EACS 2013

- **Switch data Rilpivirine: Swing-trial**
- **Elvitegravir: Flamingo-trial**
- **Simplification**
  - **Dual-Therapy: LPV/r + 3TC in the Gardel-trial**
  - **Mono-Therapy: Darunavir/r mono in clinical setting**
- **Boceprevir/Telaprevir in difficult-to-treat patients**

Dominique Braun
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Rilpivirine

- Rilpivirine + 2 NRTIs demonstrated:
  - Efficacy (non inferiority to EFV + 2 NRTIs in naïve patients)
  - Favorable tolerability and safety profile
  - Potential as switch strategy in virologically suppressed patients

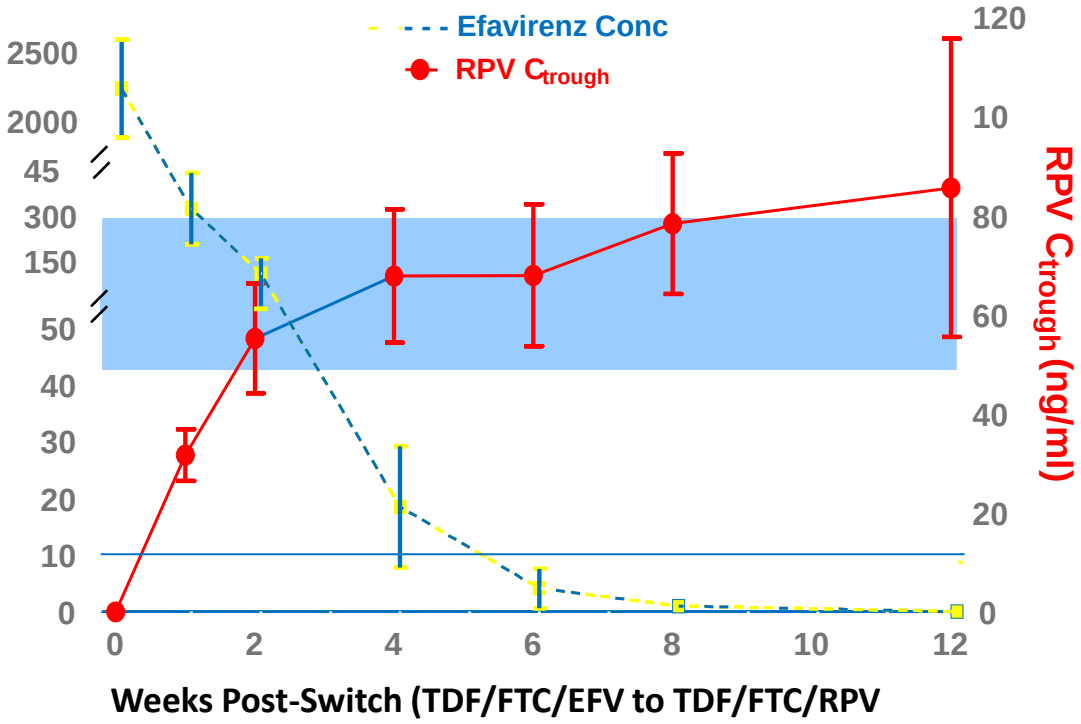
- TDF/FTC/RPV single tablet regimen :
  - Convenience of one pill once-a-day dosing
  - Taken with a meal (390 Kcal and 12 g fat)

- Some patients are willing to change their current regimen to a single tablet regimen for convenience reason

Efavirenz to Rilpivirine switch

- RPV shares an overlapping metabolic pathway with EFV and NVP (CYP3A4)
- Potential risk of virological breakthrough due to a suboptimal plasma concentration of RPV linked to the persistent inducer effect of EFV or NVP

TDF/FTC/EFV to TDF/FTC/RPV switch (n=49)



Mills A. ICAAC 2011, abs H2-794c; Crauwels H. CROI 2011, abs 630

Switching from TDF/FTC + Nevirapine to TDF/FTC/Rilpivirine STR in Virologically Suppressed, HIV-1 Infected Subjects: 24 Weeks outcome

SWING

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Switch Nevirapine/TDF/FTC → Rilpivirine: Swing-trial

N=32

On stable TDF/FTC + NVP for ≥ 6 months

HIV-1 RNA < 50 c/mL ≥ 6 months

No previous virologic failure on NNRTI

No genotypic resistance

(historical genotype or current DNA)

No comedication with PPI

Open label

TDF/FTC/RPV
1 tablet a day

D0 W1 W2 W4 **W12** W24

<u>Primary endpoint</u>

% of subjects with HIV-1 RNA < 50 c/mL at W12

Rilpivirine: safety and tolerability

Adverse events (AEs)		**4**
	Insomnia	1
	Grade 2 hepatic cytolysis	3
	Grade 3 or 4 AEs	0
Treatment discontinuation		**3**
	Patient's decision to resume TDF/FTC + NVP after W12 because of food constraint with TDF/FTC/RPV	2
	Insomnia related to RPV* (W1)	1

* resumption after switch back to TDF/FTC + NVP

Primary Endpoint

HIV-1 RNA < 50 copies/mL at Week 12

	W12	W24
On Treatment	**31 / 31** **100%**	28* / 29 **97%**
Intent To Treat, NC/D = F	**31 / 32** **97%**	28 / 32 **88%**

* Blip at 91 c/mL
(< 50 c/mL at W28)

1 discontinued for insomnia

2 resumed TDF/FTC+ NVP becuase of food constraints

Self-administered questionnaires : Food intake with TDF/FTC/RPV

Questionnaire at W1, W2, W4, W12		Kcal		Fat (g)		Meals with < 390 Kcal and/or < 12g Fat	
	N	**Mean**	SD	**Mean**	SD		
Breakfast	49 (42%)	**514**	203	**18**	11	18	(**37%**)
Lunch	17 (14%)	**1034**	238	**51**	15	0	(0%)
Dinner	52 (44%)	**879**	395	**41**	20	4	(8%)
Total	118	**750**	368	**33**	21	22	**(19%)**

No correlation between RPV C_{trough} (W2, W4, W12) and meals' composition

- kcal [r = -0.07 p = 0.51]
- fat [r = 0.05 p = 0.64]

W24 results : Conclusion

- Switching from TDF/FTC + NVP to TDF/FTC/RPV is a safe strategy.
  - 97% of patients maintain HIV-RNA < 50 c/mL at W24 (blip in one patient)
  - Only 1 AE leading to discontinuation (insomnia)

- NVP had only a short and limited inductive effect on RPV metabolism, which was not clinically significant.

- Meals composition was below the recommended food intake in 19% of the cases and occured most often at breakfast with no deleterious impact on treatment efficacy.

More Rilpivirine switch data

Immuno-virological and pharmacological follow-up of virologically-suppressed patients switching to RPV/TDF/FTC in a clinical cohort: week 24 interim analysis

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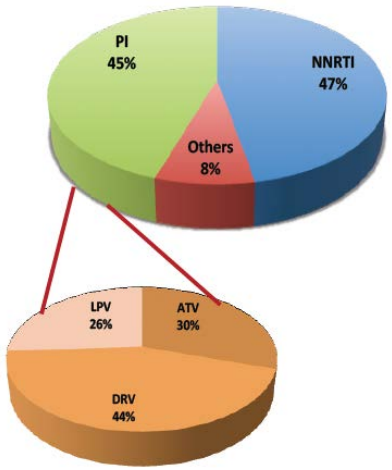
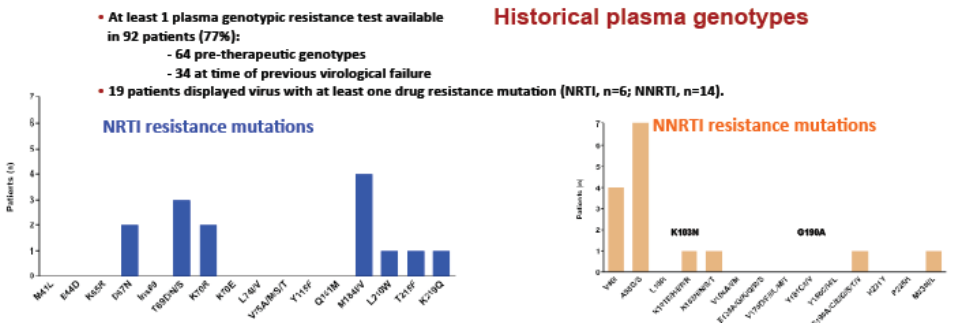
- **Objectives: to assess, in a clinical cohort, the efficacy of switching PIs- or NNRTIs-based regimens in virologically-suppressed patients to rilpivirine tenofovir/emtricitabine as a single-tablet -regimen (STR).**

- **Methods: A prospective observational single-center cohort study enrolling between September 2012 and February 2013 all patients with a viral load (VL)<50 copies/mL, with available historical genotype (interpreted using ANRS algorithm-Version 22) or treatments**

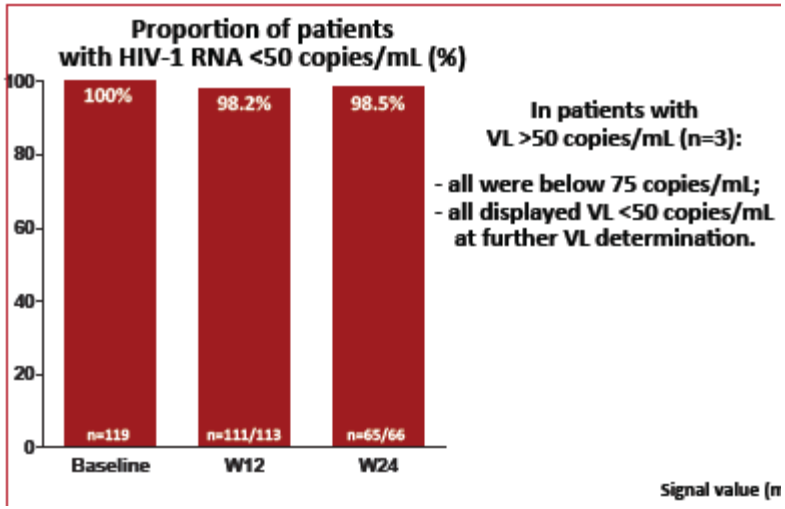
Characteristics (n = 119)	
Men, n(%)	79 (66%)
Median age, years (IQR)	43 (38-49)
Median CD4 nadir, /mm³ (IQR)	234 (140-324)
Pre-therapeutic viral load (log_{10} copies/mL)	5.08 (4.72-5.48)
Time since first antiretroviral (years)	6 (2-9)
Number of lines	3 (2-4)
Time since HIV-1 RNA<50 copies/mL (months)	17 (6-41)
CD4 at RPV initiation (/mm³)	632 (468-786)
HIV-1 subtypes (n = 92)	
B	39 (42%)
CRF02_AG	31 (34%)
Other "Non-B"	22 (24%)
R5-tropic viruses (n = 40)	30 (76%)





Results

Virological outcome



Follow up of patients exhibiting STR-resistant viruses

- All 5 patients with STR-drug-resistant viruses maintained VL<50 copies/mL until W24.

Patient ID	NRTI DRM	NNRTI DRM	W12 viral load (copies/mL)	W24 viral load (copies/mL)
1	D67N-T69D-M184V-L210W-T215F	None	<20	NA
2	T69S-M184V	None	<20	<20
3	M184I/V	None	<20	<20
4	M184V	None	<20	NA
5	None	M230I	<20	31

- **Conclusion: A high level of virological suppression was maintained in the 119 eligible patients after switching to RPV STR during follow-up using ultrasensitive VL assay. No virological failure was observed**

New drug: Dolutegravir

Once-Daily Dolutegravir Versus Darunavir/Ritonavir in Antiretroviral Naive Adults: 48 Week Subgroup Analyses From FLAMINGO

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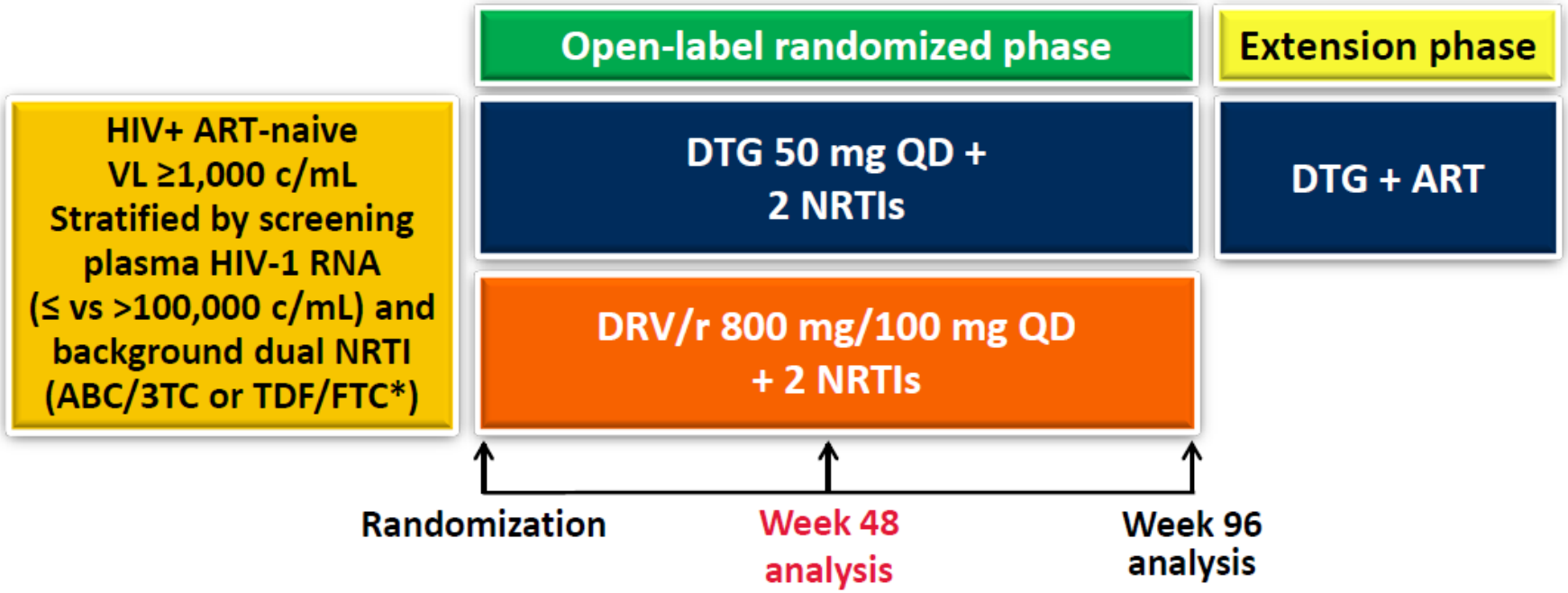
FLAMINGO (ING114915) Study Design



Primary endpoint: proportion with HIV-1 RNA <50 c/mL at Week 48, FDA Snapshot analysis, -12% non-inferiority (NI) margin

Secondary endpoints: antiviral activity, safety, tolerability, health outcomes and viral resistance

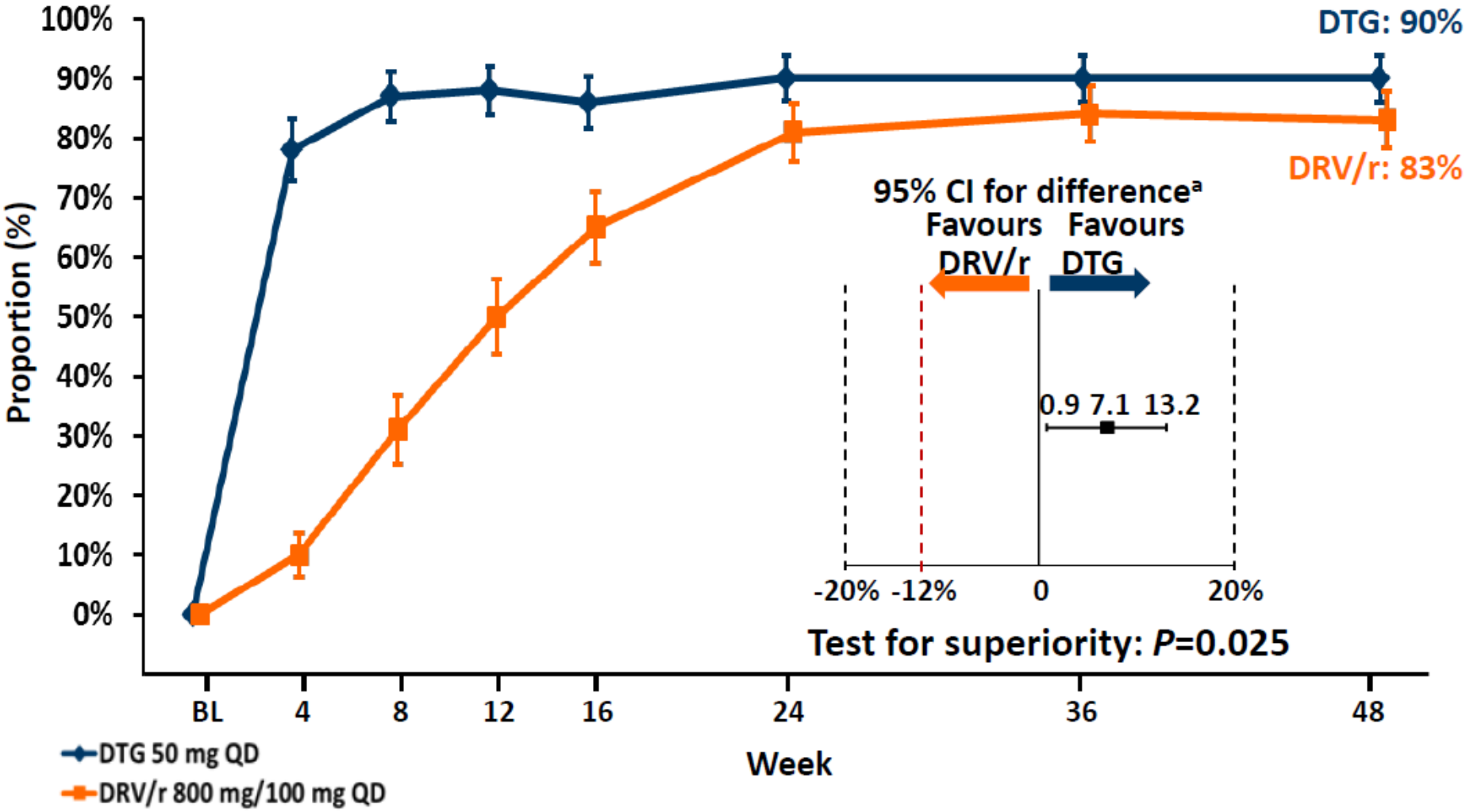
*Investigator selected backbone of choice

Baseline Characteristics

	DTG 50 mg QD (N=242)	DRV/r 800 mg/100 mg QD (N=242)	Total (N=484)
Age (years), median	34	34	34
Female (%)	13%	17%	15%
African American/African heritage (%)	25%	22%	23%
HBV/HCV positive (%)	4%/7%	2%/7%	3%/7%
CDC class C (%)	4%	2%	3%
HIV-1 RNA (log_{10} c/mL), median	4.49	4.48	4.49
>100,000 c/mL (%)	25%	25%	25%
CD4+ (cells/mm^3), median	390	400	395
<50	2%	2%	2%
50 to <200	8%	8%	8%
200 to <350	30%	21%	26%
350 to <500	33%	38%	36%
≥500	27%	31%	29%
Investigator selected ABC/3TC	33%	33%	33%

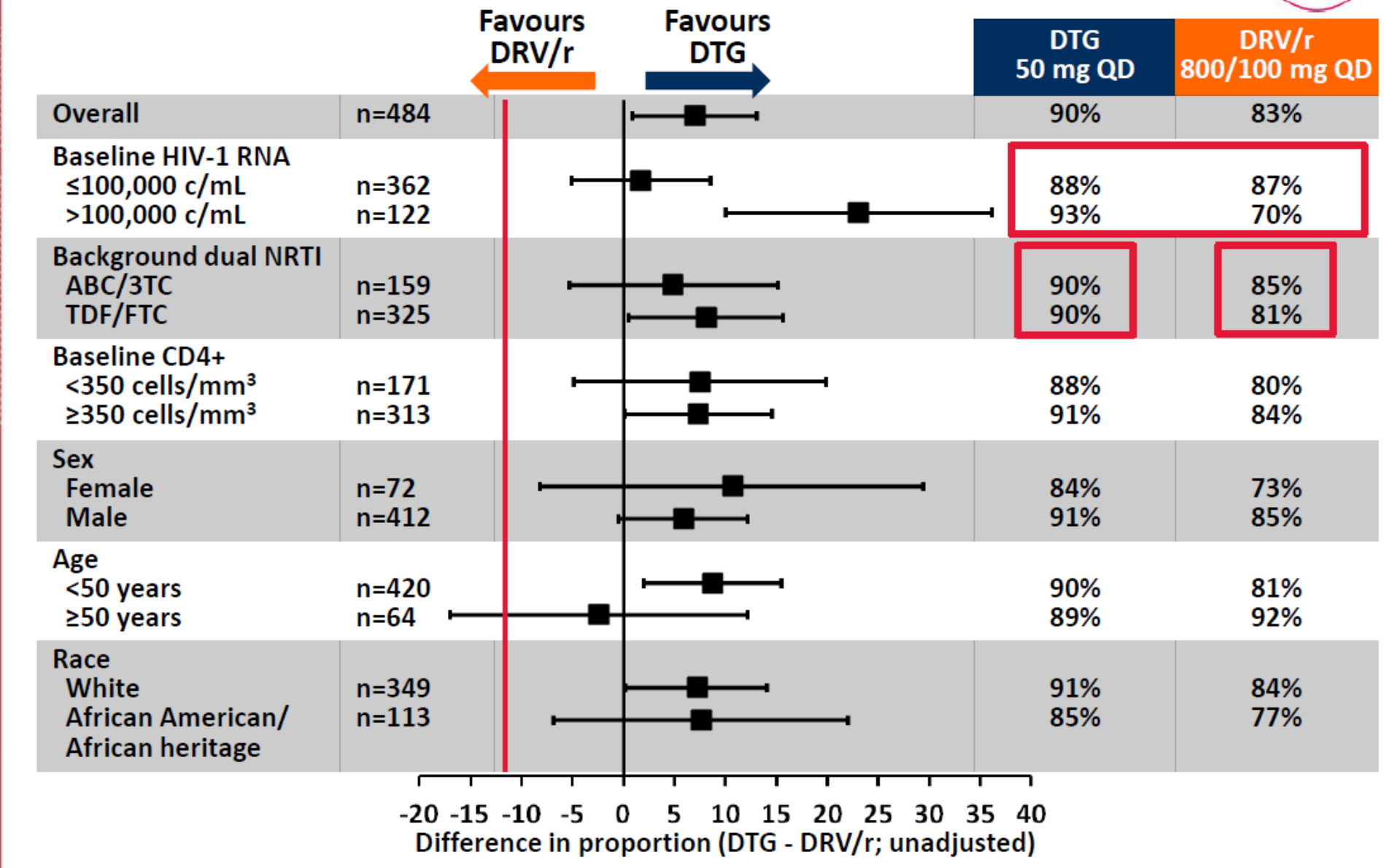
Of note, 25% of subjects in both treatment arms had BL VL >100K

Proportion (95% CI) of Individuals With HIV-1 RNA <50 c/mL Over Time – Snapshot



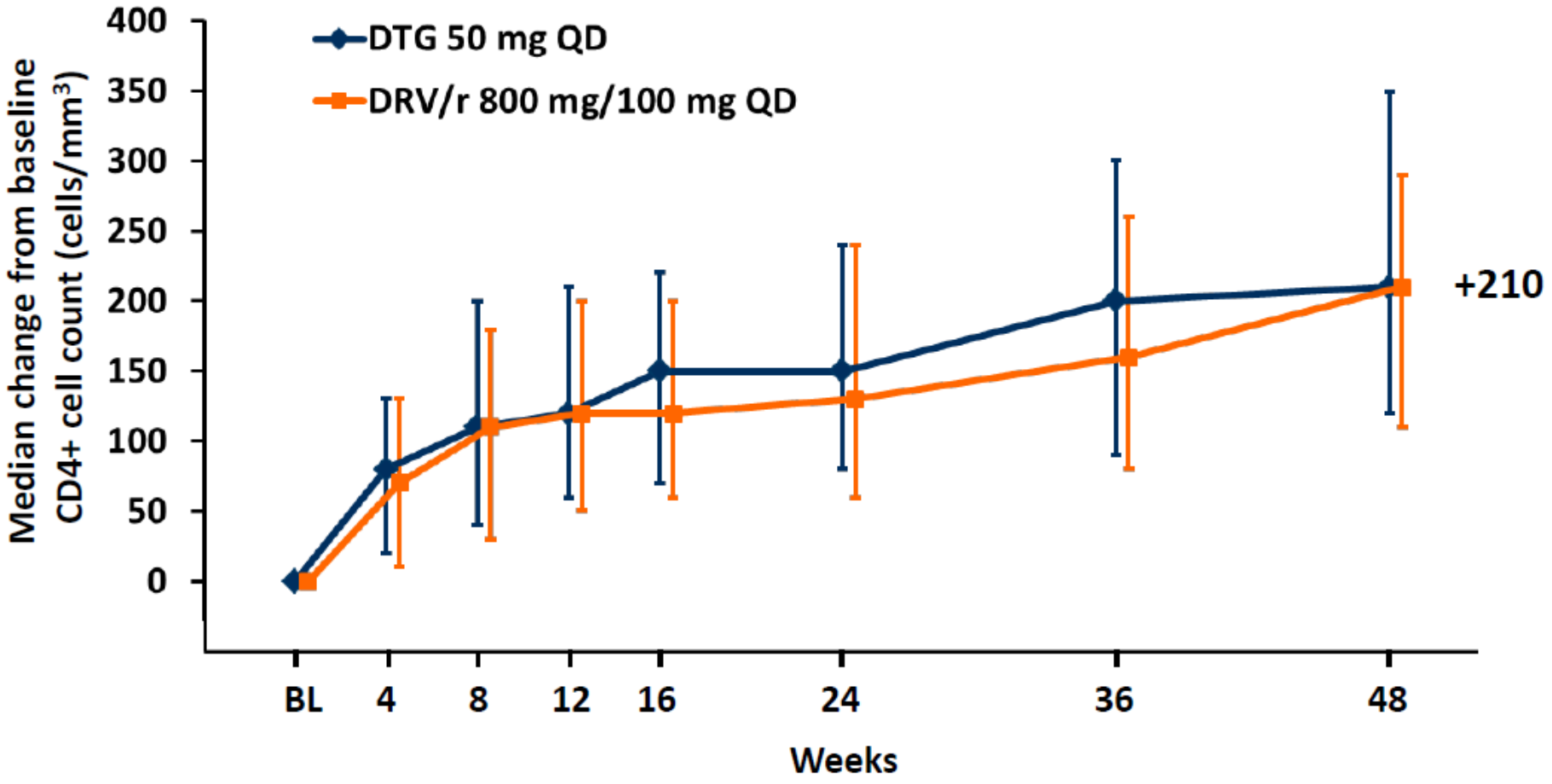
Results were confirmed in per protocol analysis: 91% DTG versus 84% DRV/r, Δ (CI): 7.4 (1.4 - 13.3)

Snapshot by Subgroup at Week 48



Differences were seen in BL VL >100K but not associated to the NRTI backbone

Median (IQR) Change From Baseline CD4+ Cell Count (cells/mm^3)



Adverse Events: Leading to Withdrawal

- Slightly lower incidence overall of events leading to withdrawal for DTG vs DRV/r

	DTG 50 mg QD (N=242)	DRV/r 800 mg/100 mg QD (N=242)
Individuals with events leading to withdrawal	**4 (2%)**	**10 (4%)**
System organ class (>1 event in either arm)		
Gastrointestinal disorders	2 (<1%)	2 (<1%)
Nervous system disorders	2 (<1%)	2 (<1%)
General disorders	0	2 (<1%)
Abnormal transaminase	0	2 (<1%)
Skin and subcutaneous tissue disorders	0	2 (<1%)

Laboratory Results

Maximum Post-Baseline Emergent Toxicity Grade 3 – 4	DTG 50 mg QD (N=242)	DRV/r 800 mg/100 mg QD (N=242)
Cholesterol	0	3 (1%)
LDL cholesterol	2 (<1%)	6 (2%)
Alanine aminotransferase	3 (1%)	4 (2%)
Creatine kinase	16 (7%)	9 (4%)
Creatinine	0	0

- **As previously described,[a] small (0.1-0.18 mg/dL) nonprogressive increases in serum creatinine were observed on DTG arm due to inhibition of OCT2**
- **Mean change from baseline in fasting LDL cholesterol was significantly lower for DTG vs DRV/r (3.1 mg/dL vs 14.1 mg/dL[b])**
- Significantly fewer ≥Grade 2 LDL values on DTG (2% vs 7%[b])

[a] Curtis et al. IAS 2013; Kuala Lumpur, Malaysia. Abstract 1634.

[b] Pre-specified, statistically significant and adjusted for multiplicity

FLAMINGO: Conclusions at 48 Weeks

- Non-inferiority of DTG to DRV/r was demonstrated
  - Statistical superiority of DTG was concluded using a pre-specified testing procedure
  - Difference driven by discontinuations due to AEs/other reasons and fewer virologic non-responders in high viral load subgroup
- Baseline HIV-1 RNA subgroup analysis revealed a larger treatment difference in favor of DTG in high viral load group
- There were no significant differences in AEs leading to withdrawal by subgroup
- DTG provides a potent and well-tolerated alternative to DRV/r for this naive population

Simplification strategies

- In the current era, HAART has been extremely successful.

- Current challenges include: tolerability, toxicities, user friendliness, pill count, simplicity, applicability to different populations (pregnant women, children, drug-users, elderly, etc) and cost.

- Different strategies tested in naïve patients, including PI/r-monotherapy, generally failed to show non-inferiority when compared to standard triple-drug combinations.

14th EUROPEAN AIDS CONFERENCE
OCTOBER 16–19, 2013
BRUSSELS, BELGIUM

GARDEL
GLOBAL ARV DESIGN ENCOMPASSING LOPINAVIR/RITONAVIR AND LAMIVUDINE VS LOPINAVIR/RITONAVIR BASED STANDARD THERAPY

Dual therapy with Lopinavir/ Ritonavir (LPV/r) and Lamivudine (3TC) is non-inferior to standard triple drug therapy in Naïve HIV-1 infected subjects : 48-week results of the GARDEL Study.

ClinicalTrials.gov : # NCT01237444

Pedro Cahn on behalf of the GARDEL study group

FUNDACION HUESPED
en acción contra el sida

Dual therapy with LPV/r + 3TC

- Phase 3, randomized, open label, multicenter, international trial
- To compare the efficacy and safety of a dual therapy (DT) combination of LPV/r 400/100 mg BID+3TC 150 mg BID to a triple therapy (TT) with LPV/r 400/100 mg BID+3TC or FTC and a third investigator-selected NRTI in fixed-dose combination in ARV-naïve patients.
- Primary endpoint : % of patients with HIV-1 RNA< 50 copies/mL at 48 weeks

Dual therapy: less discontinuation

543 SCREEENED

426 RANDOMIZED

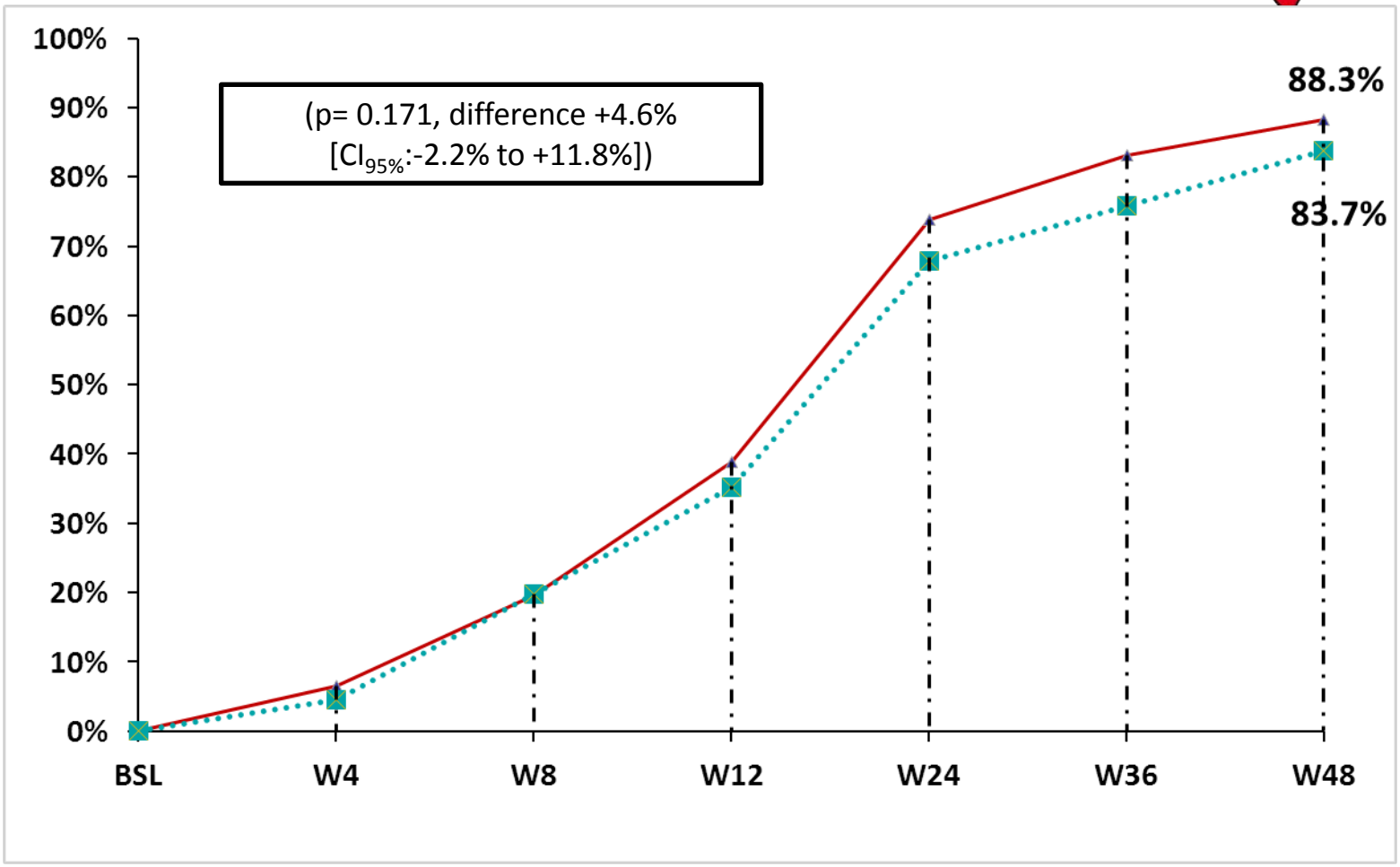
(10 not exposed)

Dual therapy (DT) 214	Triple therapy (TT) 202
Discontinued 16 (7.5%)	Discontinued 27 (14.3%)
Completed W 48 198 (92.5%)	Completed W 48 175 (85.7%)

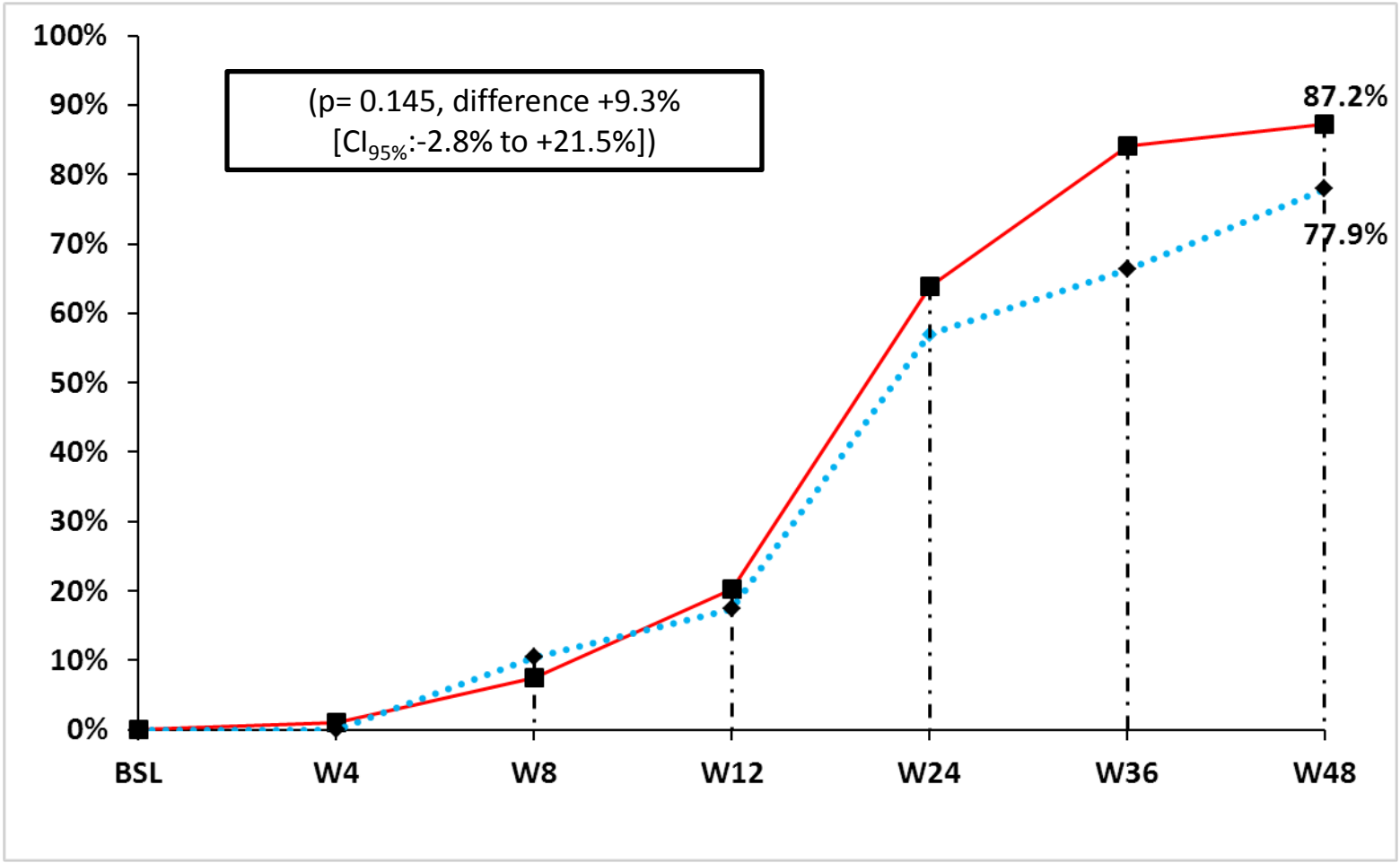
Similar baseline characteristics

Baseline Characteristics	DT n=214	TT n=202
Gender, male: n (%)	179 (83.6)	168 (83.1)
Age, years: median (range)	34 (19–67)	35 (18–68)
Mode of transmission n (%) MSM Heterosexual Other	 132 (61.6) 74 (34.5) 8 (3.7)	 119 (58.9) 75 (37.1) 8 (3.7)
HIV RNA, $\log_{10}$: (median-IQR)	4.87 (4.30-5.35)	4.87 (4.34-5.33)
HIV RNA > 100,000 copies/mL: n (%)	94 (43.9)	86 (42.6)
CD4 count, cells/mm^3:(median-IQR)	319 (215-422)	329 (226-414)
CD4 count ≤ 200 cells/mm^3: n (%)	45 (21.1)	38 (18.8)
CDC stage 3 n (%)	6 (2.8)	6 (2.9)
Background NRTIs	N/A	ABC/3TC:19 TDF/FTC: 74 ZDV/3TC: 109

Viral load <50 copies/mL at week 48: Non-inferiority dual vs triple therapy



Viral load <50 copies/mL at week 48 baseline VL > 100.000 cp/mL: non inferiority confirmed



Conclusions

- Dual therapy with LPV/r+3TC was non-inferior to triple therapy after 48 weeks of treatment, regardless of baseline viral load.
- The DT regimen showed fewer discontinuations due to safety and tolerability .
- Virologic failure did not result in PI resistance development
- Results suggest that a dual LPV/r+3TC regimen warrants further clinical research and consideration as a potential therapeutic option for ARV naïve subjects.

What's about mono-therapy?

MONOTHERAPY WITH DARUNAVIR/RITONAVIR (DRV/r) IN CLINICAL PRACTICE: WEEK 96 ANALYSIS.

Valencia La Rosa JA.[1], Sanz Sanz J.[1], de los Santos Gil I.[1], Martínez Colubi M.[2], Moreno A.[2], Sepúlveda MA.[3], Estrada V.[4], Carranza M.[4], Pérez Elías MJ.[2]

OBJECTIVES:

- The aim of this study was to evaluate the effectiveness, durability and reasons for change of the monotherapy with DRV /r in clinical practice at 96 weeks.

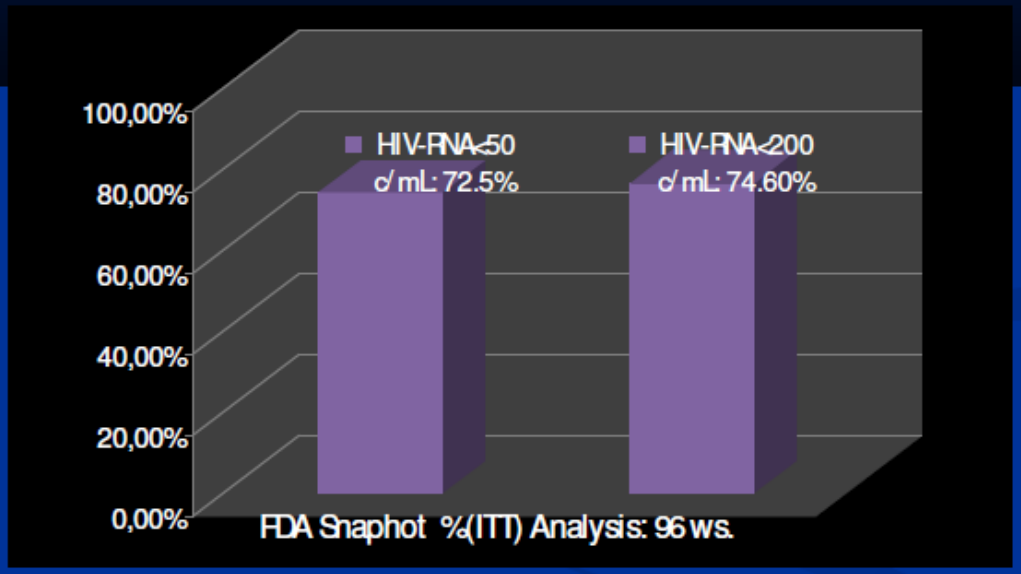
PATIENTS AND METHODS:

- Retrospective Multicenter Observational Study.
- We included all HIV-infected adult patients on antiretroviral therapy (ART) from four Spanish Hospitals, who switched to MTX with DRV/r 800/100 mg /day and that completed 96 weeks of follow up.
- The descriptive and means statistical analysis was performed using SPSS. The effectiveness was measured using the FDA Snapshot-ITT analysis (%) [Treatment Switch and Missing = Failure], with two HIV-viral load breakpoints (VL < 50 copies/ml and CV < 200 copies / ml) at 96 weeks.

BASELINE CHARACTERISTICS	
FEMALE gender	30,60%
AGE (years) [Median (IQR)]:	49[46- 53]
ROUTE OF HIV INFECTION : IDU (%)	45%
AIDS stage:	32%
BASELINE HIV- RNA < 1.7 log cop/mL (%)	93%
DURATION OF ART, years (±SD)	12.79±4.6
HCV coinfected (%)	48%
Nadir CD4 cells /uL, Median [RIQ]	180 [97-301]
Baseline CD4 cells/ uL, Median [RIQ]	669 [440-831]
96 ws. CD4 cells/ul, Median [RIQ]	768.8 [550- 890] p 0.08
DURATION OF RNA-HIV < 1.7 months(±SD)	67.6± 42
MAIN REASON FOR PRESCRIBING MTX (%):	
ADVERSE EVENTS (AE) (%)	63%
SIMPLIFICATION (%)	24%
OTHERS (%)	13%
PREVIOUS REGIMEN (%)	
2 NRTIs + PI	45,90%
2 NRTIs + NNRTI	18,10%
3 NRTIs	8,60%
OTHERS MONOTHERAPY	10,00%

72.5% with VL <50 cp/ml at week 96

- Only eight (5.8%) patients had a scheme that included DRV/r as part of ART prior to MTX.
- At 96 weeks, 74.6% (103 patients) continued on monotherapy with DRV /r. HIV-VL <50 copies/mL in 100 patients (72.5%) and HIV-VL <200 copies/mL in 103 patients (74.6%) **(Figure 1)**.



- Three patients (2.2%) had HIV-VL ≥50 and ≤200 copies /ml. The reasons for switching MTX and adverse effects that led to it are showed in **Table 2**.

- All the seven patients that changed MTX due to low-grade viremia and were reinduced, and those with virological failure that changed the ART, reached HIV-VL <50 copies/mL at 96 weeks, except one patient (VL <200 copies/ml). No resistance mutations were observed in the patients with virological failure during MTX who had resistance test (4/7 patients).

REASONS FOR WITHDRAWAL FROM MONOTHERAPY	Nº
VIROLOGICAL FAILURE (>200 copies/mL)	7
LOW GRADE VIREMIA (< 200 copies/mL)	7
ADVERSE EVENTS:	6
DYSLIPIDEMIA	3
ASH	1
FOLLICULITIS	1
SKELETAL MUSCLE ALTERATION	1
DRUGS INTERACTIONS	4
LOST TO FOLLOW-UP	2
PATIENT DECISION	2
DEATH (UNRELATED TO AIDS/ADVERS EVENT)	2
SIMPLIFICATION	1
IRREGULAR ADHERENCE	1
OTHERS REASONS	3
TOTAL:	**35 (25.3%)**

HIV-Hepatitis C Co-Infection

- Cirrhotic HIV/HCV co-infected patients had low rate (14%) of sustained virological response (SVR) with peg-interferon/ribavirin regimen (PegIFN/RBV), mostly when infected with HCV genotype 1

- The efficacy of triple therapy in HCV mono infected cirrhotic patients was recently studied in CUPIC cohort

- The SVR rate was 40% in Telaprevir (TVR) and 41% in Boceprevir (BOC) group, lower than in non cirrhotic patients but we lack of data in HIV HCV co-infected patients with cirrhosis.

Objectives and study-population

- To describe virological responses at W4, W12, W24 and W48 after initiation of triple therapy with TPV or BOC in cirrhotic HIV/HCV co-infected patients
- To describe adverse events and premature stops
- Includes individuals: cirrhotic HIV/HCV co-infected patients from several European cohorts: France, Germany, Netherlands, Italy

Most-difficult-to-treat patients

Results (2). Baseline characteristics of patients before anti-HCV triple therapy

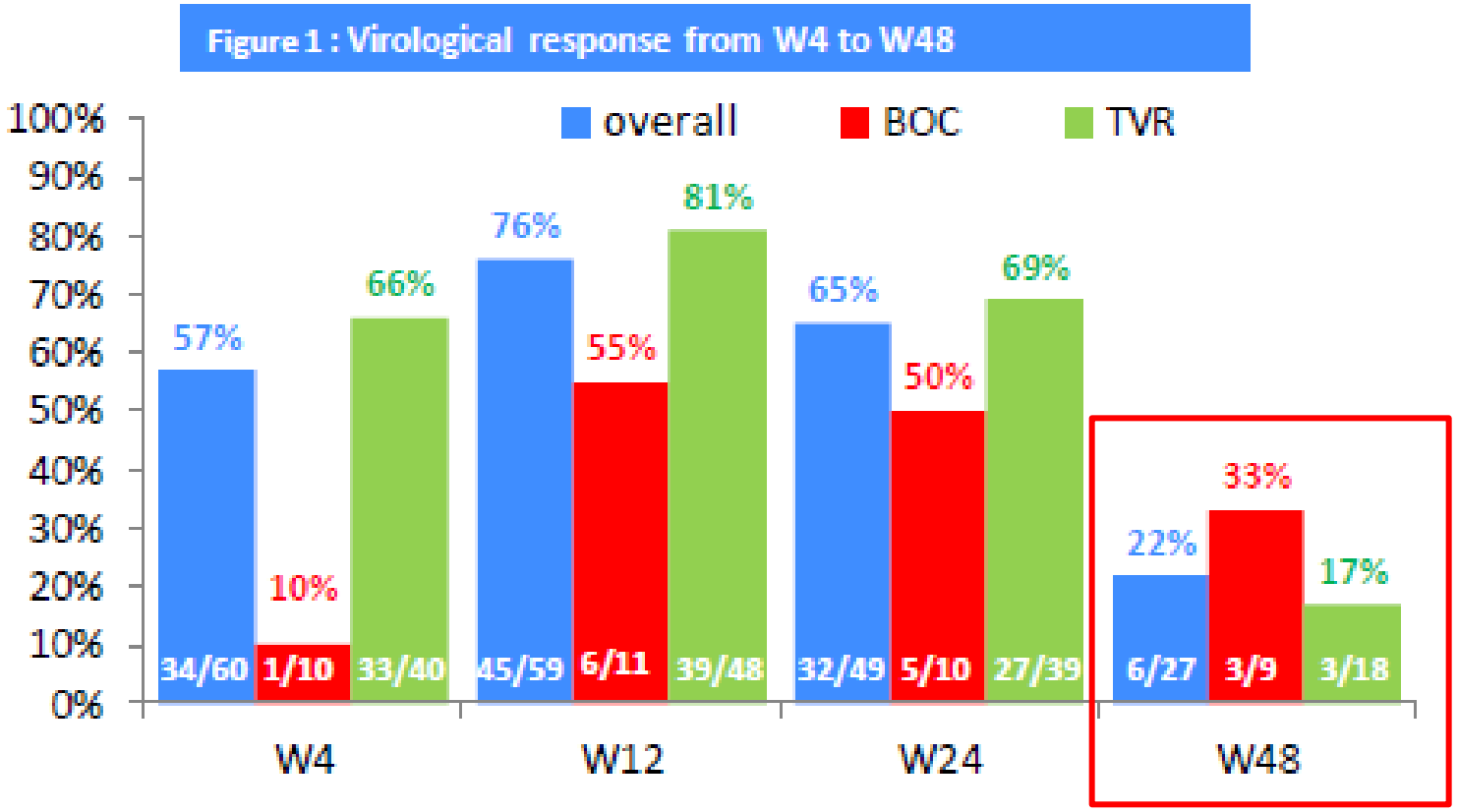
Variables [1]	Overall (n=65)	Boceprevir (n= 11)	Telaprevir (n=54)	p[2]
Age (years)	51 (48-53)	51 (50-56)	50 (48-53)	0.42
Male	53 (82%)	8 (73%)	45 (83%)	0.41
HCV RNA (log_{10} UI/ml) (n= 63)	6.11 (5.43-6.51)	5.98 (5.37-6.21)	6.13 (5.43-6.54)	0.25
IL28B (n=17) [3]				1
CC	9 (53%)	1 (100%)	8 (50%)	
CT	7 (41%)	0 (-)	7 (44%)	
TT	1 (6%)	0 (-)	1 (6%)	
HCV genotype				0.05
1a	52 (80%)	6 (55%)	46 (85%)	
1b	10 (15%)	4 (36%)	6 (11%)	
Genotype 1, subtype unknown	3 (5%)	1 (9%)	2 (4%)	
Previous anti-HCV treatment status				0.24
Naive	9 (14%)	2 (18%)	7 (13%)	
Relapser	11 (17%)	0 (-)	11 (20%)	
Non responder	45 (69%)	9 (82%)	36 (67%)	
Type of ARV (n=64) [4]				0.24
Raltegravir	30 (47%)	8 (73%)	22 (42%)	
Atazanavir	23 (36%)	2 (18%)	21 (40%)	
Efavirenz	2 (3%)	0 (-)	2 (4%)	
Darunavir	3 (5%)	1 (9%)	2 (4%)	
other ARV [5]	6 (9%)	0 (-)	6 (10%)	
CD4 (/mm^3) (n=59)	459 (288-595)	478 (323-708)	454 (288-593)	0.72
HIV viral load < 50 copies/ml	59 (91%)	11 (100%)	48 (89%)	0.58
Transient elastometry (kPa) (n=53) [6]	19.1 (13.3-29.9)	19.6 (8.6-32.4)	18.7 (13.3-27.4)	0.93
Decompensated cirrhosis (n=64) [7]	6 (9%)	2 (20%)	4 (7%)	

Early discontinuation in 32% of all patients

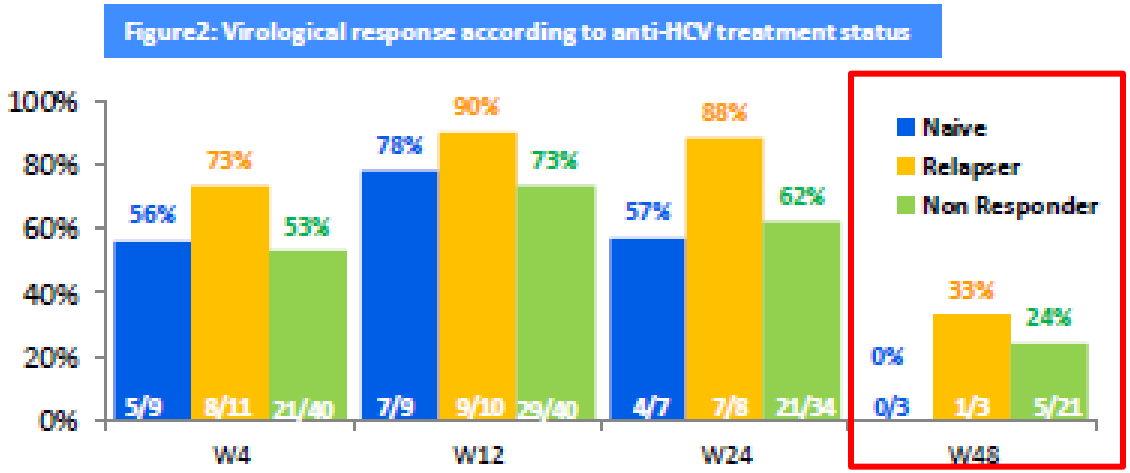
	Overall (N=65)	BOC (n=11)	TVR (n=54)	p
Early discontinuation of HCV therapy .	21 (32%)	6 (55%)	15 (28%)	0.15
Discontinuation reasons : n= 21				0.56
Virological failure	10 (48%)	4 (66%)	6 (40%)	
Relapse	6 (29%)	1 (17%)	5 (33%)	
Side effects [1]	5 (23%)	1(17%)	4 (27%)	
Rash	15 (23%)	1 (9%)	14 (26%)	ns
Severe anemia (< 9 g/dl or decrease >4.5 g/dl).	29 (45%)	4 (36%)	25 (46%)	ns
EPO use	37 (57%)	5 (45%)	32 (59%)	ns
Blood transfusion	9 (14%)	1 (9%)	8 (15%)	ns

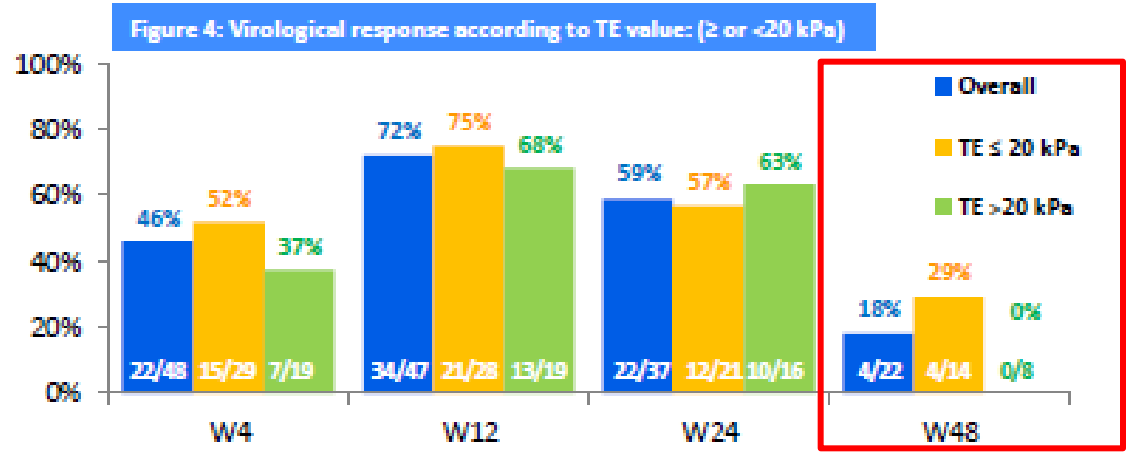
Notes. 1. Among them, only one severe bacterial infection.

Week 48%: 22% reponse rates



Fibroscan >20kPa: 0% response rates





Conclusions

- This cohort of HIV/HCV cirrhotic patients was composed predominantly of patients non responder to PegIFN/RBV (69%) with a genotype 1a (80%).

- Discontinuations due to virological failures, relapses or side effects were common and accounted for a lower rate of virological response at W48 (17% in TVR and 33% in BOC group) than in CUPIC cohort (56% in TVR and 57% in BOC group at W48).

- The highest rate of virological response occurred in subjects with a genotype 1b and in those previously relapsers to PegIFN/RBV (33% at W48).

- Severe anemia was frequent (45%). Only one severe bacterial infection was observed