JNI 15es Journées Nationales d'Infectiologie
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Palais des Congrès de Bordeaux

Bon Usage des Antirétroviraux dans l'Infection par le VIH

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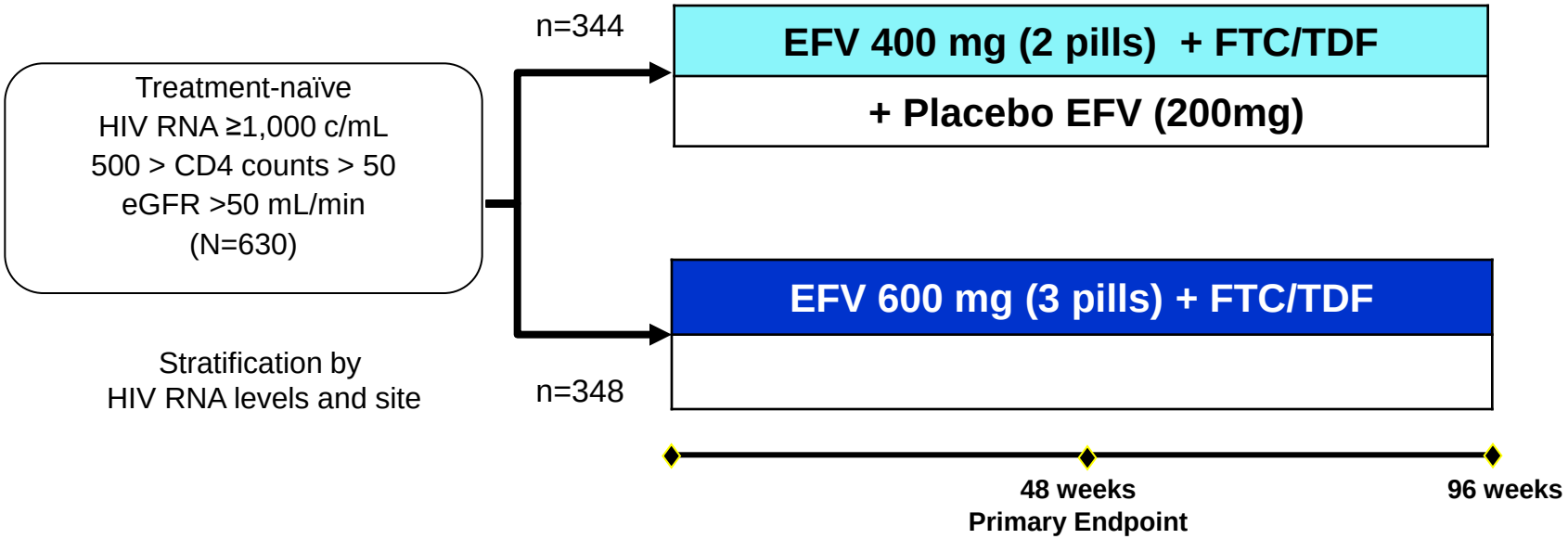
Liens d'Intérêt

- Participation à des Advisory Board et Conférences
  - Gilead, Merck, BMS, Janssen, ViiV, Abbvie

- Bourse de Recherche
  - Merck et GIlead

EFV 400 mg vs. 600 mg in Treatment Naïve Patients ENCORE[1] study

Randomized, double-blind, placebo-controled, non-inferiority study

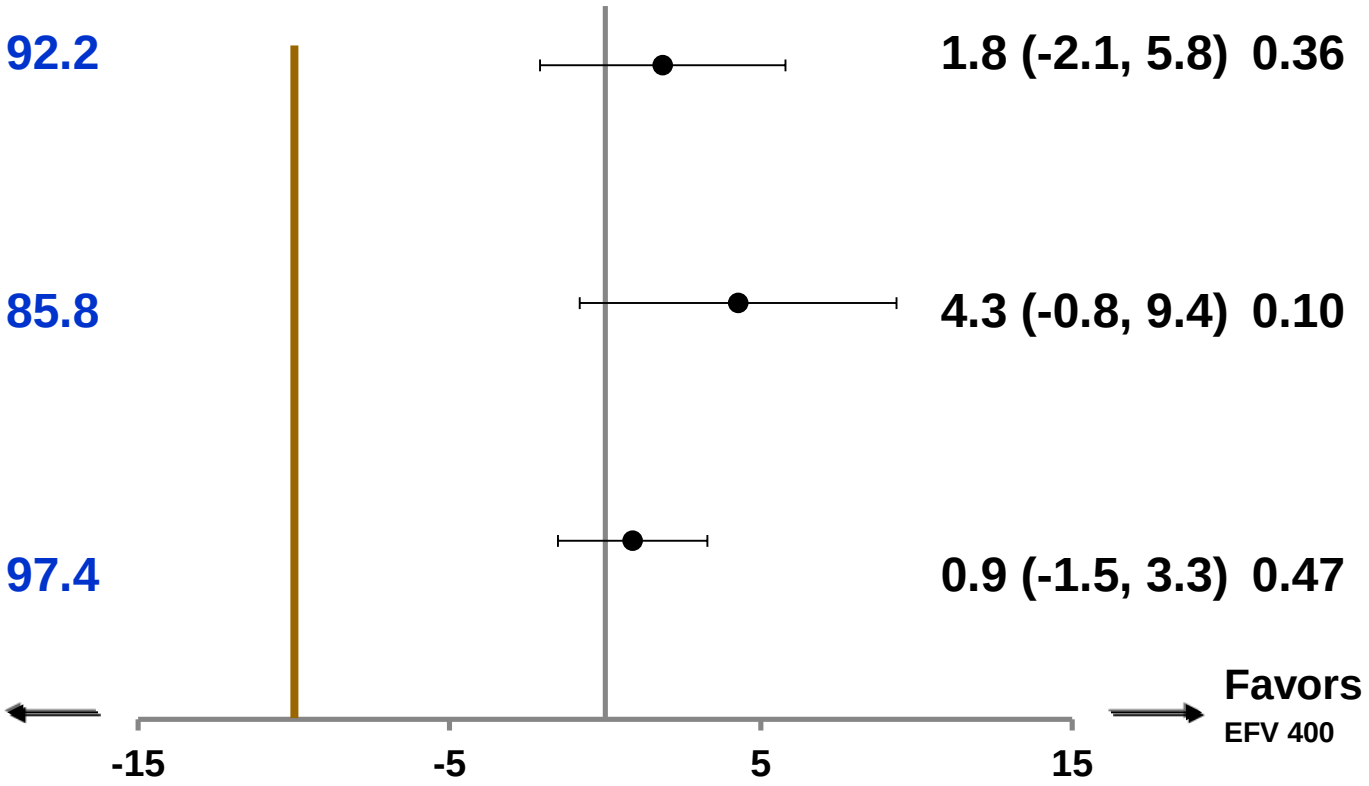


Primary endpoint: Non-inferiority (**10% margin**) of EFV 400 vs 600 in proportion patients with pVL < 200 cp/ml at week 48 using ITT M=F analysis

R. Puls et al., Lancet 2014

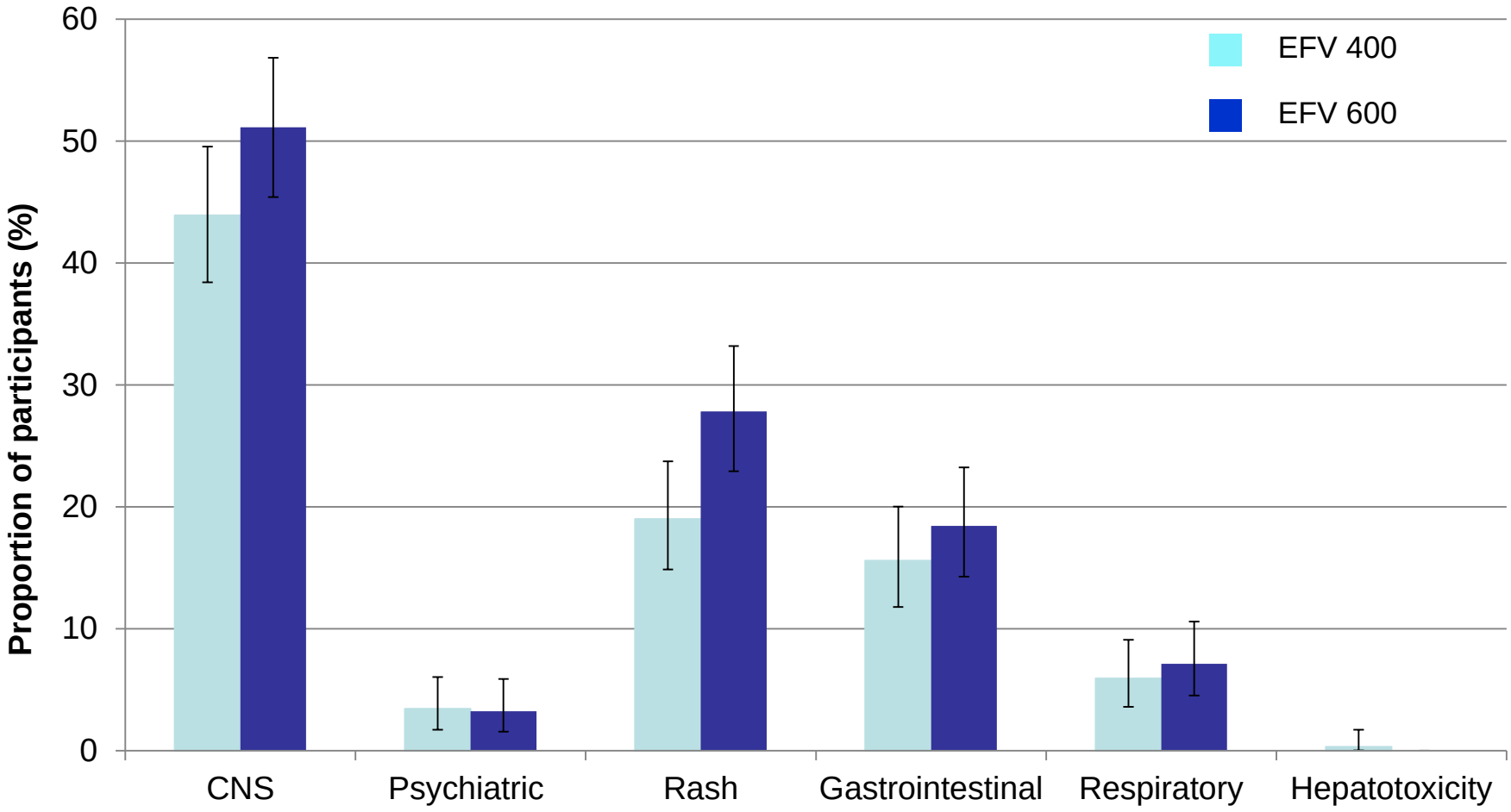
Primary Endpoint (<200 c/ml) Non-Inferiority at Week 48

	EFV400 %	EFV600 %	Difference (95%CI)	p
ITT	94.1	92.2	1.8 (-2.1, 5.8)	0.36
NC=F	90.0	85.8	4.3 (-0.8, 9.4)	0.10
PP	98.3	97.4	0.9 (-1.5, 3.3)	0.47



R. Puls et al., Lancet 2014

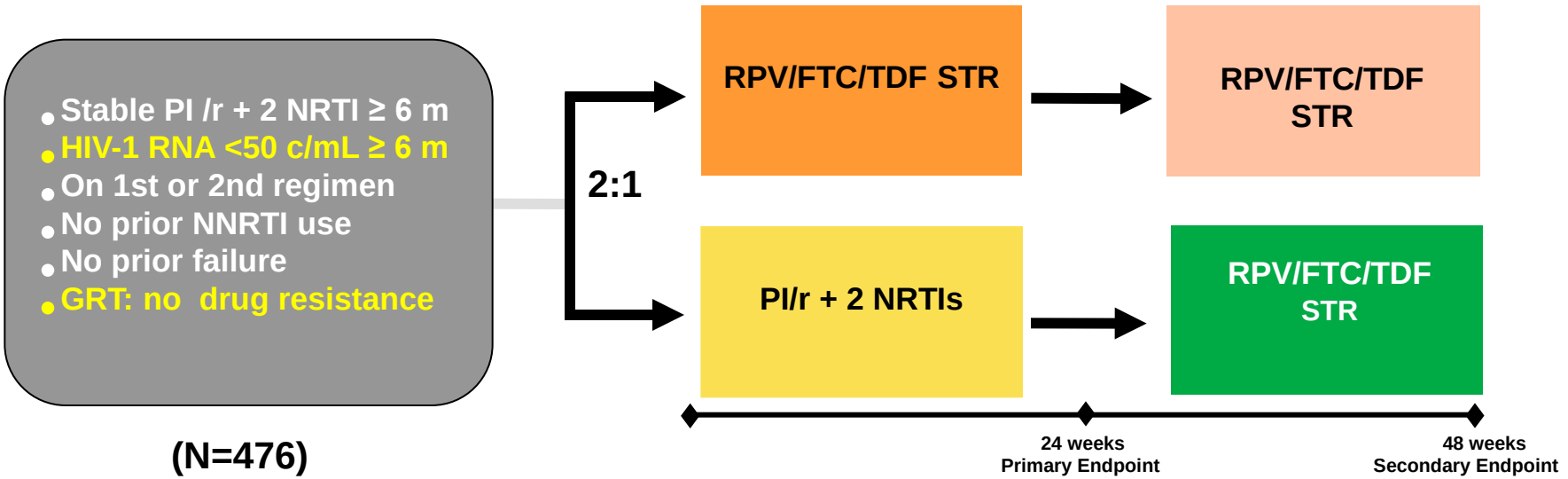
Limited Improvement in Tolerability



R. Puls et al., Lancet 2014

Switch IP to RPV: Spirit Study Design

Switching boosted PI to Rilpivirine in combination with Truvada as an STR
Multicenter, international, randomized, open-label, Phase 3b, 48-week study



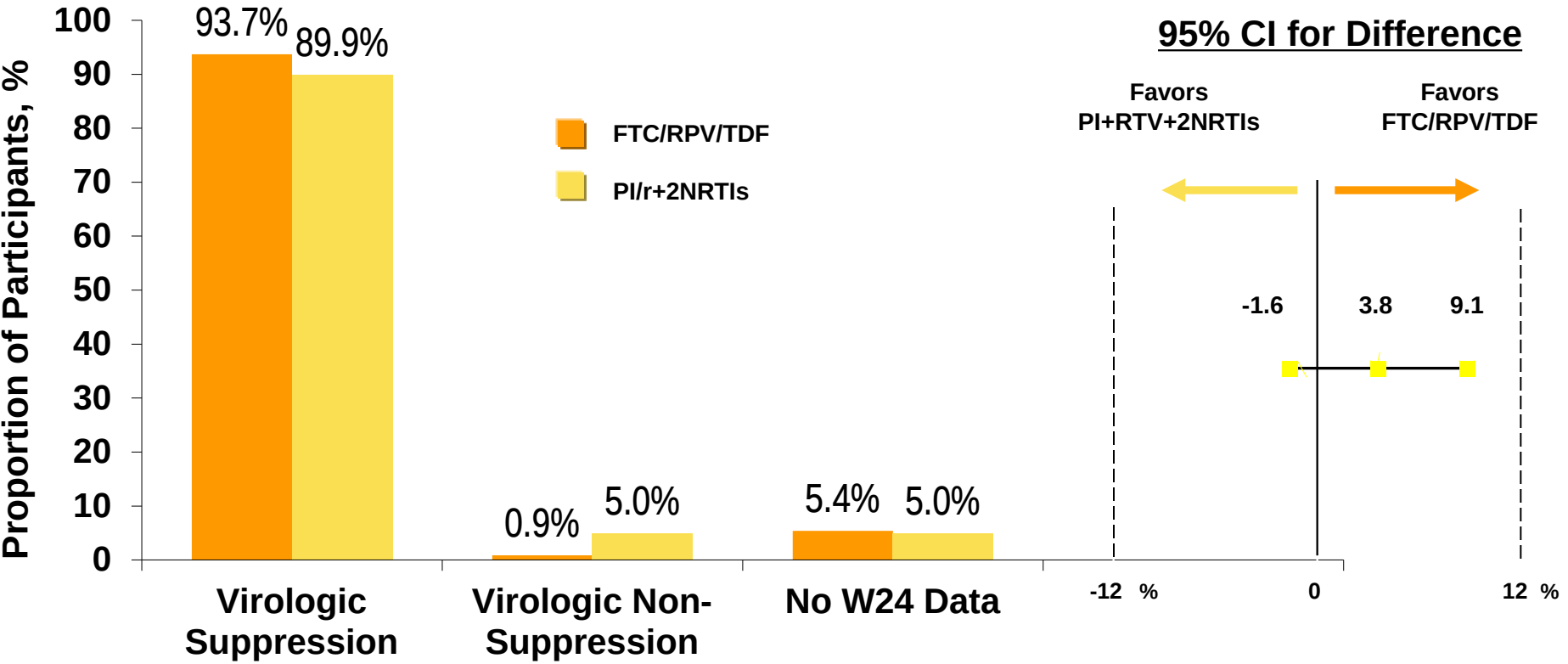
Primary Endpoint: Non-inferiority (12% margin) of RPV/FTC/TDF to PI+RTV+2 NRTIs by FDA snapshot analysis HIV RNA <50 copies/mL at 24 weeks

Secondary Endpoints: Change in fasting lipid parameters and CD4 cell count at 24 and 48 weeks
Safety and tolerability to PI+RTV+2NRTIs at 24 and 48 weeks
Proportion of subjects who have HIV1 RNA <50 copies/mL (missing = excluded) through Week 48

Palella F, et al. AIDS 2014;28:335-44.

Virologic Suppression (< 50 cp/ml) at Week 24 FDA Snapshot Analysis – ITT Population

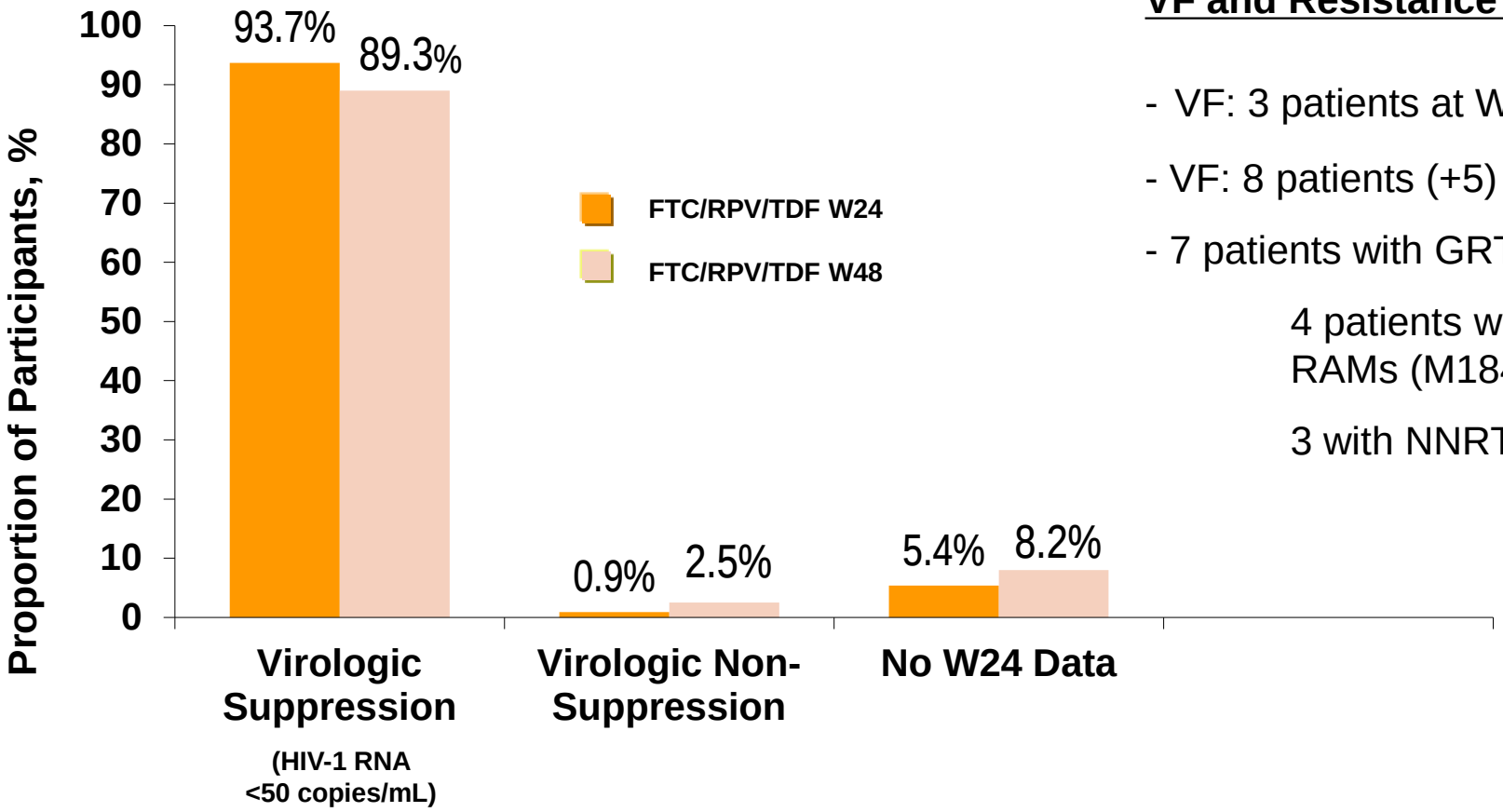
Switching to FTC/RPV/TDF was non-inferior to remaining on PI+RTV+2NRTIs



Change in CD4 count (cells/mm3): FTC/RPV/TDF +20 vs PI+RTV +32 (p=0.28)

Palella F, et al. AIDS 2014;28:335-44

Virologic Suppression at W24 and W48 FDA Snapshot Analysis – ITT Population



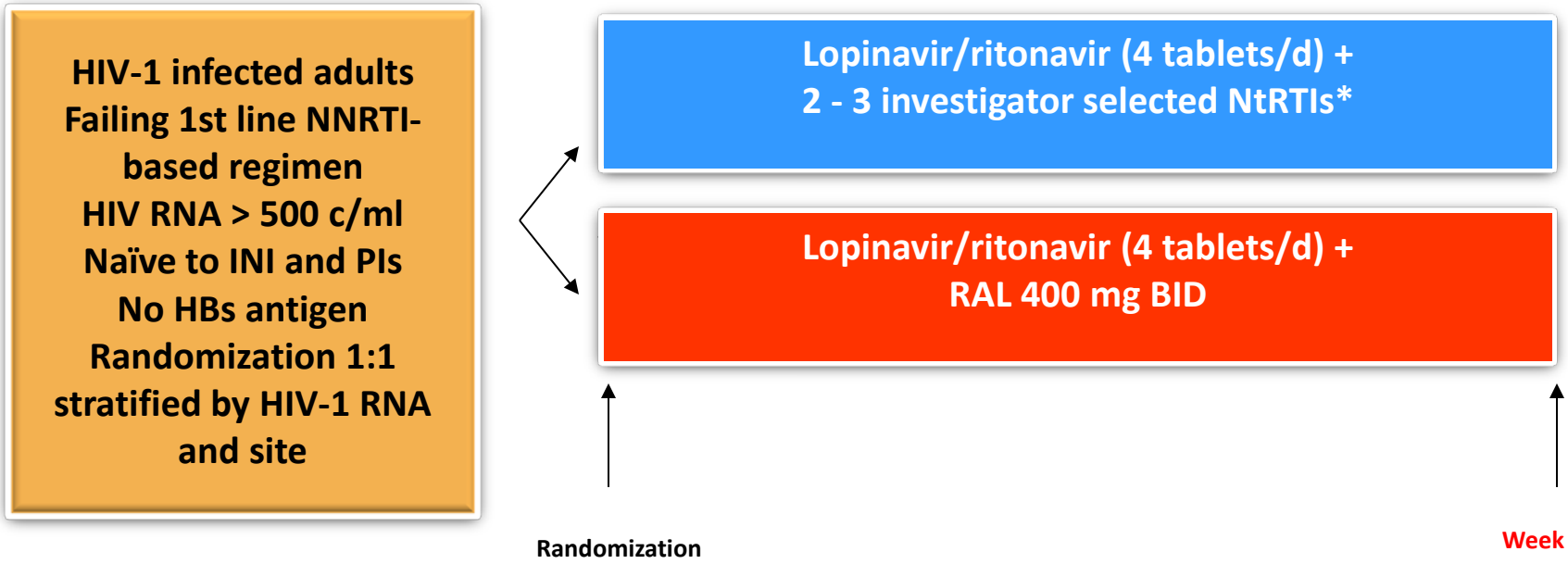
VF and Resistance Analysis

- VF: 3 patients at W24
- VF: 8 patients (+5) at W48
- 7 patients with GRT
  - 4 patients with NRTI RAMs (M184V/I)
  - 3 with NNRTI RAMs

Palella F, et al. AIDS 2014;28:335-44.

Second-line: LPV/r + 2 NRTIs or Raltegravir for Patients Failing First Line NNRTI-based ART

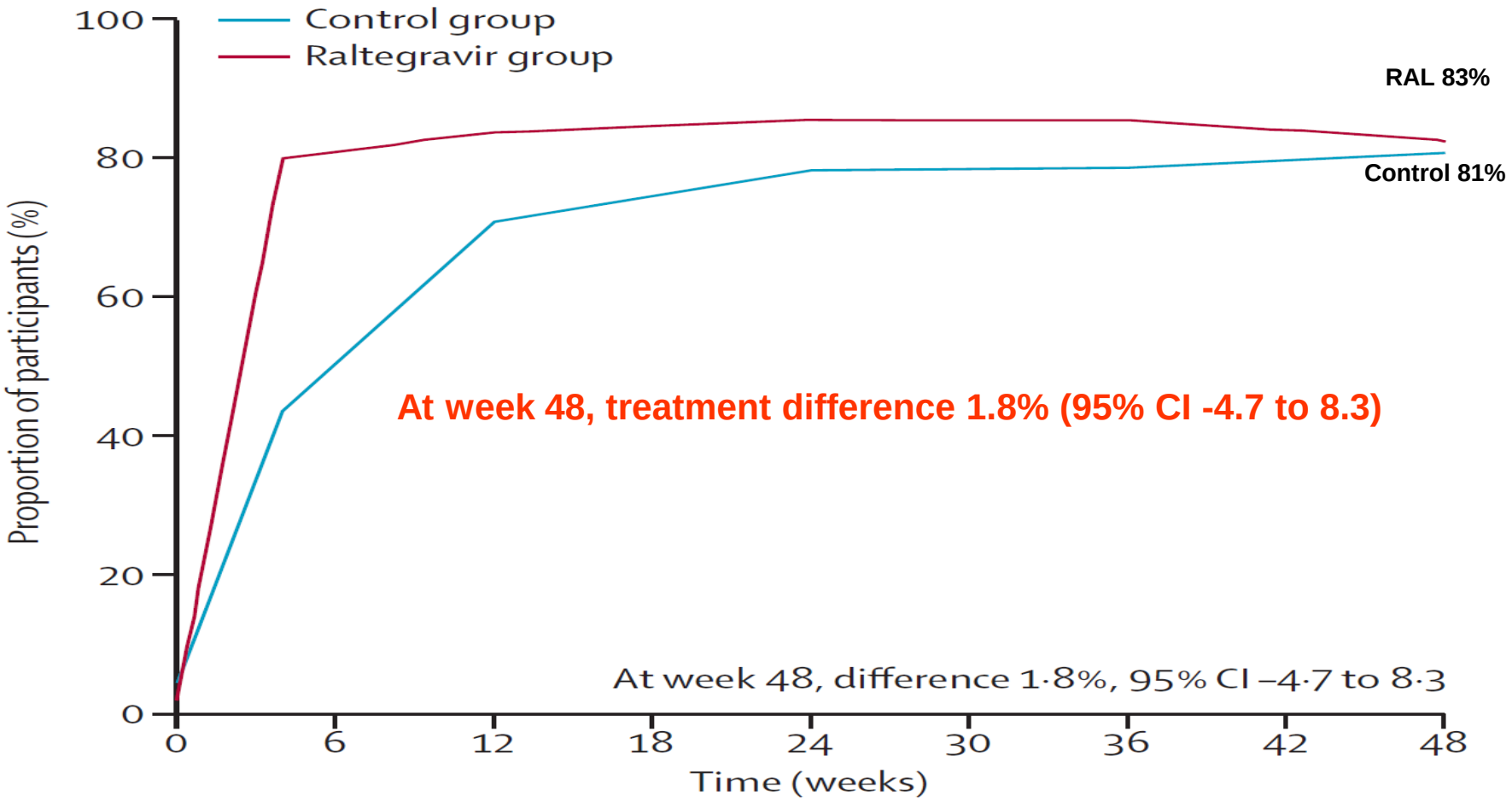
A randomized, open-label, multicenter trial



* TDF: 81%, 3TC/FTC: 87%, AZT: 45%, 3 NRTIs: 23%
GART was allowed but optional to select NRTIs.

Boyd et al, Lancet 2013; 381:2091-99

Proportion of Participants with Plasma HIV Load < 200 c/ml

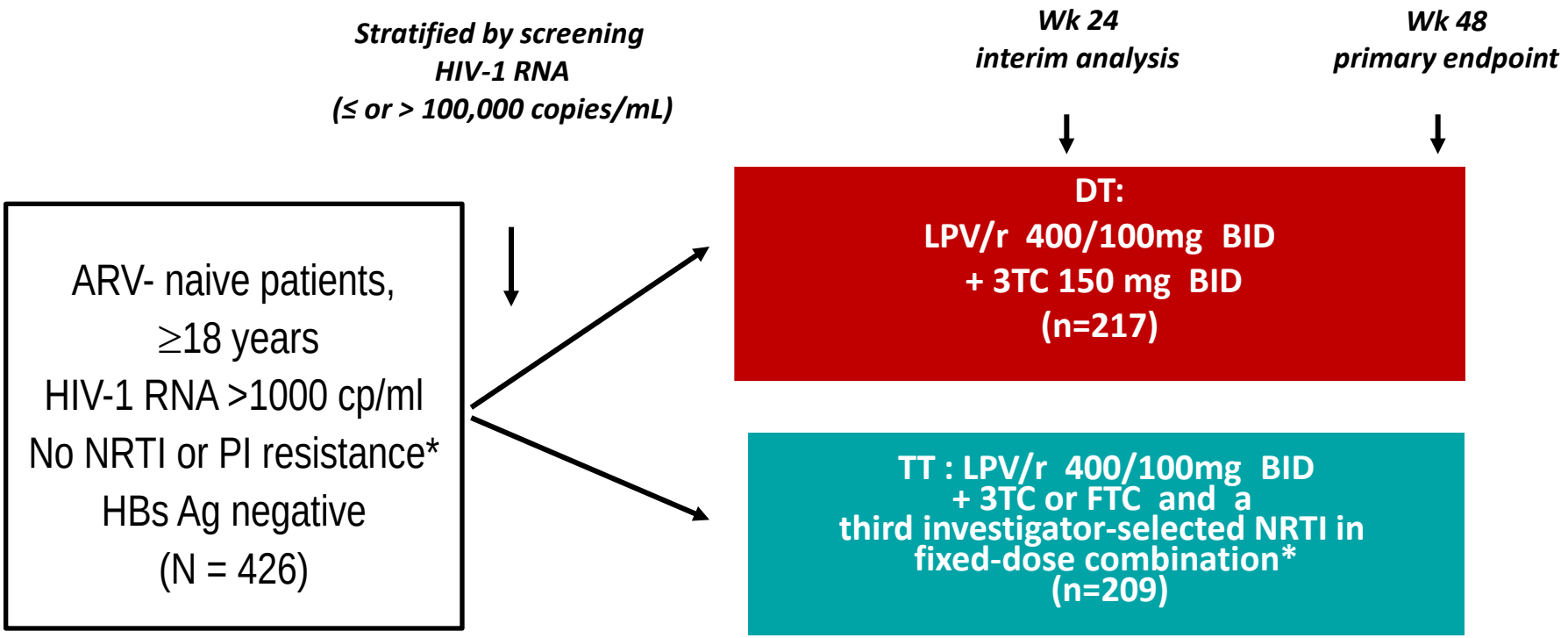


- **Mean CD4+ change from BL: control: 132 cells/mm3; RAL: 167 cells/mm3**
- **Emergence of resistance mutation: 6/43 (14%) NRTIs, 7/47 (15%) RAL**

Boyd et al, Lancet 2013; 381:2091-99

Dual Therapy with LPV/r + 3TC

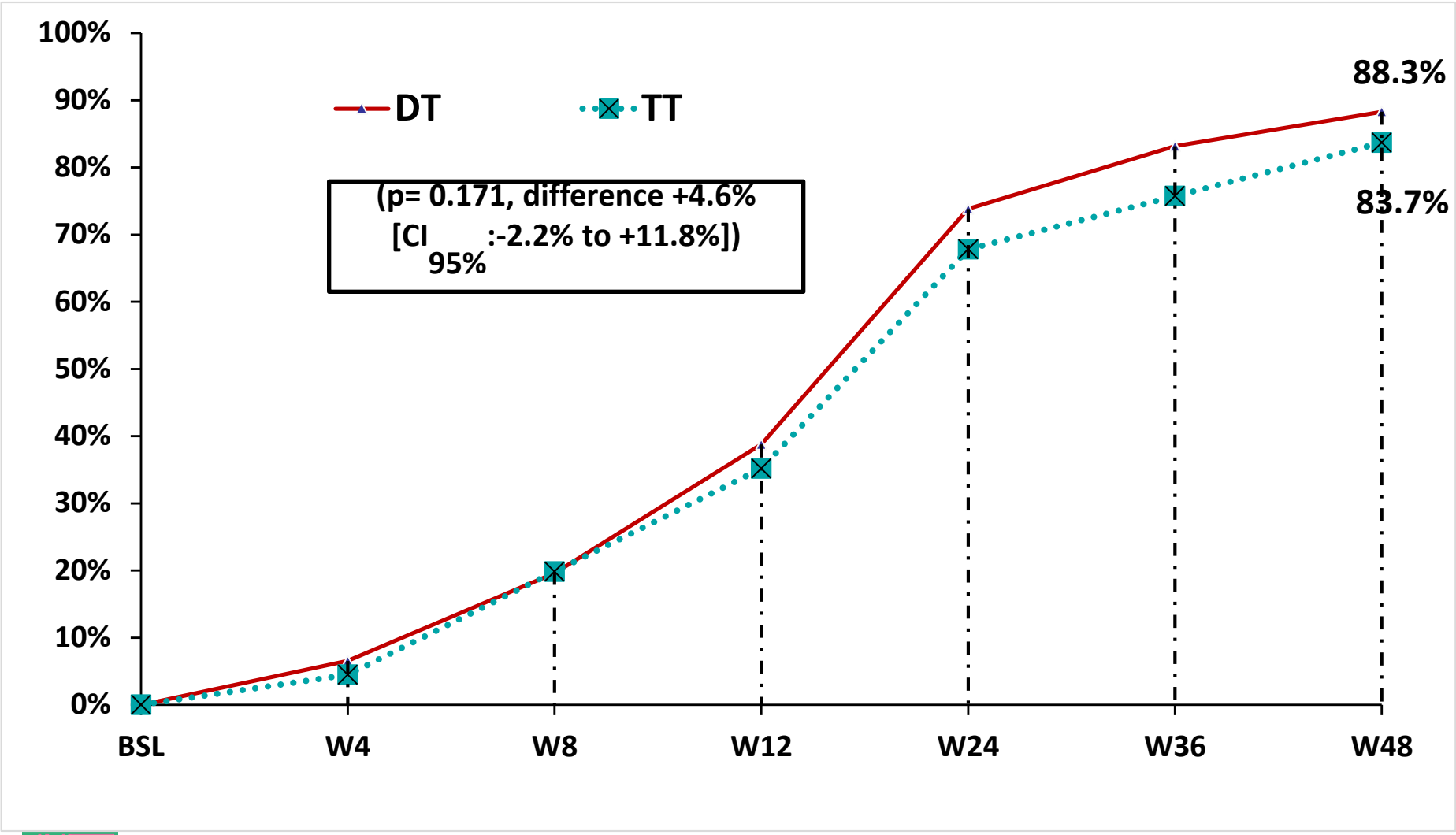
- Gardel: Phase III, randomized, controlled, open-label study, non-inferiority study
- Study included adult patients from Argentina, Chile, Mexico, Peru, Spain, US.



LPV major mutations : V32I; I47V/A; L76V; V82A/F/T/S
* 54% used AZT/3TC

Cahn et al, Lancet ID 2014

Gardel: Viral load <50 c/mL W48 (ITTe)



Cahn et al, Lancet ID 2014

Gardel: Virologic Failure and Emergent Resistance Mutations

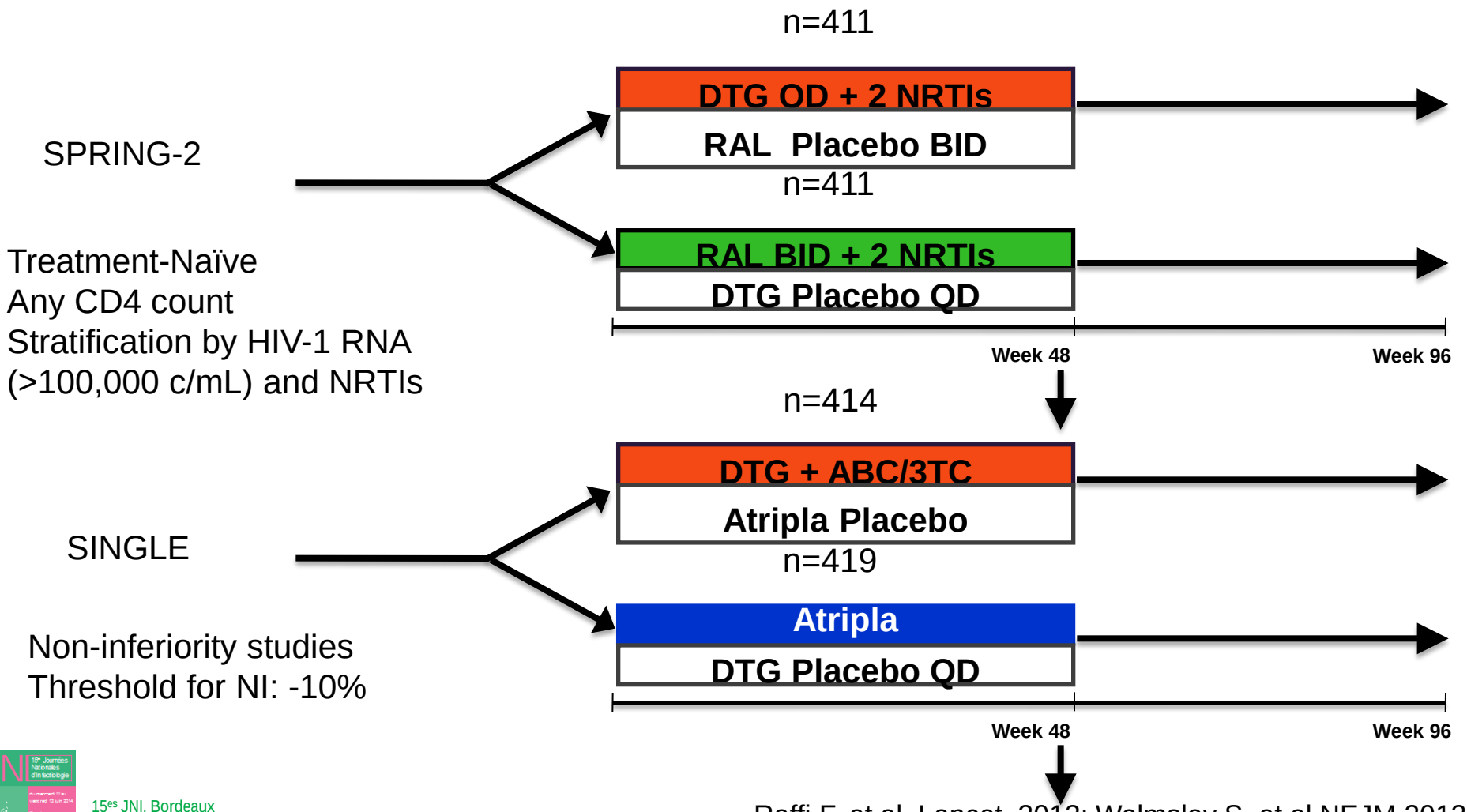
Number of patients, n (%)	DT (N=214)	TT (N=202)
Confirmed virological failures	10 (4.6 %)	12 (5.9 %)*
HIV-1 RNA (copies/ml) (median-IQR)	236 (183-17,687)	1027 (123-4,880)
Never suppressed	2	8
Rebounders	8	4
Primary PI RAMs	0	0
NRTI RAMs (M184V)	2	0

*p = 0.72

2 out of 5 amplified virus in the DT arm had 3TC resistance

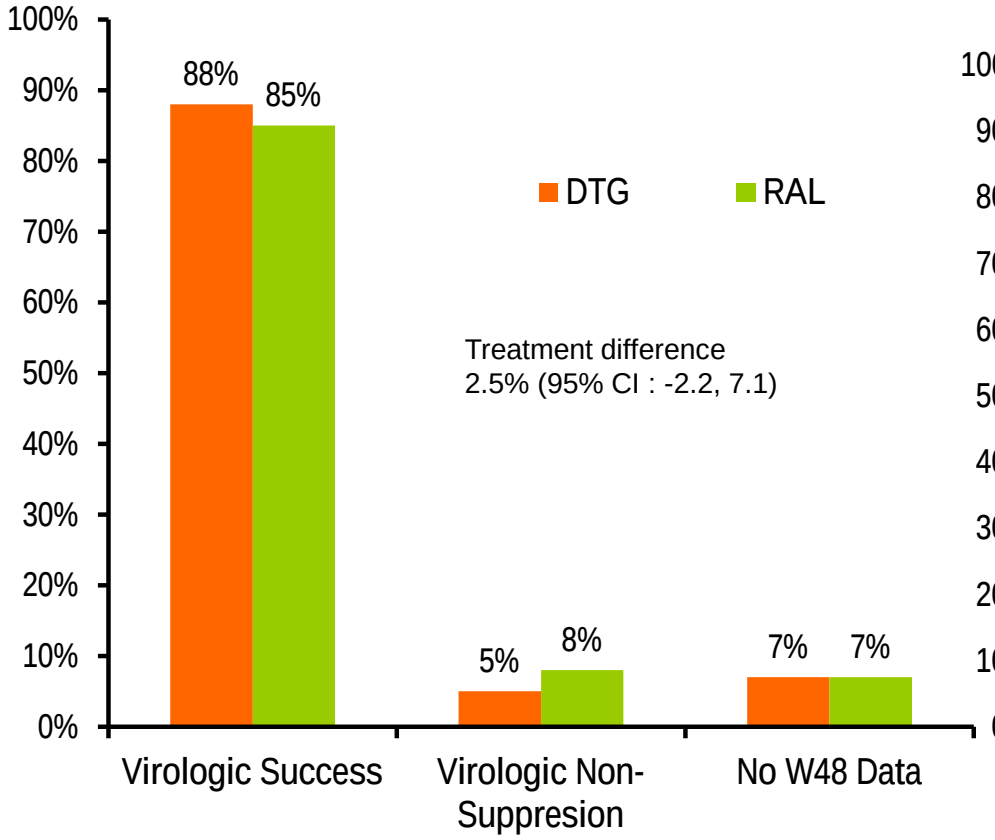
Cahn et al, Lancet ID 2014

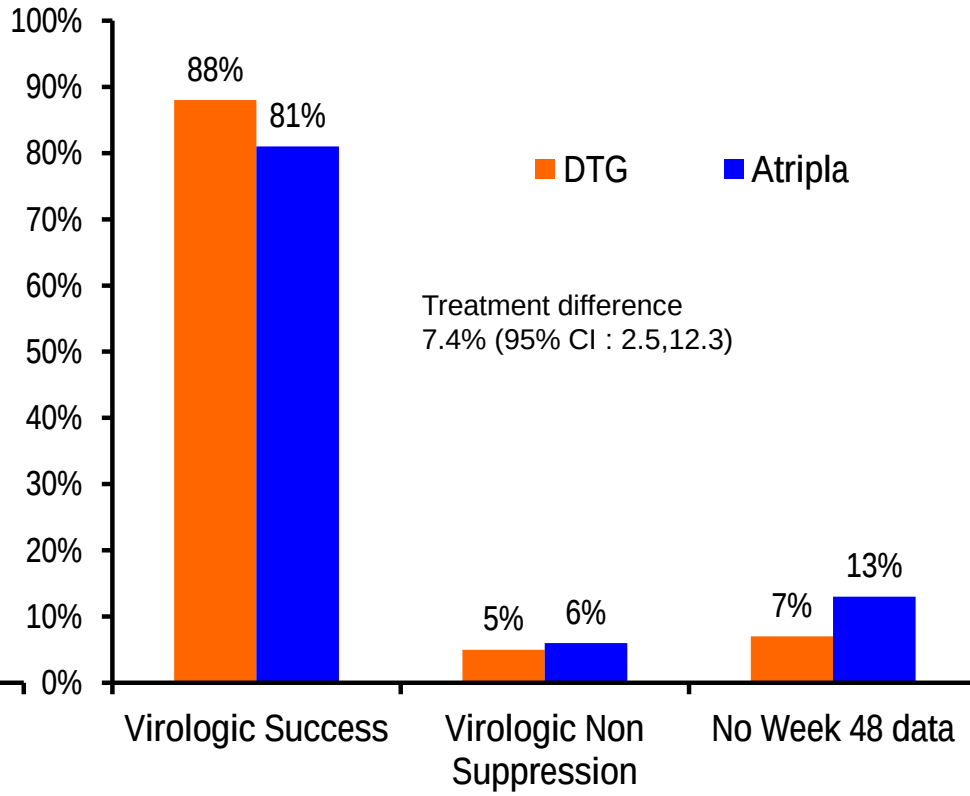
Dolutegravir vs. RAL or EFV



Raffi F. et al, Lancet 2013; Walmsley S. et al NEJM 2013

Studies SPRING-2 and SINGLE Efficacy at 48 Weeks





CD4 Change: DTG +230 vs. RAL +230 Cells/µL and DTG +267 vs. Atripla +208 (P<.0001)

Raffi F. et al, Lancet 2013; Walmsley S. et al NEJM 2013

Virologic Failure and Emergence of Resistance

	DTG 50 mg QD n=411	RAL 400 mg BID n=411
Subjects with virologic failure (VF)	20 (5%)	28 (7%)
IN genotypic results at BL and time of VF	8	18
INI-r mutations	0	1/18 (6%)[a]
RT genotypic results at BL and time of VF	12	19
NRTI-r mutations	0	4/19 (21%)[b]

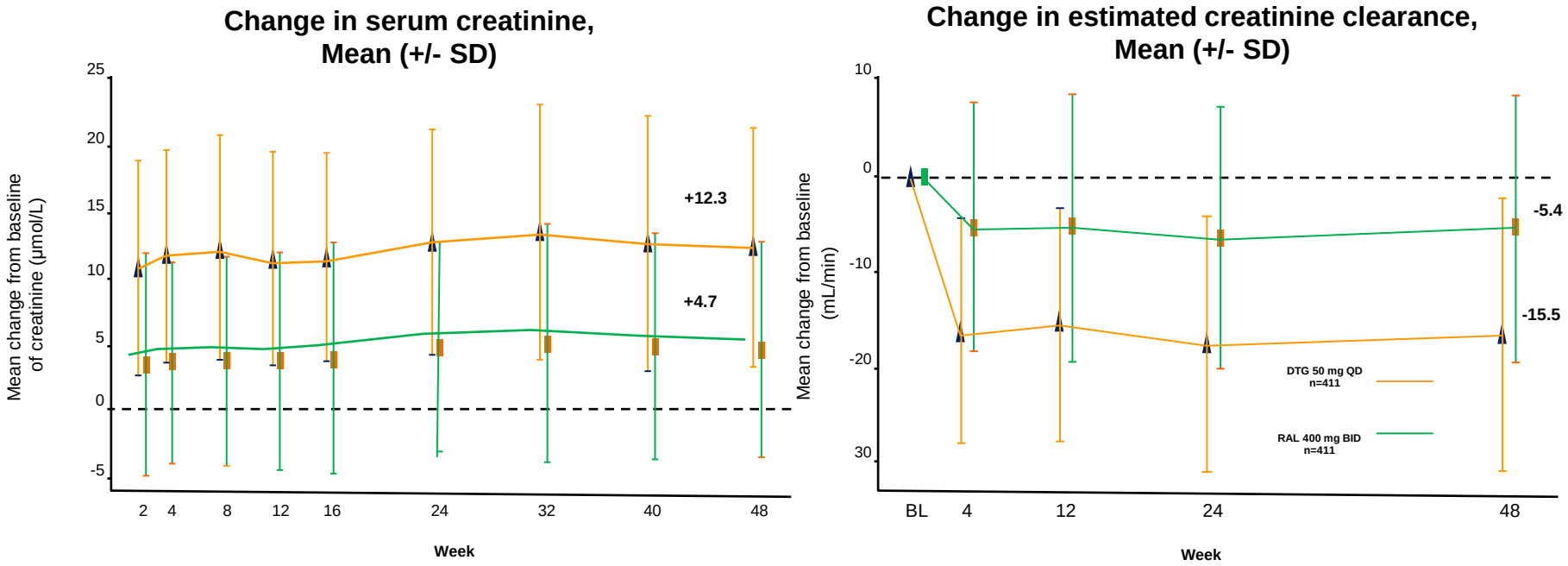
Mutations by subject in the RAL 400 mg BID arm:

[a] N155H, T97T/A, E138E/D, V151V/I,

[b,] M184M/I (n=3), A62A/V (n=2), K65K/R (n=1), K70K/E (n=1)

Raffi F et al, Lancet 2013; 381:735-43

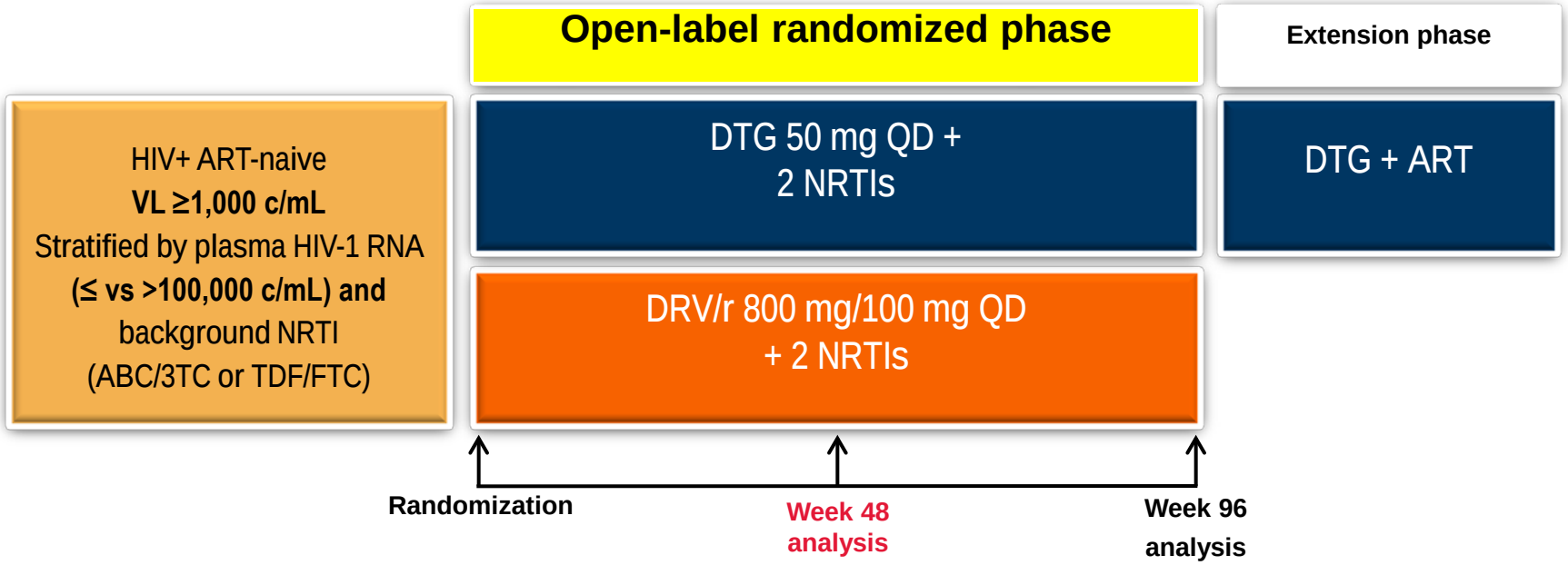
SPRING-2 Renal and Overall Safety



- Most common events : nausea (14%), headaches (12%) and diarrhea (11%)
- Only 3 patients (<1%) discontinued DTG because of AEs and 5 (1%) with RAL
- Two patients had a possible DTG-associated drug induced liver injury with HSR
- DTG inhibits OCT2, decreases tubular secretion of creatinine without affecting GFR
- No patient in either group discontinued treatment because of renal events.

Raffi F et al, Lancet 2013; 381:735-43

FLAMINGO: DTG vs Darunavir/r in ART-Naive Adults

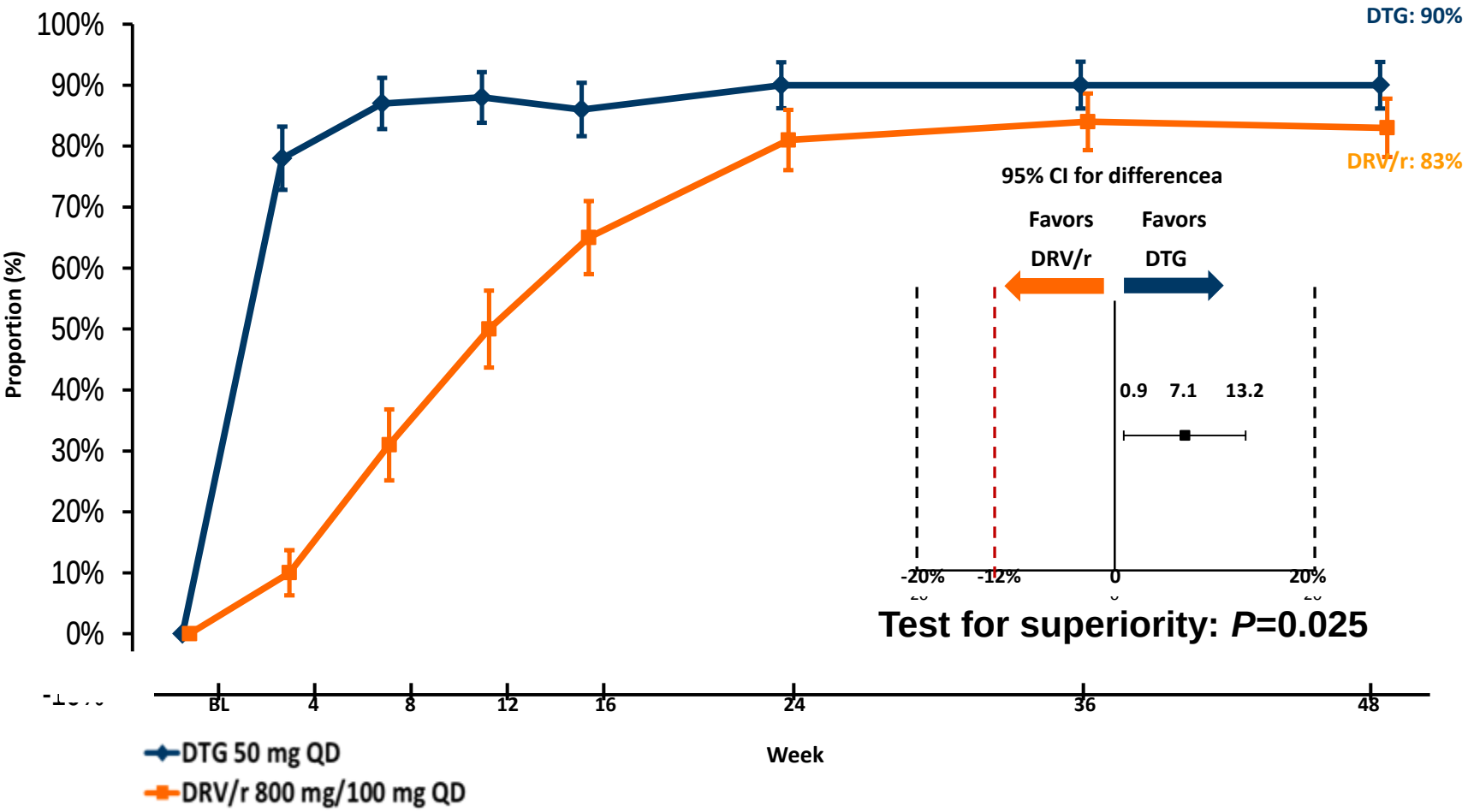


Primary endpoint: proportion with HIV-1 RNA <50 c/mL at Week 48, FDA Snapshot analysis, -12% non-inferiority (NI) margin

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

Clotet et al Lancet 2014

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



Superiority driven by fewer withdrawals due to AEs and other reasons prior to W 48

Clotet et al Lancet 2014.

PDVF and Treatment-Emergent Resistance

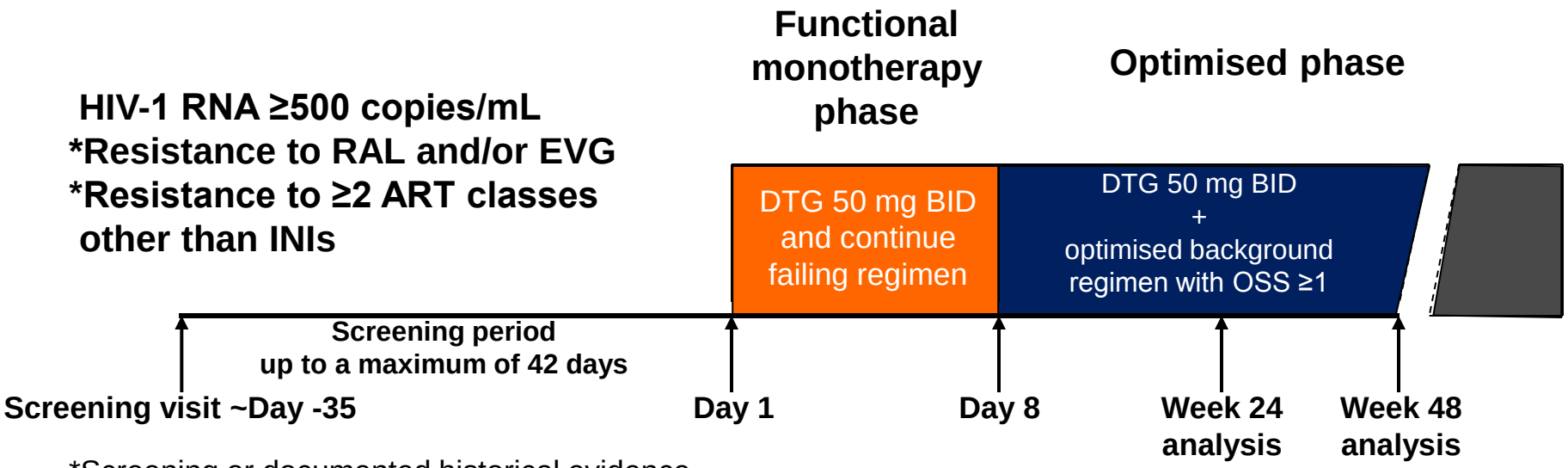
- PDVF: Protocol defined virologic failure was defined as 2 consecutive HIV-1 RNA values >200 c/mL, on or after Week 24

	DTG 50 mg QD	DRV/r 800 mg/100 mg QD
PDVF, n (%)	**2 (<1)**	**2 (<1)**
Treatment-emergent primary mutations (INI, NRTI, PI)	0	0

Clotet et al Lancet 2014.

Dolutegravir in Patients with INSTI Resistance

Single-arm, open-label phase III study in ART-experienced adults



*Screening or documented historical evidence.

Primary endpoint: mean change from baseline in HIV RNA at day 8 and proportion of subjects with HIV RNA < 50 cp/ml at week 24

Castagna A et al., JID 2014

Day 8 Responses by Baseline Resistance

Primary INI-resistance mutations at BL	N	Mean HIV-1 RNA (log_{10}) change from BL (SD) at Day 8	% >1-log_{10} HIV-1 RNA decline or <50 copies/mL at Day 8
Total	183	-1.4 (0.61)	82%
No primary mutations	60	-1.6 (0.55)	95%
T66	1	-1.9	100%
Y143	28	-1.7 (0.42)	96%
N155	33	-1.4 (0.51)	82%
≥2 Primary mutations	8	-1.4 (0.76)	75%
Q148 + ≤1 Secondary mutation*	32	-1.1 (0.51)	69%
Q148 + ≥2 Secondary mutations*	21	-1.0 (0.81)	48%

*Key secondary mutations were G140A/C/S, L74I, and E138A/K/T

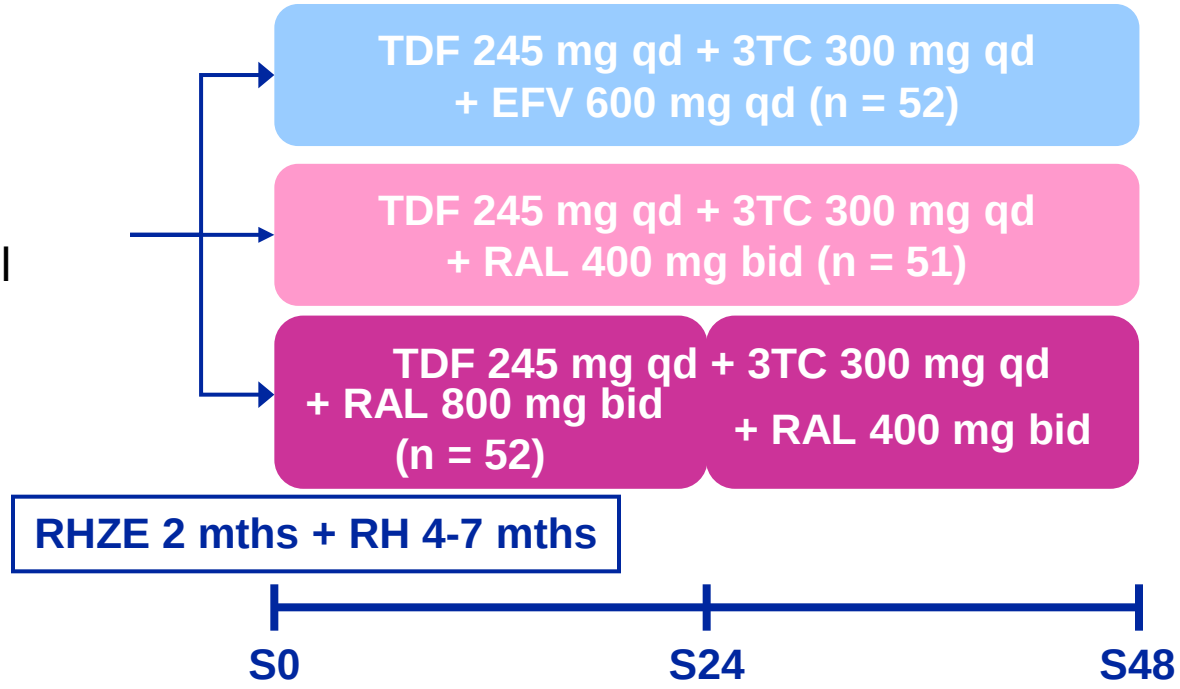
- **In multivariate analyses of baseline factors at Day 8, Q148 + ≥2 mutations and increasing DTG FC were highly correlated with smaller reductions in HIV-1 RNA (*P*<0.0001)**
- **Overall 63% were fully suppressed at week 24 in snapshot analysis**

Castagna A et al., JID 2014

REFLATE TB : RAL 400 or 800 mg bid vs EFV in HIV/TB Co-infected Patients

- **Open-label phase 2, randomized study**

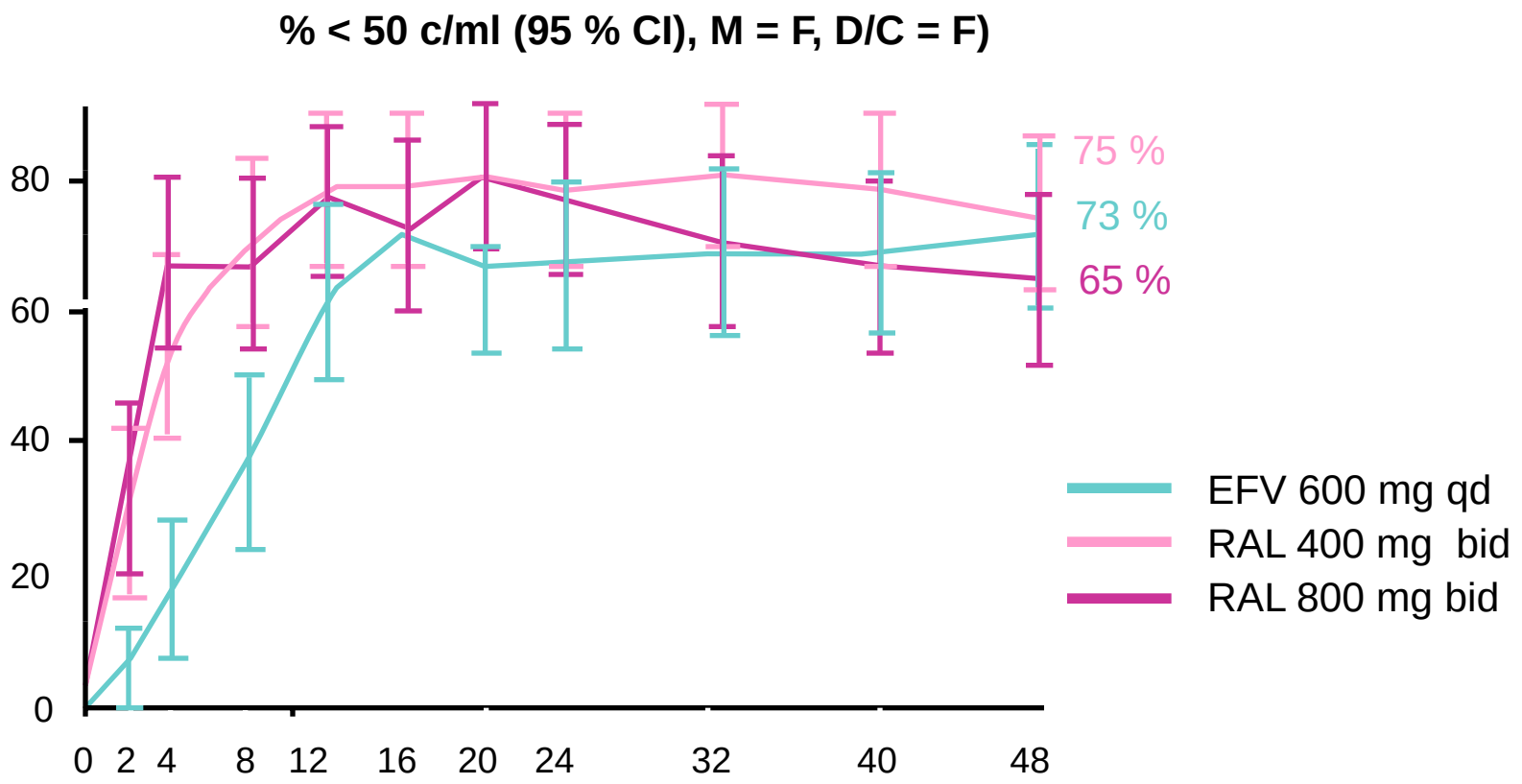
HIV/TB Co-infected
ART naive
No CD4 threshold
HIV RNA > 1 000 c/ml
RFP-based TB Rx
(n=155)



Primary endpoint: HIV RNA levels < 50 cp/ml at week 24 (ITT TLOVR analysis)
Median baseline CD4 cell count : 140 cells/mm3
Median time between TB Rx initiation and ART : 6 weeks

Grinsztejn B, et al Lancet ID 2014

ANRS REFLATE TB Efficacy Outcome Proportion < 50 c/ml at Week 48



- A high rate of virologic success was achieved at W48 with RAL 400 mg bid in combination with TDF + 3TC

Grinsztejn B, et al Lancet ID 2014

ANRS REFLATE TB Safety Results

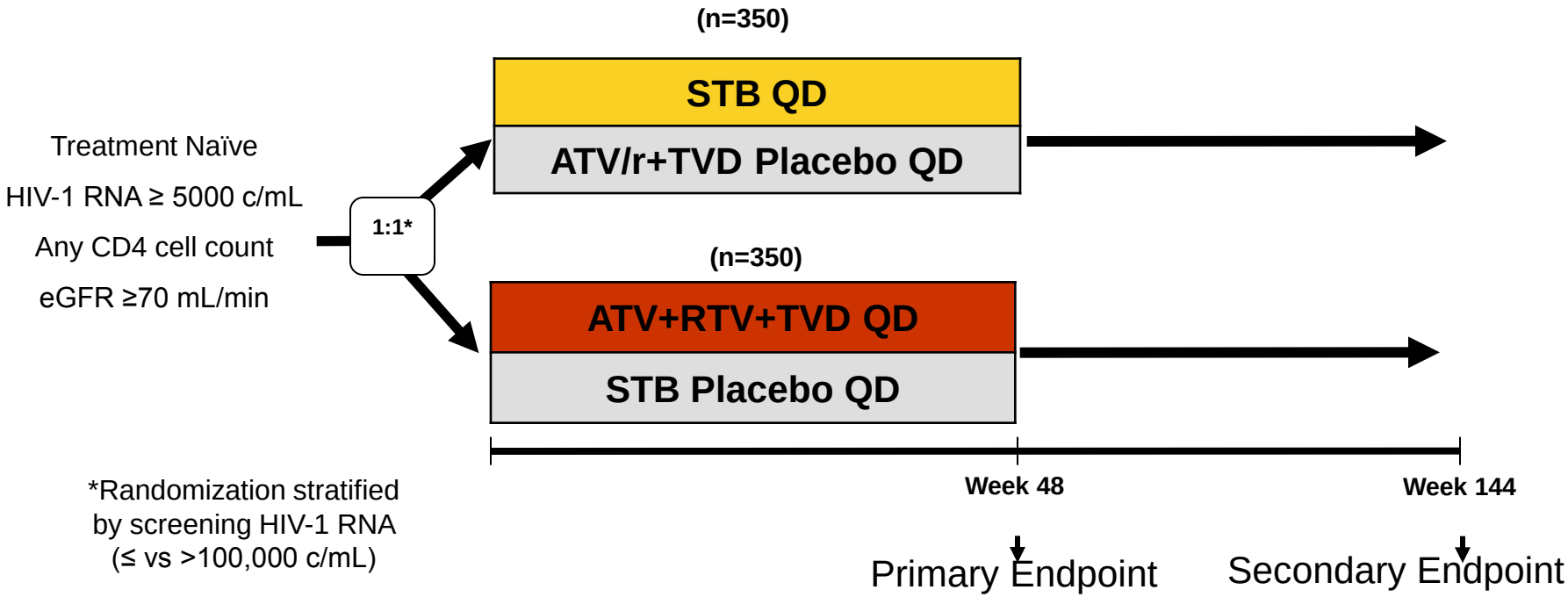
	EFV	RAL 400	RAL 800
	n = 51	n = 51	n = 51
Any AE ≥ grade 3, n (%)	19 (37)	17 (33)	17 (33)
AE leading to drug D/C, n	3	0	3
*Hepatotoxicity**	0	0	2
Cutaneous rash	1	0	1
Gynecomastia	1	0	0
Pregnancy	1	0	0
Grade 3-4 ALT	3	1	1
Death, n (%)	2	1	4

** Both related to TB drugs: fulminant hepatitis with liver transplant in one patient*

Grinsztejn B, et al Lancet ID 2014

Elvitegravir/Cobicistat vs ATV/r in Naive

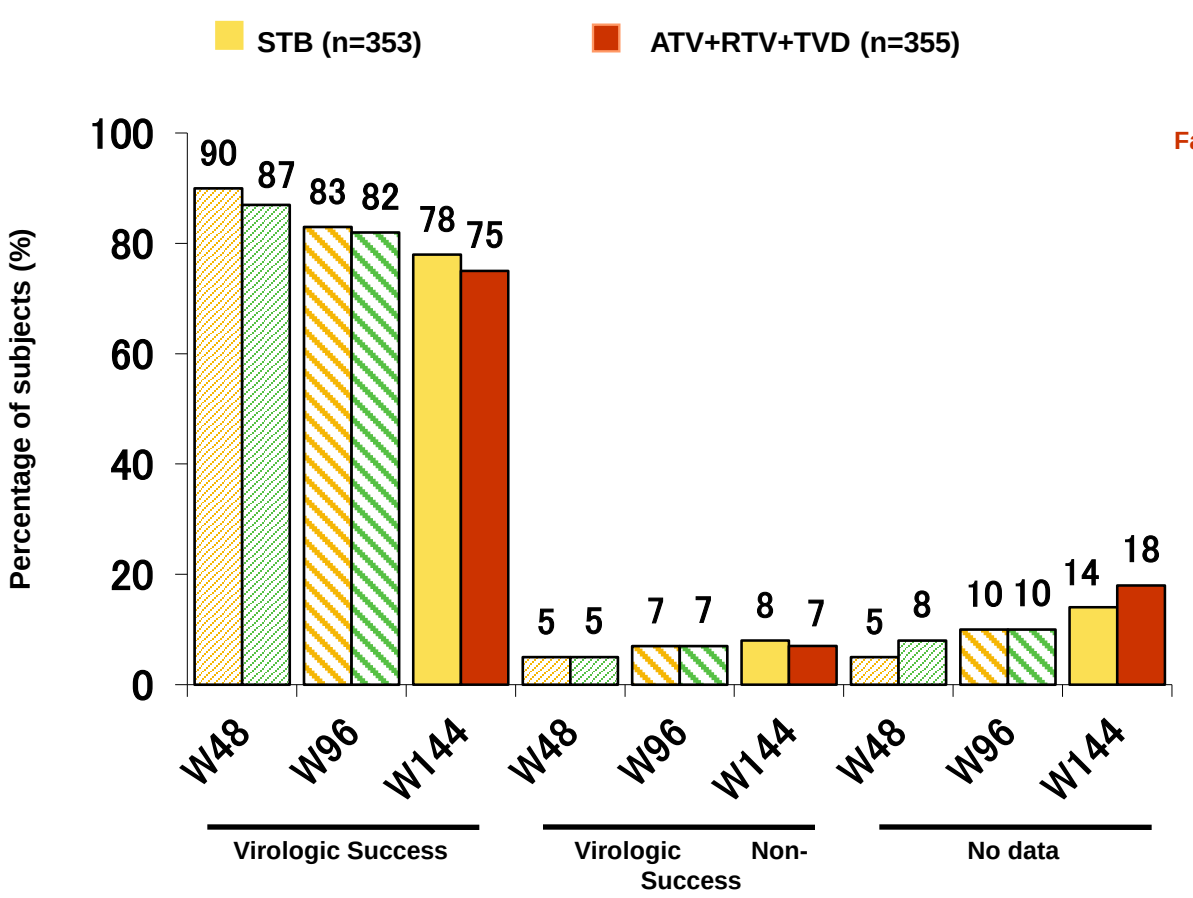
Randomized, double-blind, double dummy, active-controlled, international study

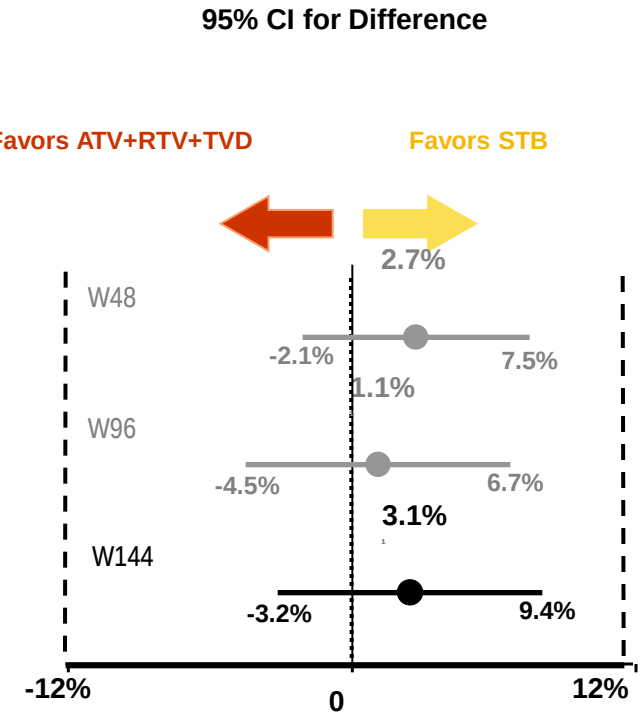


Primary Endpoint: HIV-1 RNA < 50 c/mL by snapshot analysis (ITT)
Non-inferiority margin (Wk48): 12%

Clumeck et al JAIDS 2014

Efficacy Endpoint: HIV-1 RNA <50 c/mL





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Integrase, PI, NRTI Resistance

		STB (n=353)			ATV+RTV+TVD (n=355)	
		W96	W144		W96	W144
Emergent Resistance, n (%)		**6 (1.7%)**	**+2 (+0.6%)**		**0**	**+2 (+0.6%)**
Primary INSTI-R or PI-R, n (%)		**5 (1.4%)**	**+1 (+0.3%)***		0	0
	T66I	1	0	I50L	0	0
	E92Q	2	0	I84V	0	0
	T97A	0	+1	N88S	0	0
	N155H	2	0			
	Q148R	2	0			
Primary NRTI-R, n (%)		**5 (1.4%)**	**+2 (+0.6%)**		**0**	**+2 (+0.6%)**
	M184V/I	5	+2	M184V/I	0	+2
	K65R	1	0	K65R	0	0

Clumeck et al J AIDS 2014

Summary of Adverse Events

	STB (n=353)		ATV+RTV+ TVD (n=355)	
	W96	**W144**	**W96**	**W144**
Any Grade	95%	+2%	97%	+1%
Related to study drug	46%	+1%	60%	+1%
Grade 2 to 4	66%	+4%	71%	+5%
SAE	10%	+5%	14%	+3%
AE leading to study drug DC	4%	+2%	6%	+3%
Death*, (n)	0	0	1% (3)	0

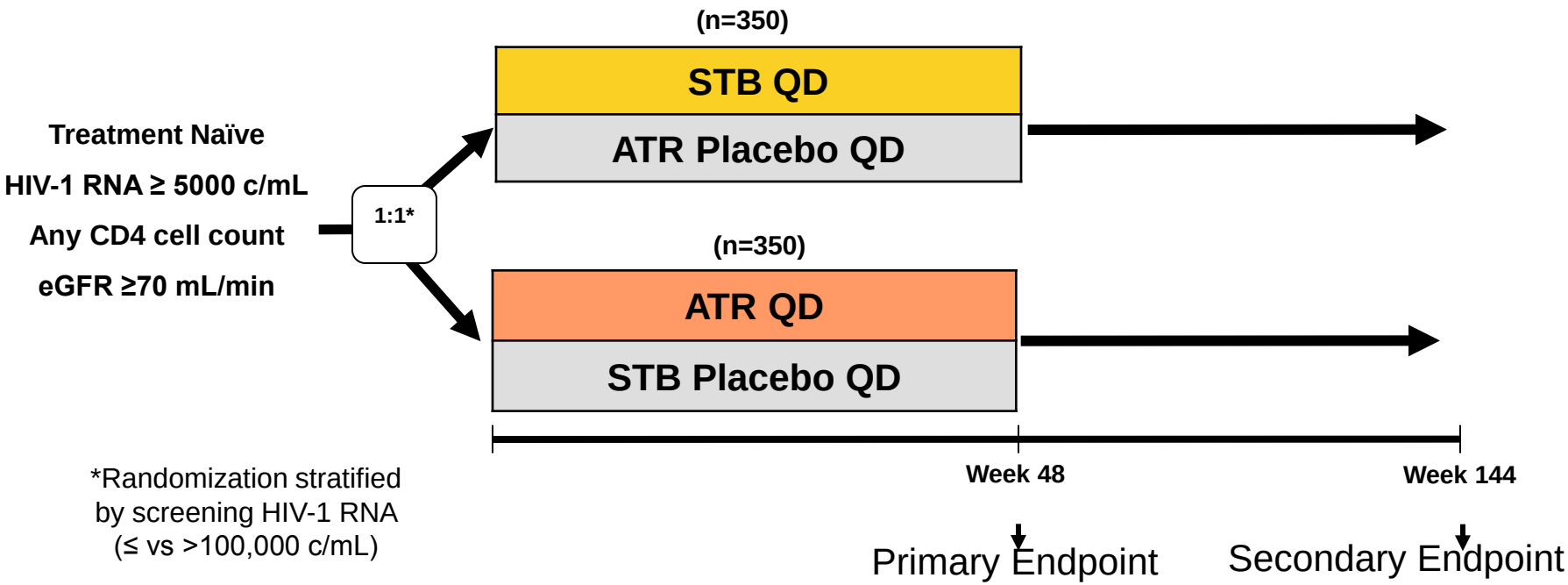
*Causes of death included septic shock, Pneumocystis carinii pneumonia, and cardiopulmonary arrest

3 cases of proximal renal tubulopathy with ATV+RTV+TVD, none with STB with similar rise in creatinine

Clumeck et al J AIDS 2014

Elvitegravir/Cobicistat vs Atripla in Naive

Randomized, double-blind, double dummy, active-controlled study

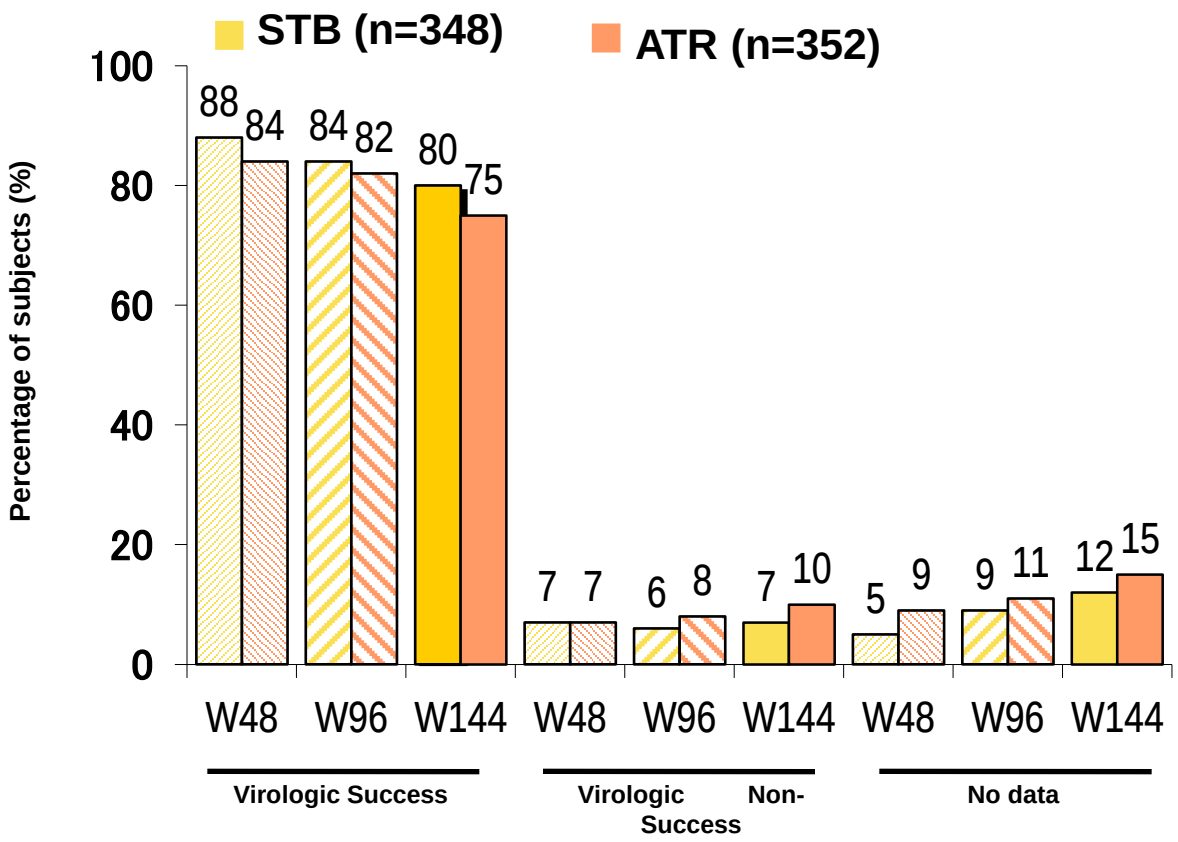


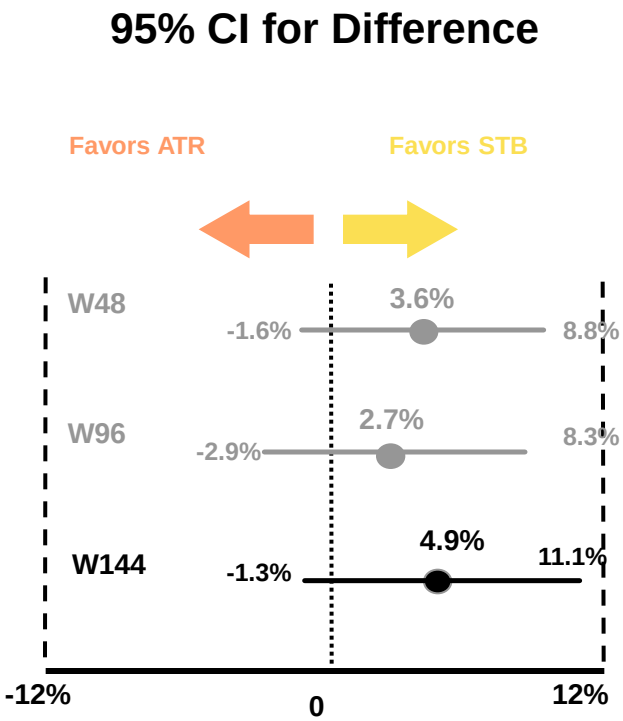
*Randomization stratified by screening HIV-1 RNA (≤ vs >100,000 c/mL)

HIV-1 RNA < 50 c/mL by snapshot analysis (ITT)
Non-inferiority margin (Wk48): 12%

Wohl et al J AIDS 2014

Efficacy Endpoint: HIV-1 RNA <50 c/mL





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Adverse Events Leading to Study Drug DC

	STB (n=348)		ATR (n=352)	
AE Leading to Study Drug DC	**W96**	**W144**	**W96**	**W144**
Renal events	2.0%	+0.3%^	0	0
Depression	0.3%	0	1.1%	+0.3%
Fatigue	0.3%	0	0.6%	0
Abnormal dreams	0	0	0.6%	0
Anxiety	0	0	0.6%	0
Insomnia	0	0	0.6%	0
Rash events and drug hypersensitivity	0	0	1.4%	0

^One STB patient DC after Week 96 due to elevation in Cr
4 cases of proximal renal tubulopathy all before Week 24

Wohl et al J AIDS 2014