Non-inferiority of dual-therapy with darunavir/ritonavir plus 3TC vs. triple therapy with darunavir/ritonavir plus TDF/FTC or ABC/3TC for maintenance of viral suppression: 48-week results of the DUAL-GESIDA 8014-RIS-EST45 Trial

***DUAL*: "DarUnavir And Lamivudine"**

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DUAL-GESIDA-8014-RIS-EST45 Study Group

HIV Drug Therapy GLASGOW 2016

Abstract #: **O331**

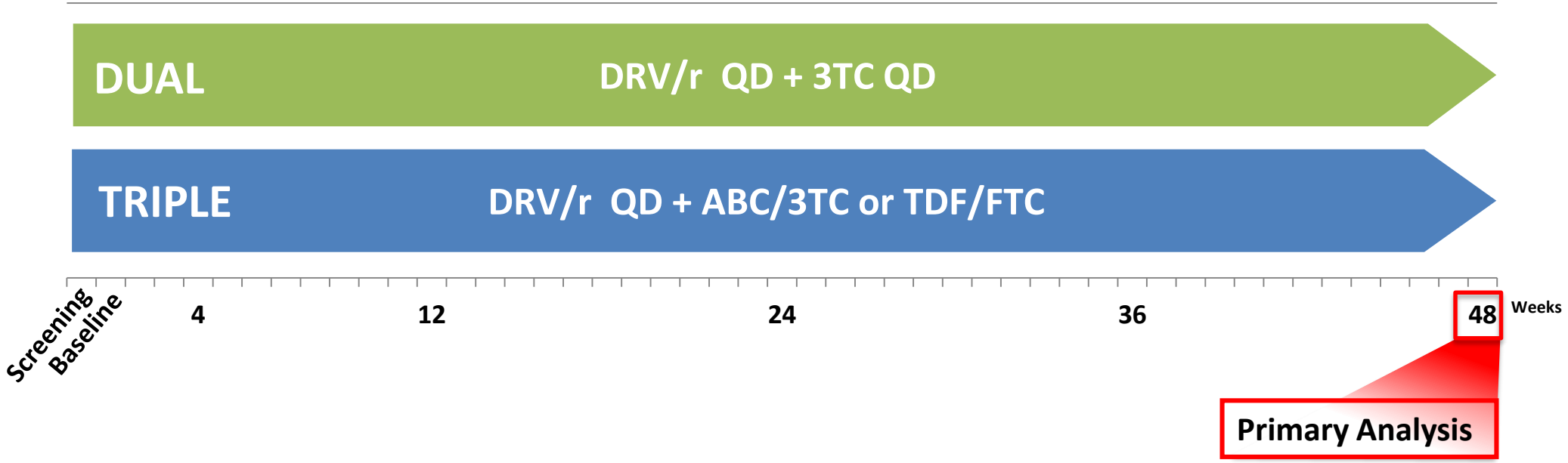
Introduction

- Dual therapy with a boosted protease inhibitor and Lamivudine can have advantages in terms of toxicity and costs
- OLE[1], SALT[2] and ATLAS-M[3] have demonstrated that dual therapy with Lamivudine and Lopinavir/r or Atazanavir/r is non inferior to triple therapy with 2 nucleos(t)ides and Lopinavir/r or Atazanavir/r for maintenance of virological suppression
- Boosted Darunavir is the preferred protease inhibitor in most international guidelines of HIV therapy.
- Currently there are no data about the efficacy/safety of the dual combination of Lamivudine and boosted Darunavir

1.- The Lancet Infectious Diseases 2015. 15:785–792.
2.- Journal of Antimicrobial Chemotherapy 2016. :dkw379.
3.- 5th European AIDS Conference. Barcelona, October 21-24,2015. Abstract BPD1/6.

DUAL Study Design

- VL < 50 c/mL > 6 months
- No resistance to DRV/r o 3TC
- On treatment with DRV/r + ABC/3TC or TDF/FTC ≥ 2 months
- HBsAg negative
- Randomized 1:1. Stratified by baseline nucleos(t)ides



DUAL Study Design

HYPOTHESIS

Dual therapy with DRV/r + 3TC could be non-inferior to triple therapy with DRV/r + 2 N(t)RTI for maintenance of virological suppression in HIV infected patients with undetectable viral load for at least 6 months while receiving triple therapy.

PRIMARY ENDPOINT

Proportion of patients with suppressed viral load (HIV-RNA < 50 copies/mL) after 48 weeks of follow-up according to the FDA snapshot algorithm in the ITT exposed population.

DUAL Study Design

SECONDARY ENDPOINTS

- Proportion of patients with suppressed viral load (HIV-RNA < 50 copies/mL) after 48 weeks of follow-up according to the FDA snapshot algorithm in the **ITT, Per Protocol, and Observed Therapy** populations
- Proportion of patients with **virologic failure** according to the FDA snapshot algorithm
- Proportion of patients with **single, double and triple blips**
- **CD4** changes
- **Safety**: adverse events, lipids, renal
- **Resistance**

Sample size

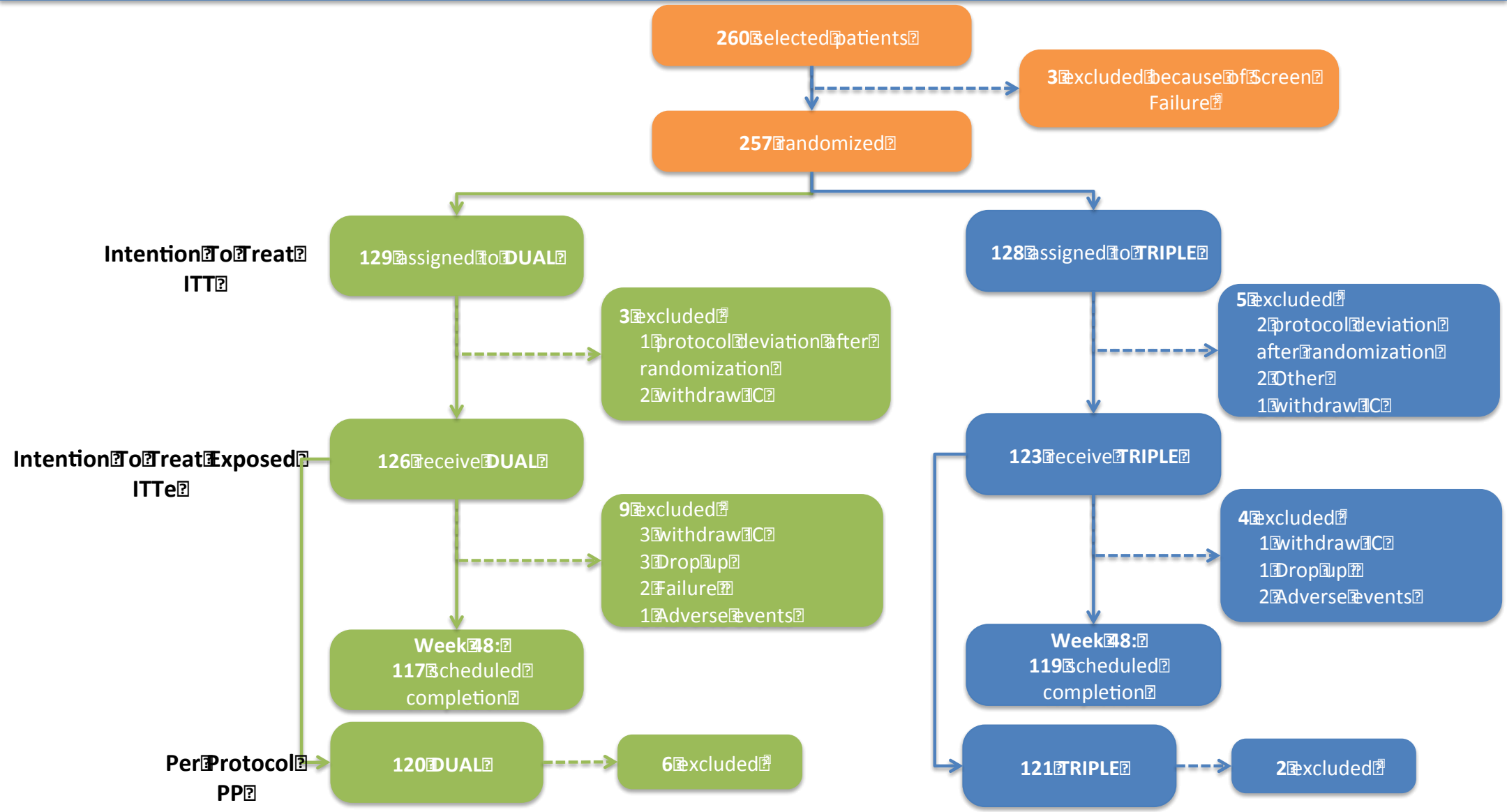
Assuming:

- Response rate at week 48: 88% (MONET study[1], triple therapy arm)
- Non inferiority margin: 12%
- Study power: 80%
- Significance: unilateral 2.5% (α = 5%)
- Losses to follow-up: 10%

128 patients per arm would be needed

1.- AIDS 2010. 24:223–230.

Trial profile



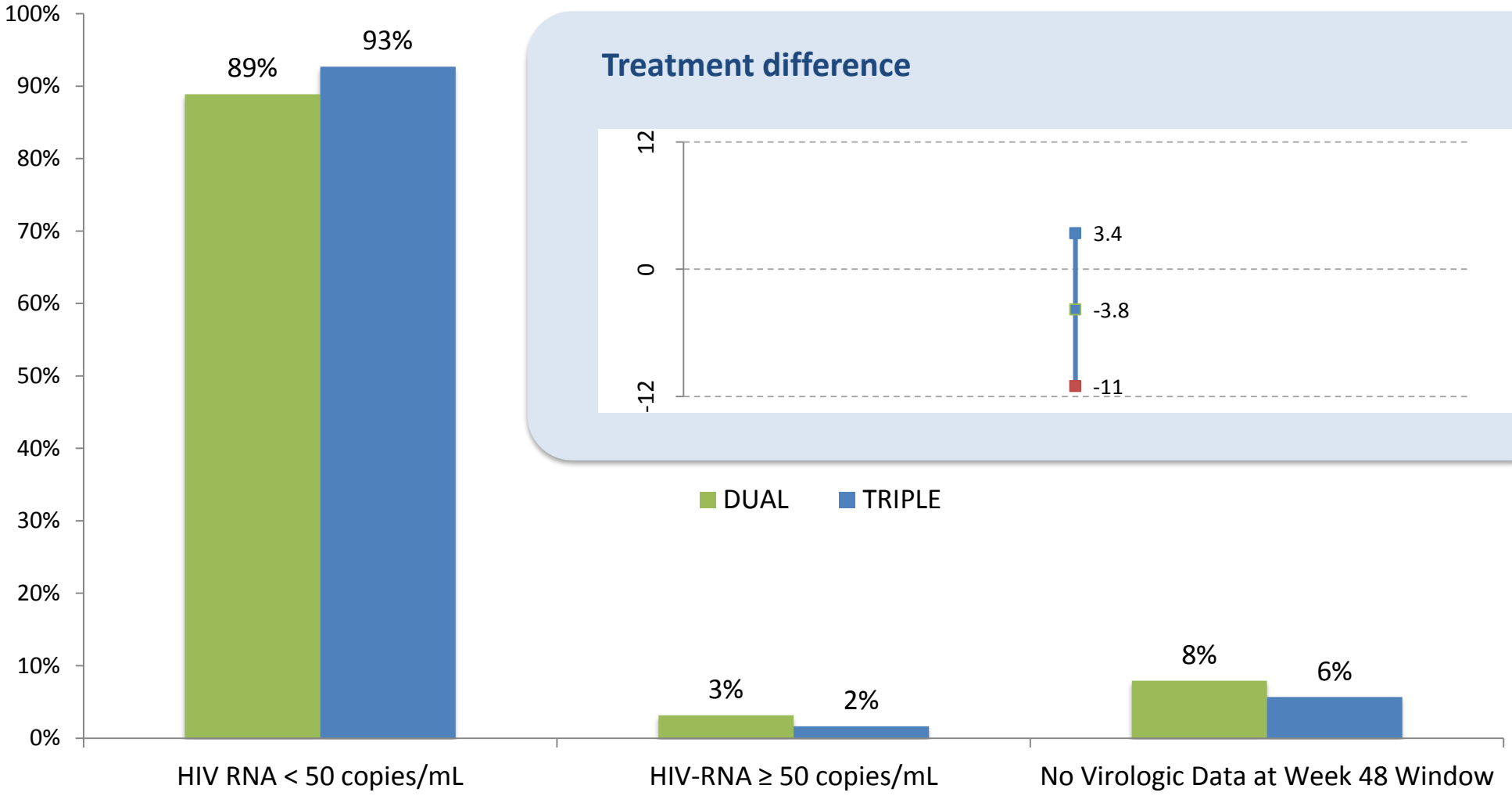
ITT: all randomized patietns, ITTe: received study intervention, PP: excluding protocol violations

Baseline Characteristics

	DUAL	TRIPLE	TOTAL
	n (%)	n (%)	n (%)
MALE	107 (85)	100 (81)	207 (83)
Age (years, median, range)	44 (36-52)	43 (37-49)	43 (36-50)
Ethnic Group			
Caucasian	106 (84)	106 (86)	212 (85)
Other	20 (16)	17 (14)	36 (15)
Hepatitis C	32 (25.4)	28 (22.8)	60 (24.1)
Mode of transmission (n, %)			
Heterosexual	34 (27.0)	32 (26.0)	34 (27.0)
Men who have sex with men	65 (51.6)	72 (58.5)	65 (51.6)
Drug user	19 (15.1)	15 (12.2)	19 (15.1)
Weeks with suppressed viremia (median, range)	79.5 (38-157)	113 (57-184)*	100 (45-166)
CD4 (median, range)			
Nadir	253 (127-367)	240 (117-328)	246 (120-327)
Current	596 (433-810)	568 (451-739)	589 (443-762)
Nucleos(t)ides at baseline (n, %)			
Tenofovir/emtricitabine	93 (76)	93 (74)	186 (75)
Abacavir/lamivudine	30 (24)	33 (26)	63 (25)

*p= 0.014

Primary Endpoint: Snapshot, ITT-e population

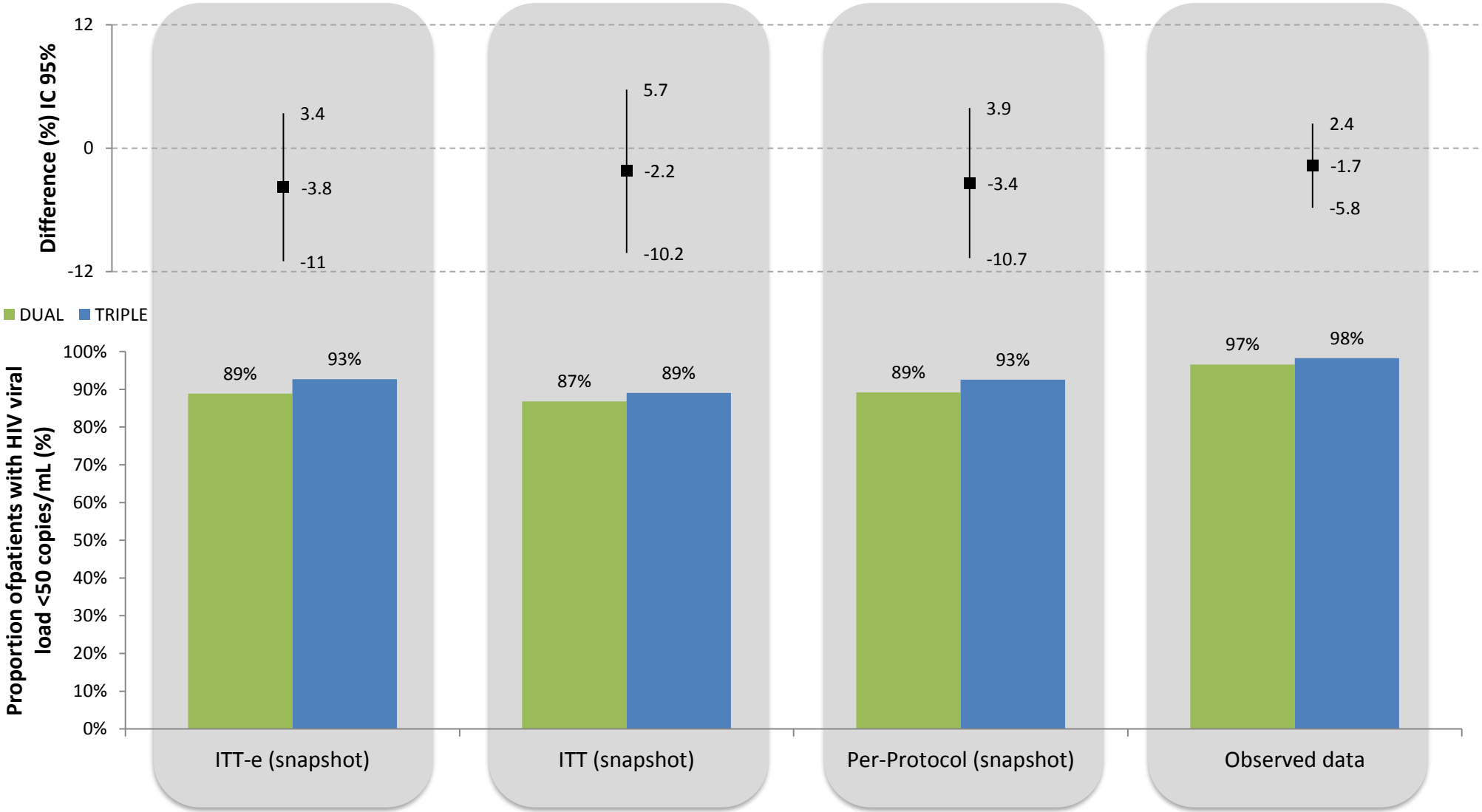


Primary Endpoint: Snapshot, ITT-e population

	DUAL (n=126)		TRIPLE (n=123)	
HIV RNA < 50 copies/mL	**112**	**89%**	**114**	**93%**
HIV-RNA ≥ 50 copies/mL	**4**	**3%**	**2**	**2%**
HIV-RNA ≥ 50 copies/mL in week 48 window	2	2%	2	2%
Discontinued Study Drug Due to Lack of Efficacy	2	2%	0	0%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥50 c/mL	0	0%	0	0%
No virologic data week 48	**10**	**8%**	**7**	**6%**
Discontinued Study Drug Due to AE/Death	1	1%	2	2%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 c/mL*	6	5%	2	2%
Missing Data During Window but on Study Drug	3	2%	3	2%

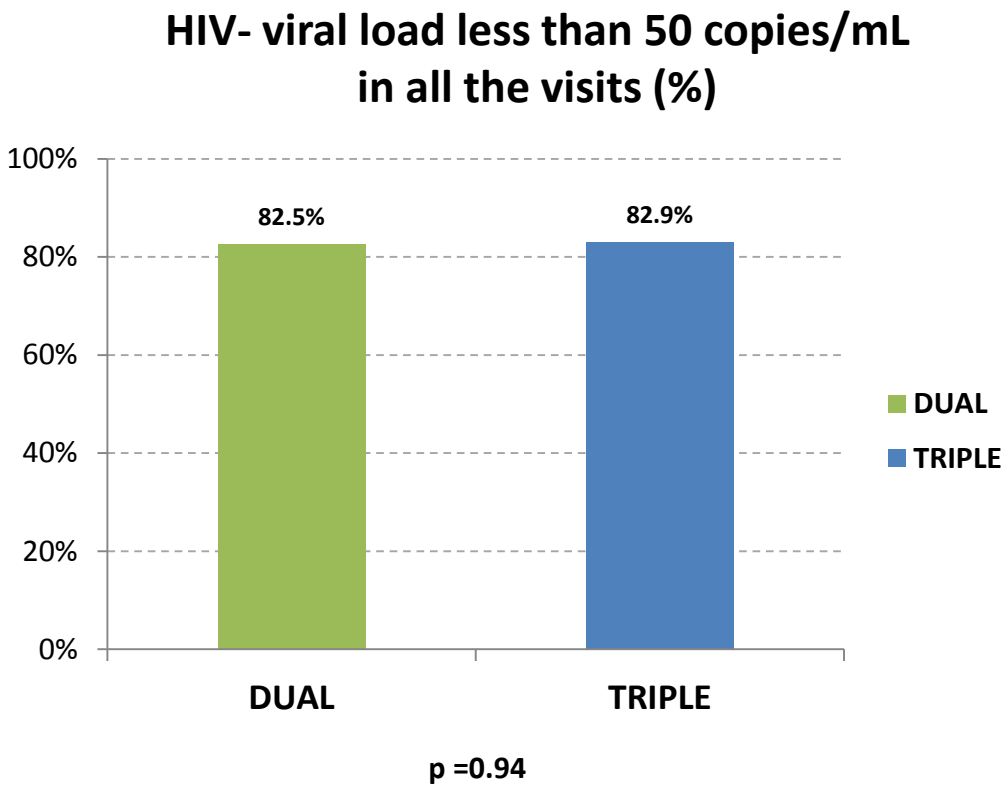
* Dual: Consent withdrawal (3), lost to follow up (3). Triple: Consent withdrawal (1). Lost to follow up (1)

Sensitivity analysis

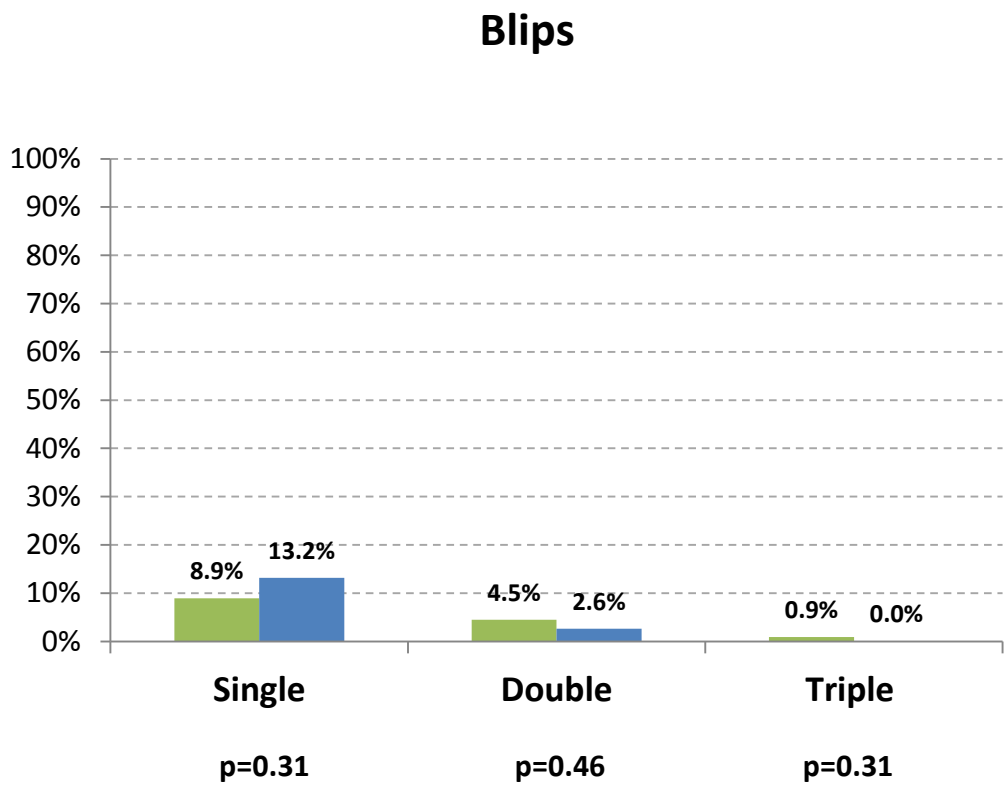


Observed data: excluding non-virological reasons for failure.

Continuous viral load suppression

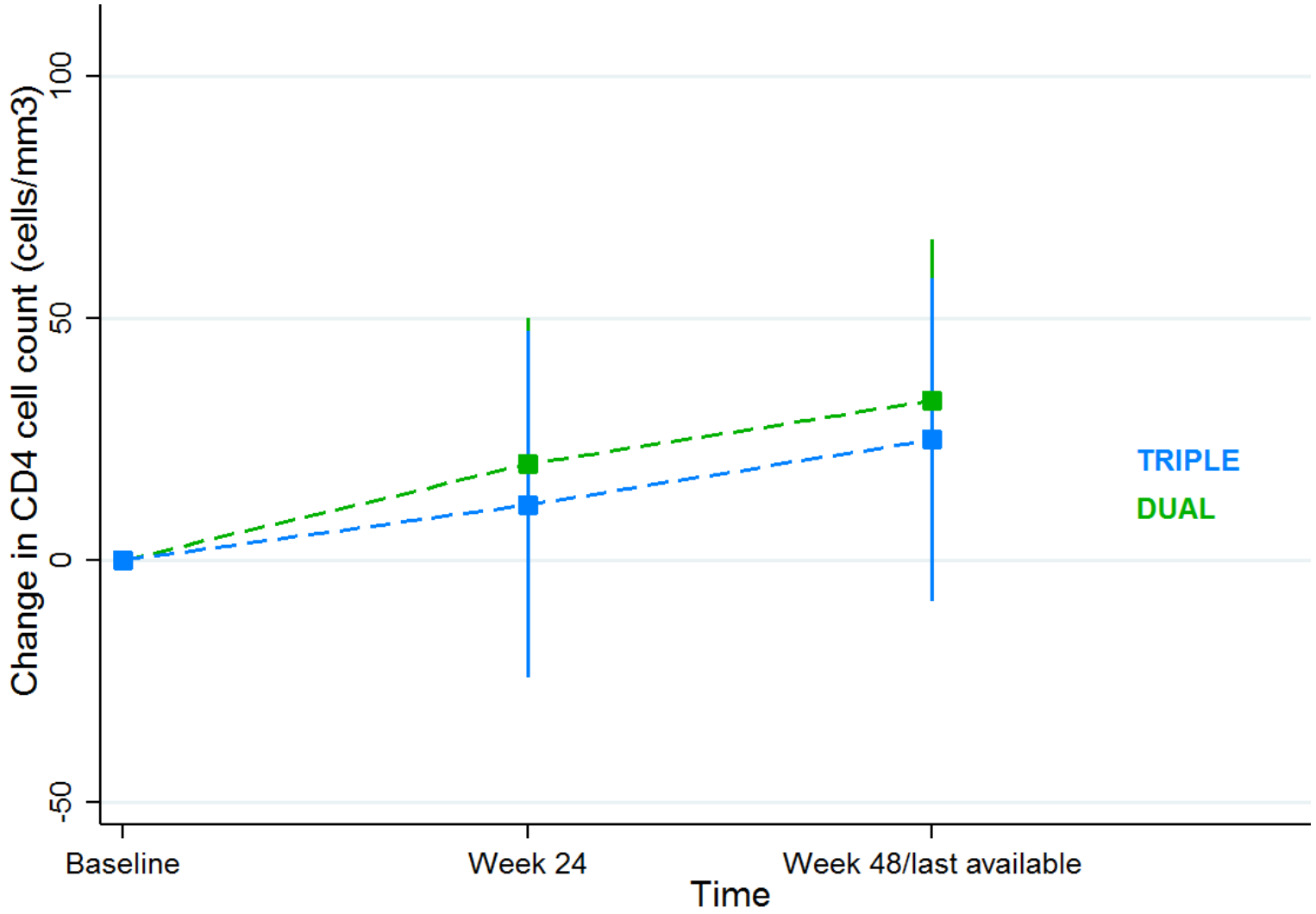


Including all patients who completed 48 weeks of treatment and had viral loads measurements in all visits.



Only patients who had HIV-RNA < 50 copies at week 48.
Blip defined as a transitory viral load ≥ 50 copies/mL

CD4 Changes


Change in CD4 cell count (cells/mm3)
100
50
0
-50
Baseline
Week 24
Week 48/last available
Time
TRIPLE
DUAL

Resistance testing
(attempted in all rebounds with viral loads > 400 HIV-RNA copies/mL)

GROUP	Week	HIV-RNA ≥ 50 c/mL week 48 (SNAPSHOT)	1st viral load	2nd viral load	Genotype	Mutations
DUAL	Baseline	Yes	80	800	Yes	None
DUAL	24	Yes	988	259	Failed	
DUAL	32	No	6,805	165	Yes	None
TRIPLE	24	No	427	<20	Failed	
TRIPLE	24	No	447,557	5,621	Yes	V10I, W71T, D76W

Adverse events

	DUAL		TRIPLE		
	Patients (%)	Events	Patients (%)	Events	p
Any Adverse Event	88 (69.8%)	197	93 (75.6%)	207	0.31
Grade 2 or 4 Adverse Event	15 (11.9%)	17	18 (14.6%)	30	0.52
Serious Adverse Event	6 (4.8%)	6	6 (4.9%)	7	0.97
Discontinuation due to AE or intolerance	1 (0.8%)	1	2 (1.6%)	2	0.55
Adverse events ocurring at in at last 5% of patients in either group					
Respiratory	31 (24.6%)	42	29 (23.6%)	36	0.85
Infections and infestations	22 (17.5%)	26	18 (14.6%)	23	0.54
Digestive	18 (14.3%)	22	22 (17.9%)	27	0.44
Muscular or skeletal	16 (12.7%)	17	22 (17.9%)	27	0.25
Neuropsychiatric	12 (9.5%)	15	12 (9.8%)	15	0.95
Metabolic	13 (10.3%)	15	8 (6.5%)	9	0.28
Genitourinary	8 (6.3%)	9	6 (4.9%)	6	0.61
General disorders and administration..	7 (5.6%)	8	7 (5.7%)	8	0.96
Ear, Nose, Throat	7 (5.6%)	7	8 (6.5%)	8	0.75
Nervous system disorders	6 (4.8%)	6	7 (5.7%)	9	0.74
Tooth and mouth	3 (2.4%)	5	7 (5.7%)	7	0.18
Grade 3 or 4 laboratory adverse events					
Any grade 3 or 4 laboratory adverse event	4 (3.2%)	6	4 (3.3%)	4	0.97
AST	0 (0.0%)	0	1 (0.8%)	1	0.31
ALT	0 (0.0%)	0	0 (0.0%)	0	-
Triglycerides	0 (0.0%)	0	0 (0.0%)	0	-
Cholesterol	4 (3.2%)	6	3 (2.4%)	3	0.73

Conclusions

- **Dual therapy with Darunavir/ritonavir plus 3TC was non-inferior and as well tolerated as DRV/r plus TDF/FTC (or ABC/3TC) for maintenance of viral suppression**

- **Persistent virological suppression was mantained after switching to dual therapy with Darunavir/ritonavir plus 3TC**

- **These results reinforce the efficacy of dual therapy with a fully active boosted PI and 3TC for maintentance of virological suppression**

Aknowledgments

Patients

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