,4% with DTG+3TC and 98,2% with DTG+RPV.
In the 3TC group we registered an overall incidence of 2,9 VF per 100 PYFU, while the incidence in the RPV group was 1,3 VF per 100 PYFU.

Time to VF was only predicted by peak HIV-RNA (per 1 log unit higher, aHR 3.10, 95% Confidence Interval [CI] 1.12-8.55, p=0.029).





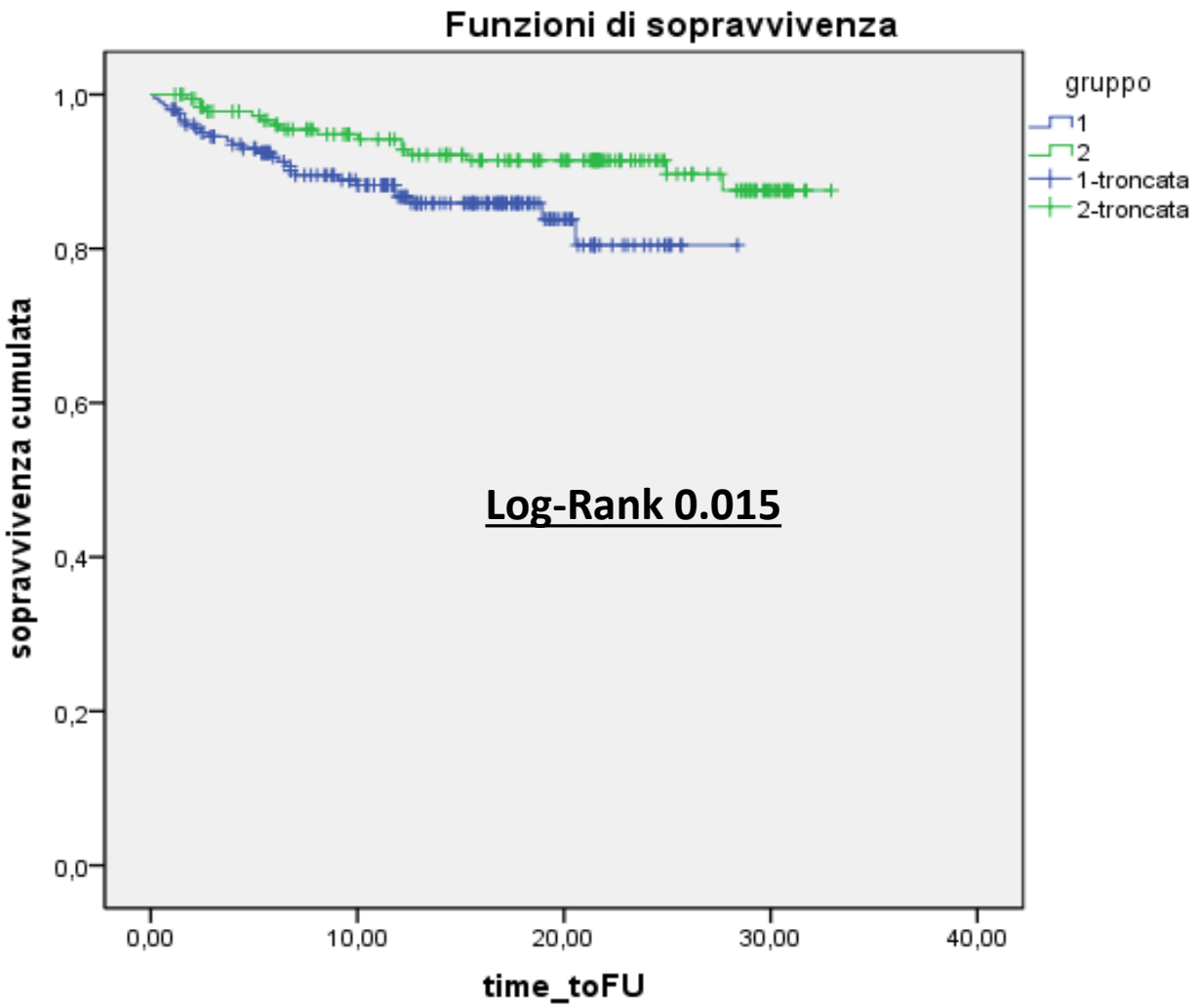
3TC+DTG



RPV+DTG

An increased rate of VF was found in patients with a peak HIV-1 RNA ≥ 500,000 copies/mL (7.3 VF per 100 PYFU). In the 3TC group, the estimated probabilities of remaining free from VF were 98.1% at week 48 and 96.3% at week 96 in the group with peak HIV-1 RNA≤ 500,000 copies/mL versus 95.2% at week 48 and 86.6% at week 96 in the group with higher peak viral load (log-rank p=0.004). Similarly, in the RPV group, the probabilities of remaining free from VF at weeks 48 and 96 were 99.2% and 98.4%, respectively, in the group with a lower peak viral load while in patients with peak HIV-RNA above 500,000 copies/ml the probabilities were 91.8% at week 48 and 87.5% at week 96 (log-rank 0.004).

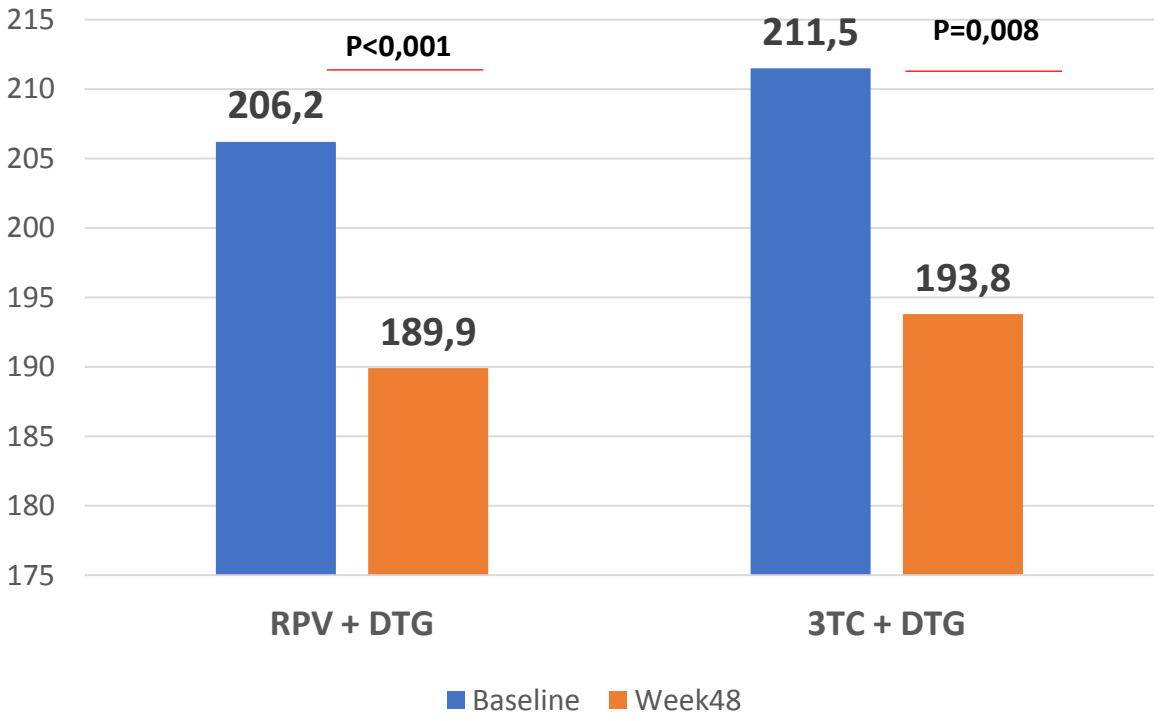
Treatment discontinuation



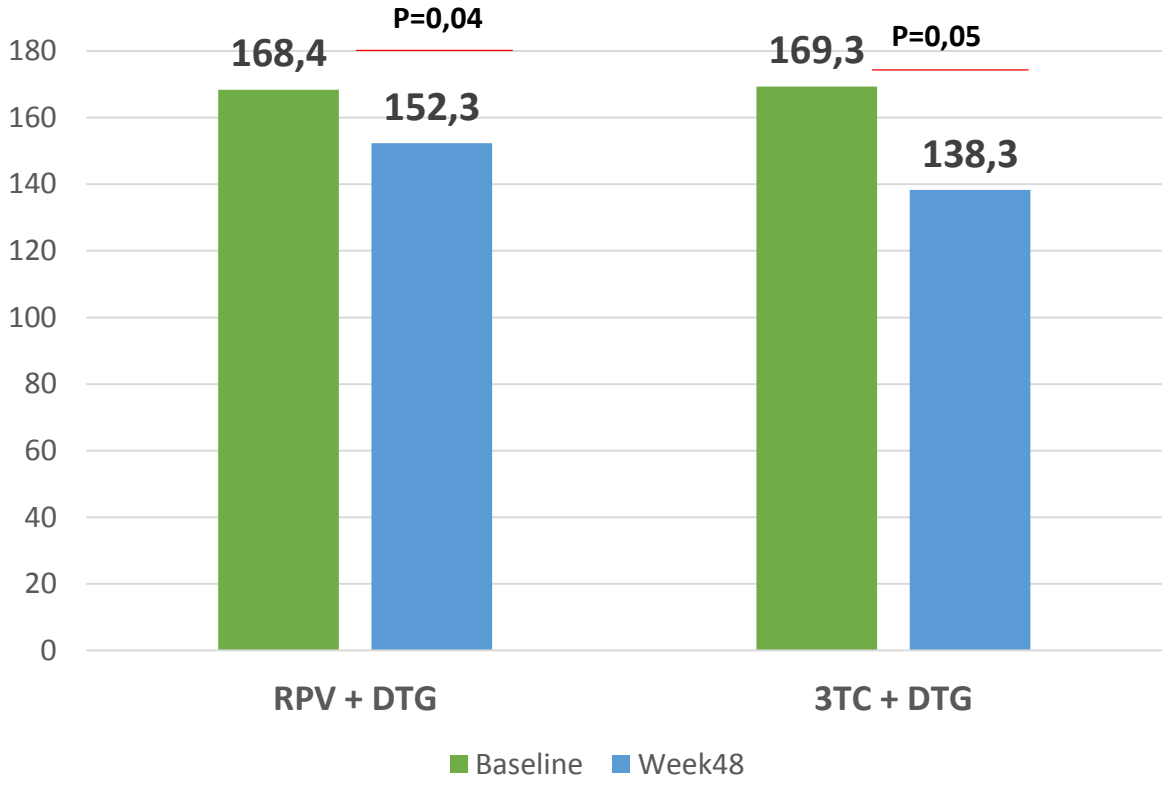
The estimated probability of remaining in the study regimen at week 48 was 89% with DTG+3TC and 96,1% with DTG+RPV

In a multivariate analysis, HBsAg-positive serostatus (versus negative, aHR: 20.82, 95%CI 3.83-113.10; p<0.001) independently predicted TD, after adjusting for significantly different parameters at baseline, treatment group and clinical center. Of note, of the 2 HBsAg-positive patients who interrupted study regimen, one discontinued for further simplification and one for his own choice; also, no liver enzyme elevation occurred during the study period.

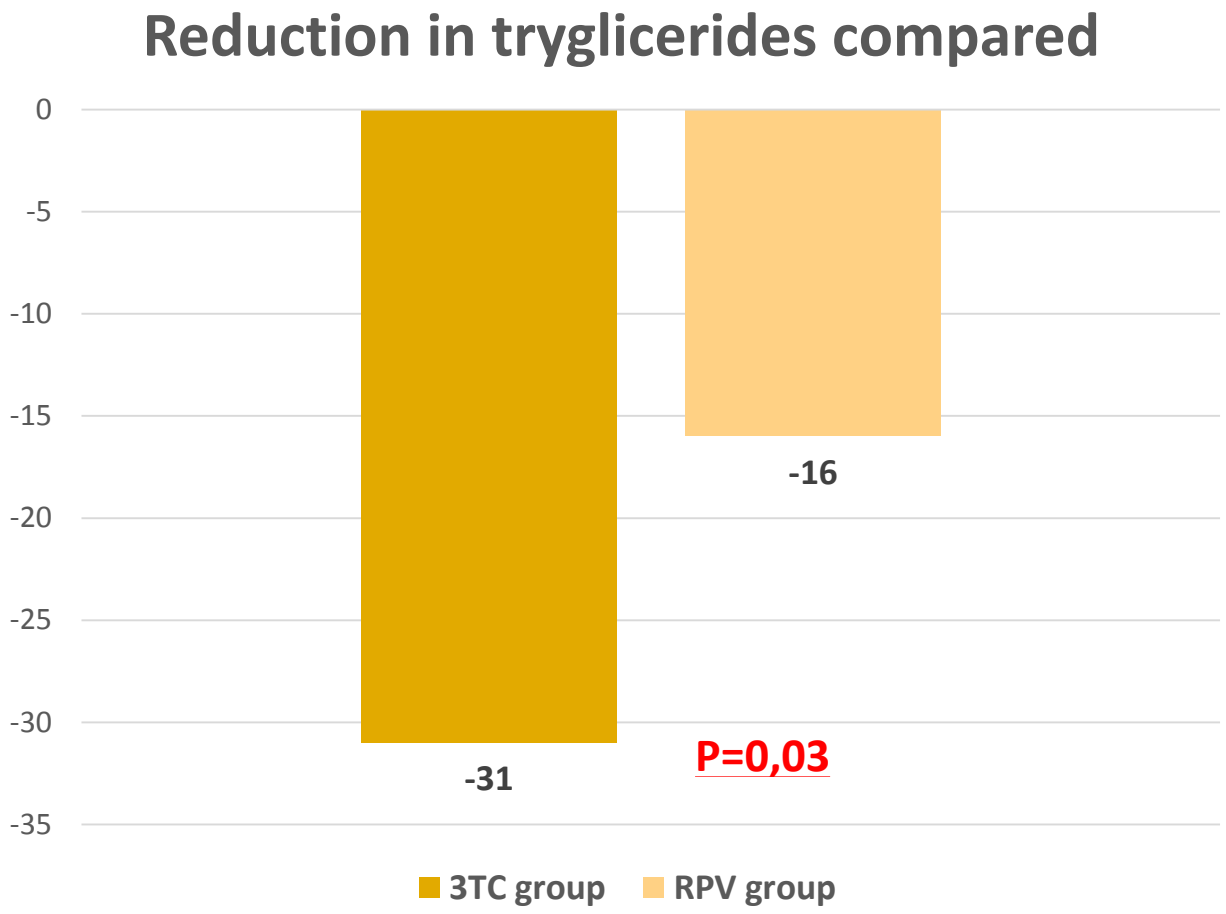
Median total cholesterol



Median triglycerides



Both dual regimens showed a marked improvement in lipid profile. A greater reduction in total cholesterol was independently predicted by higher baseline cholesterol values (per 1 mg/dl more, mean difference in change -0.53 mg/dL, 95%CI -0.67 to -0.39, p<0.001) while an increase in TC was evidenced in patients switching from FTC/TDF (versus other backbones, +53.5 mg/dL, 95%CI 8.14 to 98.88, p=0.020) after adjusting for pre-switch regimen and nadir CD4+ count.



The decrease of TG levels was significantly more pronounced in the 3TC group. A greater reduction in tryglicerides levels was only predicted by baseline triglycerides values (per 1 mg/dl more, -0.52 mg/dL, 95%CI -0.61 to -0.43, p<0.001) after adjusting for baseline TC values, pre-switch regimen and reasons for switching to study regimen.

CONCLUSIONS

- In our observational cohort, we found a similar virologic efficacy of the two strategies. Among patients experiencing VF, only one patient in the RPV group, with a history of non-adherence to ART, developed Y181C and E138Q resistance mutations after failure. Interestingly, patients with HIV-1 RNA peak ≥500,000 copies/mL showed a trend for an increased risk of VF

- Our secondary analysis on metabolic outcome at 48 weeks confirmed the improvement in the blood lipid profile in patients switching to 3TC+DTG while also showing a reduction in TC in the RPV group, that was not previously evidenced.

- Regarding renal function, neither group showed significant changes in estimated Glomerular Filtration Rate (eGFR) values at week 48 (-4.30 ml/min, 95%CI -17.80 to 9.20, p=0.476 in the 3TC group and -3.49, 95%CI -7.53 to 0.54, p=0.089 in the RPV group).

Special thanks to…

- **Institute of Clinical Infectious Diseases, UCSC, Rome:**
  - ✓ A. Borghetti, G. Baldin , D. Moschese, A. Emiliozzi, R. Gagliardini, F. Lombardi, S. Belmonti, A. Ciccullo, S. Lamonica

- **GRUPPO ODOACRE**
  - ✓ G. Madeddu, K. Sterrantino, S. Rusconi, A. Giacometti, A. Latini, G. D'Ettorre, C.M Mastroianni, J. Vecchiet, R. Gulminetti and AMEDEO CAPETTI