4-3-2-1 and Less
Optimising Drug regimens in HIV

Anton Pozniak MD FRCP

Chelsea and Westminster Hospital NHS
NHS Foundation Trust

St Stephen's
AIDS TRUST

Why optimise dosing?

- Less cost
- Less drug to be manufactured and stored
- Less chance of side effects
- Less pills

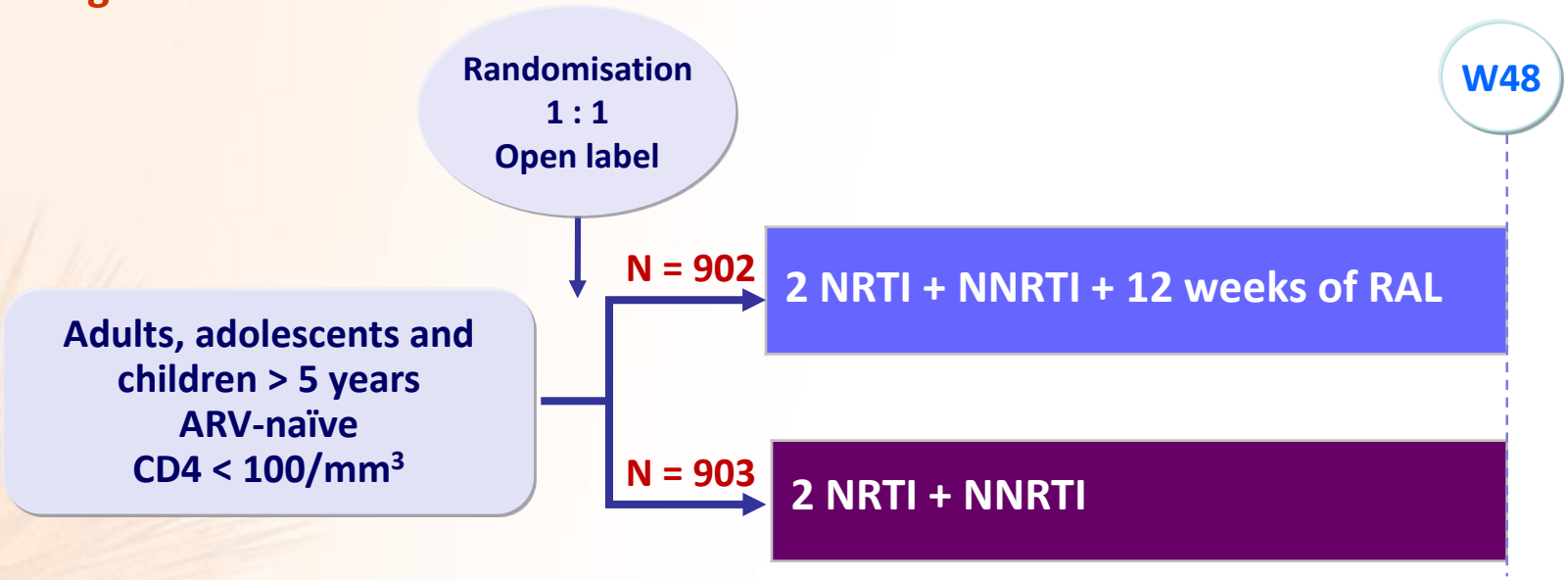
4

What about 4 Drug Therapy in ART Naive

REALITY Study: raltegravir-intensified quadruple therapy in first-line antiretroviral therapy

ARV-trials.com

- **Design**



Two other factorial randomisations: 12 weeks enhanced prophylaxis, 12 weeks supplementary food

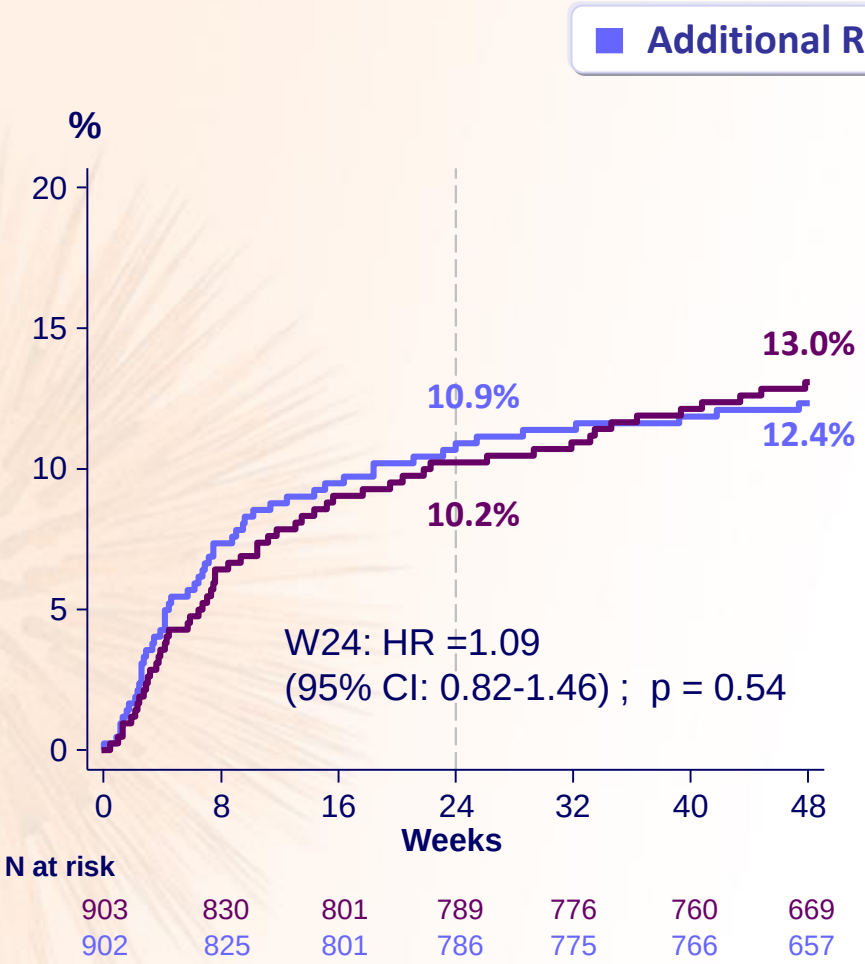
- **Objective**
  - Primary endpoint: 24-week mortality

Kityo C. AIDS 2016, Durban, Abs. FRAB0102LB

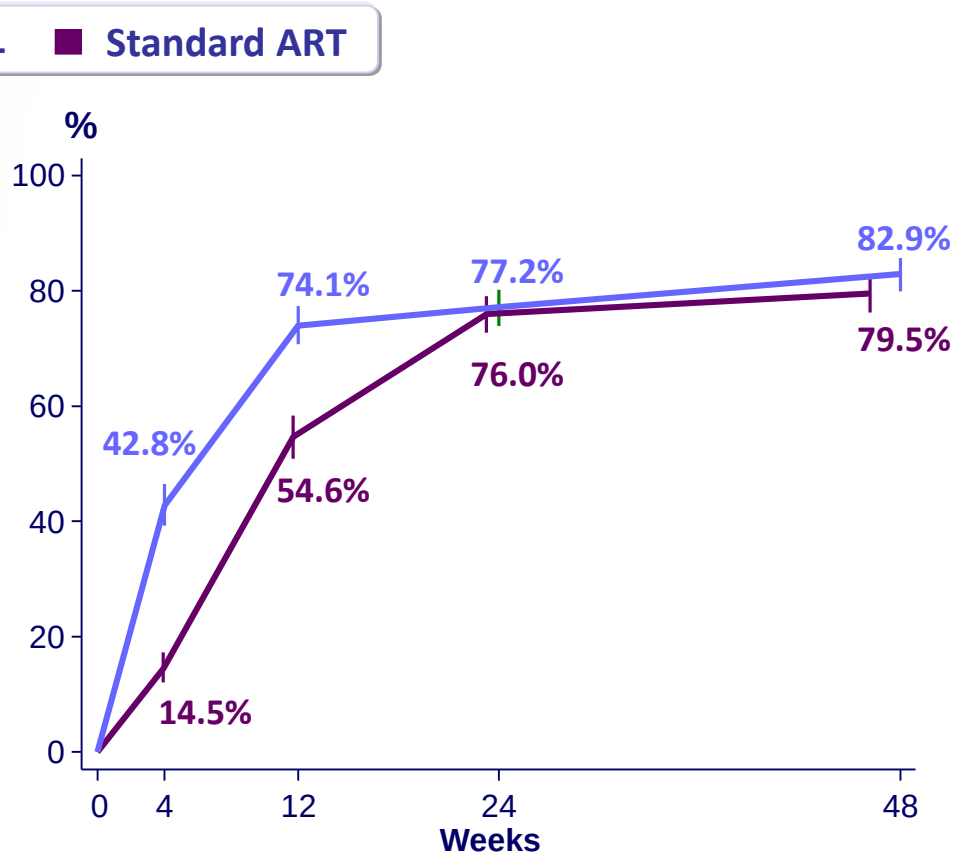
REALITY Study: raltegravir-intensified quadruple therapy in first-line antiretroviral therapy

ARV-trials.com

Mortality



HIV RNA < 50 copies/mL (95% CI)



Mean change in CD4/mm^3 at W48:
+ 163 vs **+ 148** (p = 0.04)

REALITY

Kityo C. AIDS 2016, Durban, Abs. FRAB0102LB

3

3 Drug therapy is Standard of Care in ART Naive

Regimen	EACS	IAS-USA	DHHS
RPV/TDF/FTC	Recommended or use TAF	Alternative	Alternative
DRV/r or/ c + TDF/FTC	Recommended or use TAF	Alternative	Recommended or use TAF
ATV/r + TDF/FTC	Alternative	Alternative	Alternative
EVG/c +TDF/FTC	Recommended or use TAF	Recommended* Use TAF	Recommended or use TAF
RAL + TDF/FTC	Recommended or use TAF	Recommended* Use TAF	Recommended or use TAF
DTG + TDF/3TC	Recommended or use TAF	Recommended* Use TAF	Recommended or use TAF
DTG + ABC/3TC	Recommended	Recommended	Recommended

DHHS ART Guidelines. July 2016. Günthard HF, et al. JAMA. 2016;316:191-210.
EACS ART Guidelines. October 2016.

2

What about the Efficacy of Dual versus Triple therapy – randomised studies

Dual versus Triple therapy – randomised studies

Nuke limiting Strategies

Analysing the efficacy of 2-drug versus 3-drug treatments

PI/r + raltegravir
PI/r + maraviroc
PI/r + NRTI (mainly 3TC)
DTG + 3TC
DTG + RPV
CTV + RPV

7 randomised trials of PI/r + RAL versus PI/r + 2NRTIs HIV RNA <50 copies/mL (switch = failure endpoint)

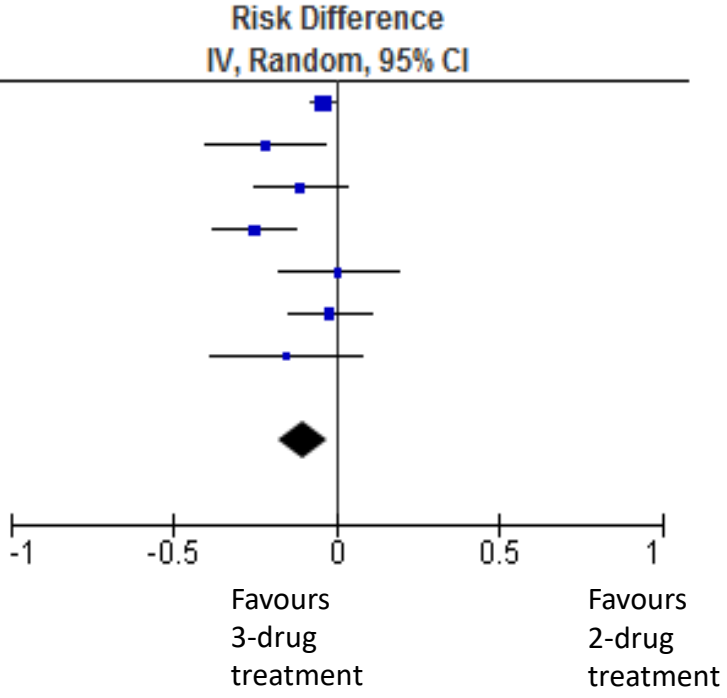
Overall, in 7 randomised trials of 1266 patients, PI/r + raltegravir showed HIV RNA suppression rates 10% lower than PI/r + 2NRTIs (p=0.008).

However there was evidence for heterogeneity between the trials (p=0.03).

	2-drug arm		3-drug arm			Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI
NEAT-001	317	356	348	374	26.4%	-0.04 [-0.08, 0.00]
RADAR	26	42	36	43	10.6%	-0.22 [-0.40, -0.03]
SPARE	24	28	29	30	13.9%	-0.11 [-0.25, 0.04]
HARNESS	50	72	35	37	15.5%	-0.25 [-0.38, -0.12]
BATAR	14	15	13	14	10.5%	0.00 [-0.18, 0.19]
PROGRESS	67	101	72	105	15.7%	-0.02 [-0.15, 0.11]
CCTG 589	17	25	20	24	7.5%	-0.15 [-0.39, 0.08]
Total (95% CI)		**639**		**627**	**100.0%**	**-0.10 [-0.18, -0.03]**
Total events	515		553			

Heterogeneity: Tau² = 0.01; Chi² = 13.98, df = 6 (P = 0.03); I² = 57%

Test for overall effect: Z = 2.67 (P = 0.008)



Has PI/r plus integrase a role in Treatment experience ?

EARNEST and SECOND-LINE studies

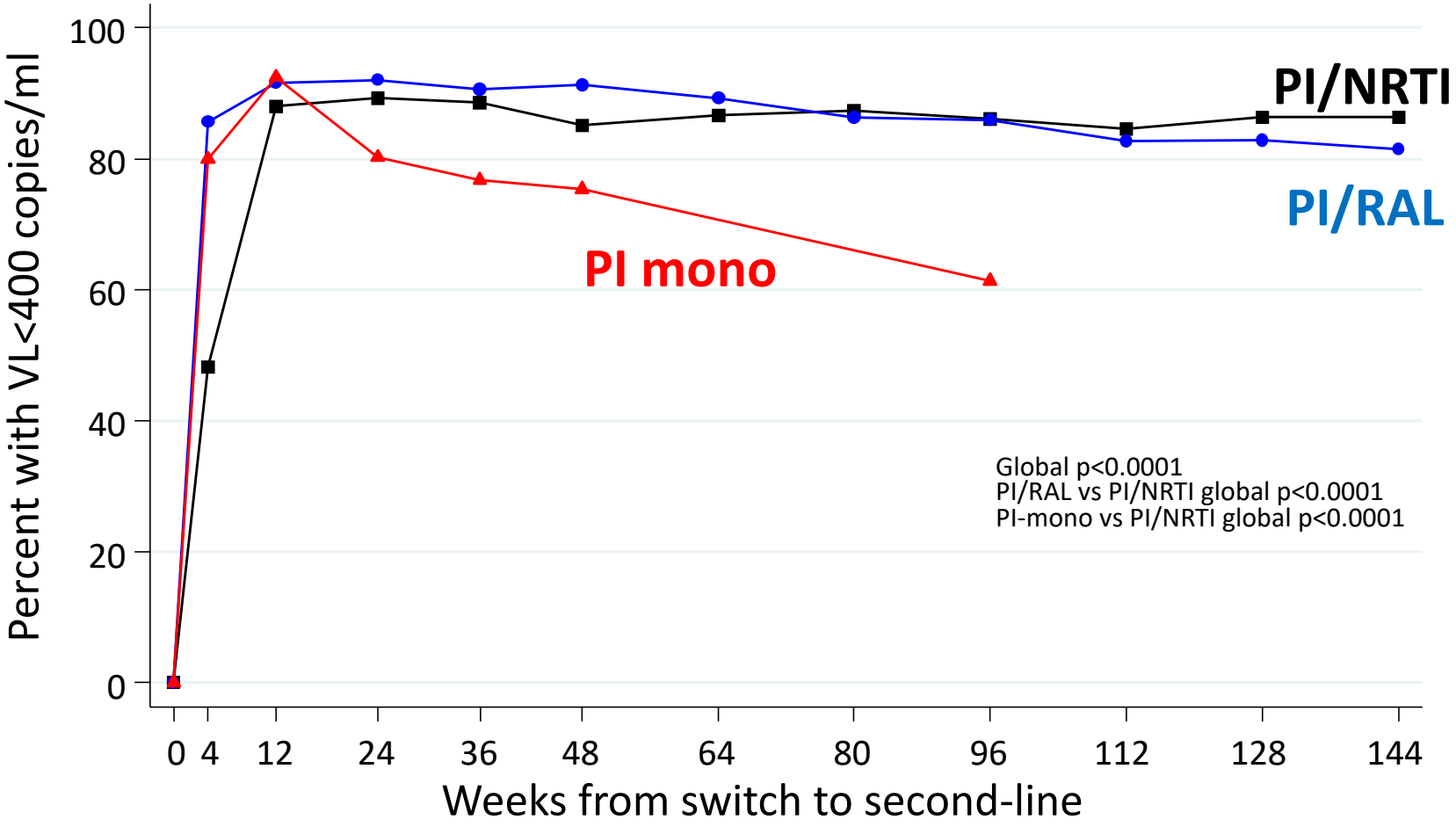
In treatment-experienced patients, RAL+LPV/r was non-inferior to 2NRTI+LPV/r

No efficacy advantage

No significant difference in number of Grade 3 or 4 adverse events

Costs of RAL+LPV/r significantly higher than 2NRTI+LPV/r in most countries

VL responses by randomized arm



Week 96 outcomes: Paton, NEJM 2014; 371; 234-47; Week 144 outcomes: Hakim, Poster 552, CROI 2015

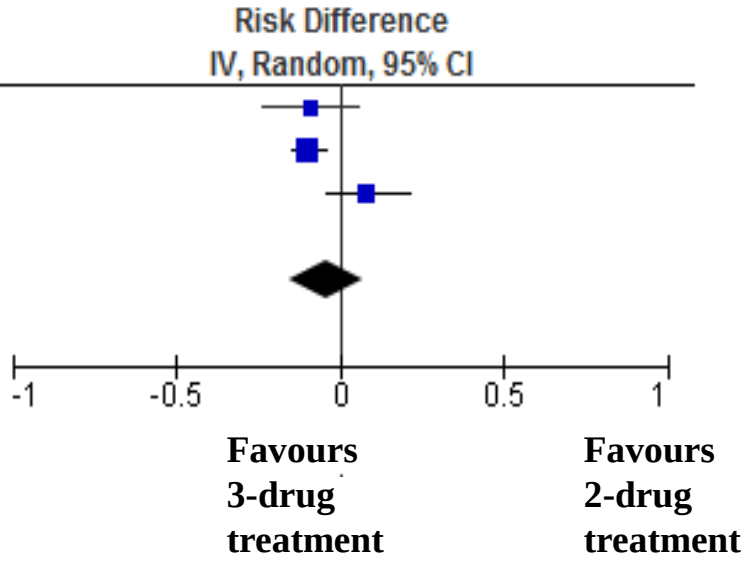
3 randomised trials of PI/r + maraviroc versus PI/r + 2NRTIs HIV RNA <50 copies/mL (switch = failure endpoint)

Overall, in 3 randomised trials of 967 patients, PI/r + maraviroc showed HIV RNA suppression rates 4% lower than PI/r + 2NRTIs.

This difference was outside the limits for non-inferiority (lower 95% confidence interval -15%)
There was evidence for heterogeneity between the trials (p=0.04).

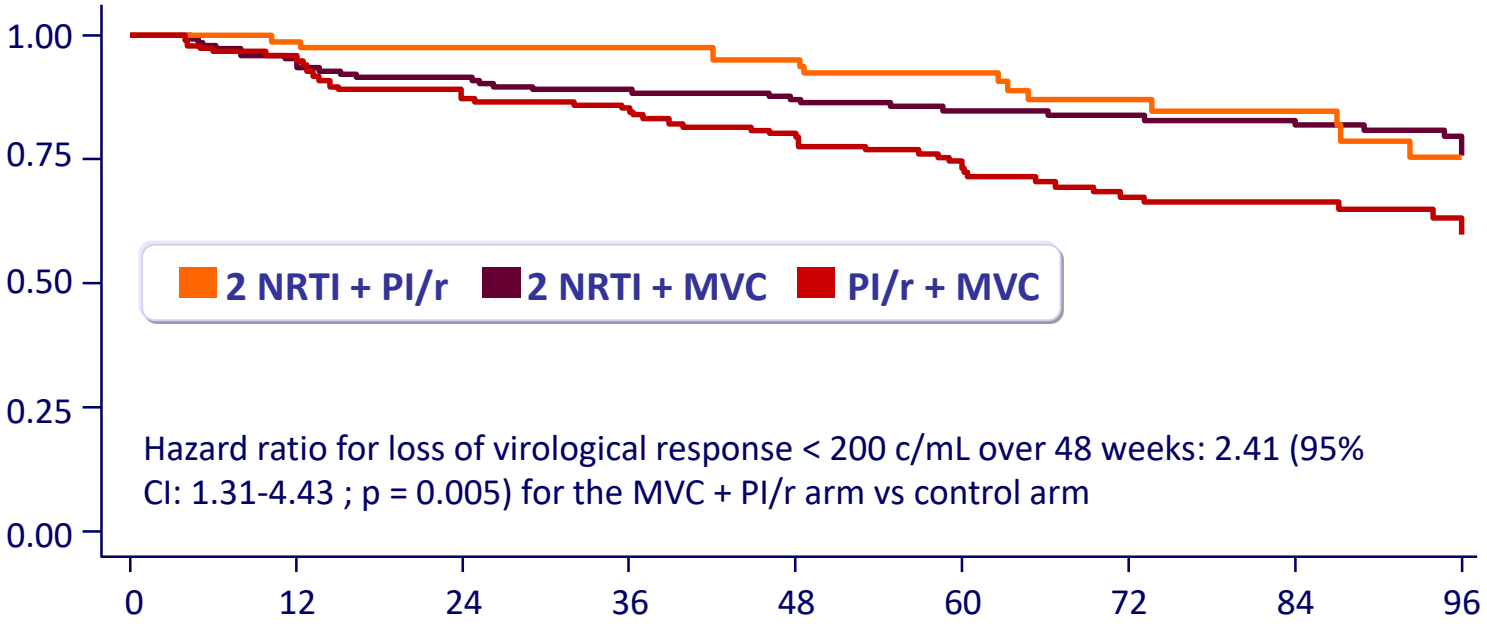
	2-drug arm		3-drug arm			Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI
A4001078	44	59	51	61	26.7%	-0.09 [-0.24, 0.05]
MODERN	306	396	349	401	43.7%	-0.10 [-0.15, -0.04]
Nozza et al.	26	26	22	24	29.6%	0.08 [-0.04, 0.21]
Total (95% CI)		**481**		**486**	**100.0%**	**-0.04 [-0.15, 0.07]**
Total events	376		422			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.61$, df = 2 (P = 0.04); $I^2 = 70\%$
Test for overall effect: Z = 0.74 (P = 0.46)



PI plus MVC
MARCH Study: switch to MVC

% with virologic response (HIV RNA < 200 c/mL), by week



Number at risk

2 NRTI + PI/r	82	81	80	80	77	59	45	36	17
2 NRTI + MVC	156	149	143	139	132	103	90	86	60
PI/r + MVC	157	151	137	134	123	98	65	54	36

MARCH

Pett SL. Clin Infect Dis 2016;63:122-32

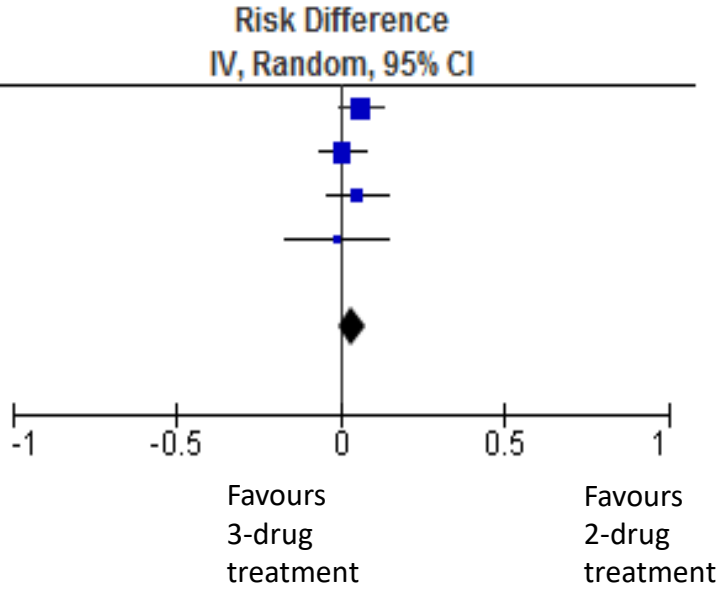
4 randomised trials of PI/r + NRTI versus PI/r + 2NRTIs HIV RNA <50 copies/mL (switch = failure endpoint)

Overall, in 4 randomised trials of 1090 patients, PI/r + 3TC showed HIV RNA suppression rates 4% higher than PI/r + 2NRTIs

This difference was within the limits for non-inferiority (lower 95% confidence interval -1%)
There was no evidence for heterogeneity between the trials (p=0.10).

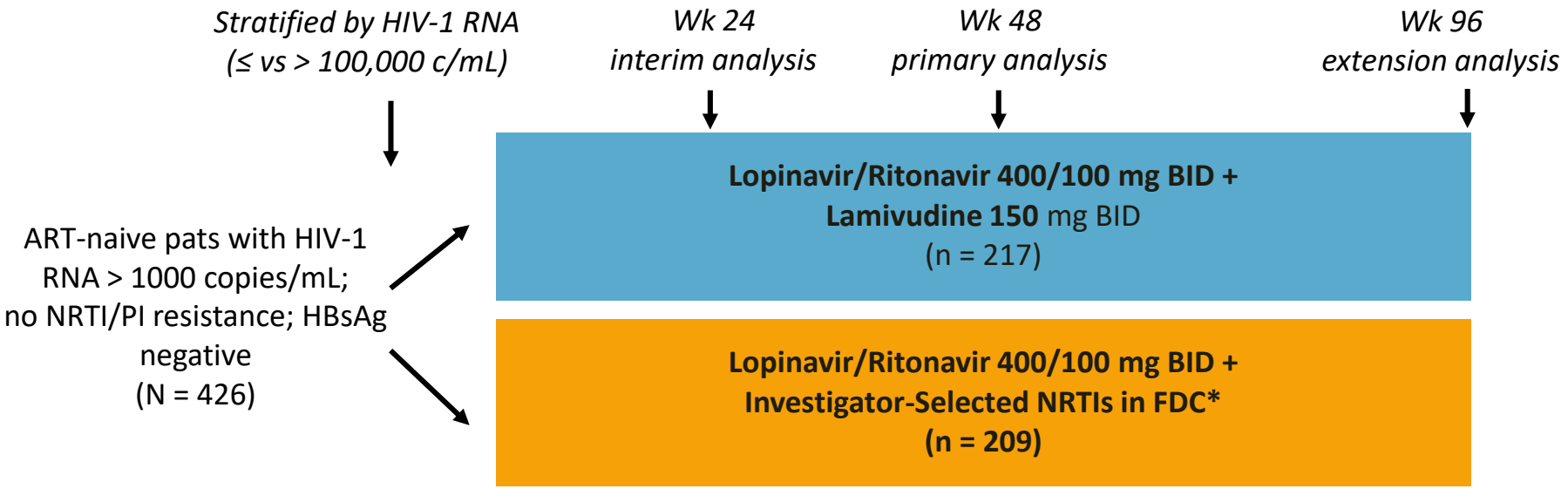
	2-drug arm		3-drug arm			Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI
GARDEL	189	217	169	209	37.2%	0.06 [-0.01, 0.13]
Ole	108	118	110	121	34.9%	0.01 [-0.07, 0.08]
SALT	112	134	109	139	20.9%	0.05 [-0.04, 0.14]
KALEAD	37	72	42	80	7.1%	-0.01 [-0.17, 0.15]
Total (95% CI)		**541**		**549**	**100.0%**	**0.04 [-0.01, 0.08]**
Total events	446		430			

Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 3 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.63 (P = 0.10)



2 Drugs in Naïve
GARDEL: Dual ART With LPV/RTV + 3TC vs Triple ART With LPV/RTV + 2 NRTIs

- Randomized, open-label phase III noninferiority trial
  - Primary endpoint: HIV-1 RNA < 50 c/mL (ITT-e, FDA snapshot analysis)
- Pts with virologic response at Wk 48 offered extension to Wk 96

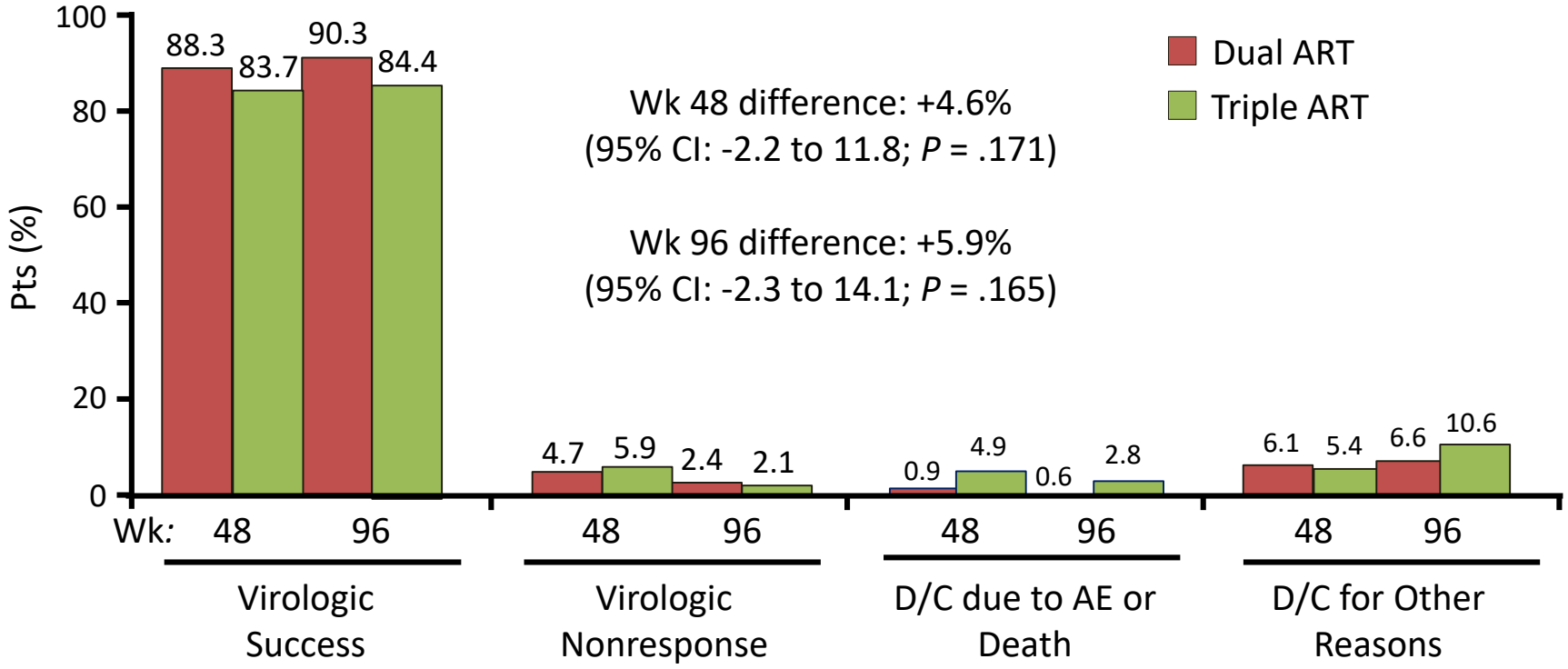


*ZDV/3TC: 54%; TDF/FTC: 37%; ABC/3TC: 9%

Cahn P, et al. EACS 2015. Abstract 961.

GARDEL: Dual ART Noninferior to Triple ART at Wk 48 and Wk 96

- Safety and tolerability also similar between treatment arms

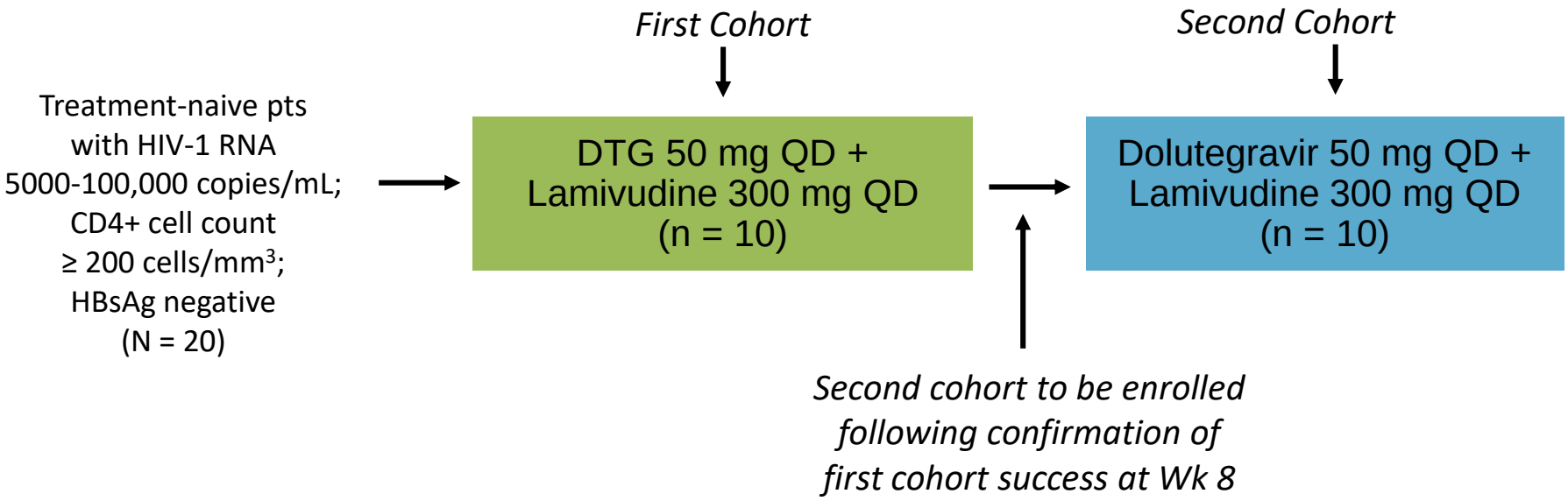


Cahn P, et al. EACS 2015. Abstract 961.

Lets treat an Integrase like a boosted PI!

PADDLE: Dolutegravir + Lamivudine in Treatment-Naive Pts

- Open-label, single-arm phase IV exploratory trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (ITT-e, FDA snapshot analysis)



Figueroa MI, et al. EACS 2015. Abstract 1066.

PADDLE Study: Efficacy-DTG and 3TC in Naïve patients

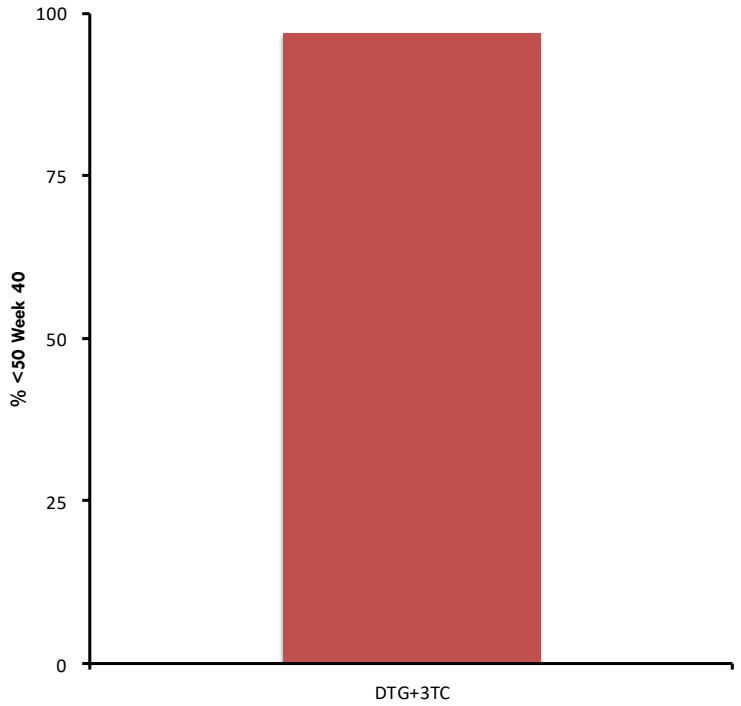
#	SCR	BSL	DAY 4	DAY 7	W.2	W.3	W.4	W.6	W.8	W.12	W.24	W.36	W.48
1	5.584	10.909	383	101	<50	<50	<50	<50	<50	<50	<50	<50	<50
2	8.887	10.233	318	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50
3	67.335	151.569	1.565	1.178	97	53	<50	<50	<50	<50	<50	<50	<50
4	99.291	148.370	3.303	432	178	55	<50	<50	<50	<50	<50	<50	<50
5	34.362	20.544	1.292	570	107	<50	<50	<50	<50	<50	<50	<50	<50
6	16.024	14.499	1.634	162	<50	<50	<50	<50	<50	<50	<50	<50	<50
7	37.604	18.597	819	61	<50	<50	<50	<50	<50	<50	<50	<50	<50
8	25.071	24.368	1.377	Not done	105	<50	<50	<50	<50	<50	<50	<50	<50
9	14.707	10.832	516	202	<50	<50	<50	<50	<50	<50	<50	SAE	
10	10.679	7.987	318	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50
11	50.089	273.676	68.129	3.880	784	290	288	147	<50	<50	<50	<50	<50
12	13.508	64.103	3.296	135	351	84	67	<50	<50	<50	<50	<50	<50
13	28.093	33.829	26.343	539	61	<50	<50	<50	<50	<50	<50	<50	<50
14	15.348	15.151	791	198	<50	61	64	<50	<50	<50	<50	<50	<50
15	23.185	23.500	4.217	192	<50	<50	<50	Not done	<50	<50	<50	<50	<50
16	11.377	3.910	97	143	<50	<50	<50	<50	<50	<50	<50	<50	<50
17	39.100	25.828	1.970	460	52	<50	<50	<50	<50	<50	<50	<50	<50
18	60.771	73.069	2.174	692	156	<50	<50	<50	<50	<50	<50	<50	<50
19	82.803	106.320	2.902	897	168	76	<50	<50	<50	<50	<50	PDVF	
20	5.190	7.368	147	56	<50	<50	<50	<50	<50	<50	<50	<50	<50

SAE = serious adverse event

PDVF = protocol defined virologic failure

Cahn P, et al. AIDS 2016; Durban, South Africa; July 18-22, 2016; Abst. FARB0104LB.

ANRS 167 LamiDol Study DTG/3TC Maintenance



- 110 Subjects
- No Hx of failure, No Hep B
- 8 week Switch to 2NRTI+DTG
- Then to DTG/3TC-40 Weeks FU

- 97% (101/104) pts maintained therapeutic success through 40 wks of dual therapy (study Wk 48)[1]
  - No INSTI resistance in 3 pts with virologic failure
  - 7 pts with serious AEs, only 2 related to dual therapy

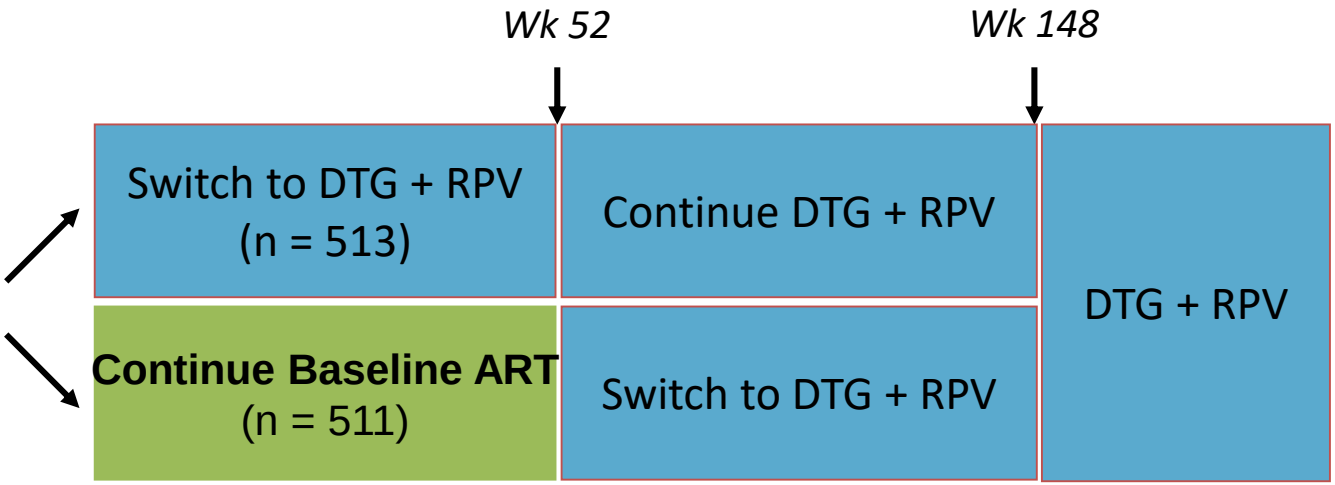
Joly V, et al. 24th CROI; Seattle, WA; February 13-16, 2017. Abst. 458.

Switch to 2 drugs
-do we need nukes?

SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV Dual Therapy

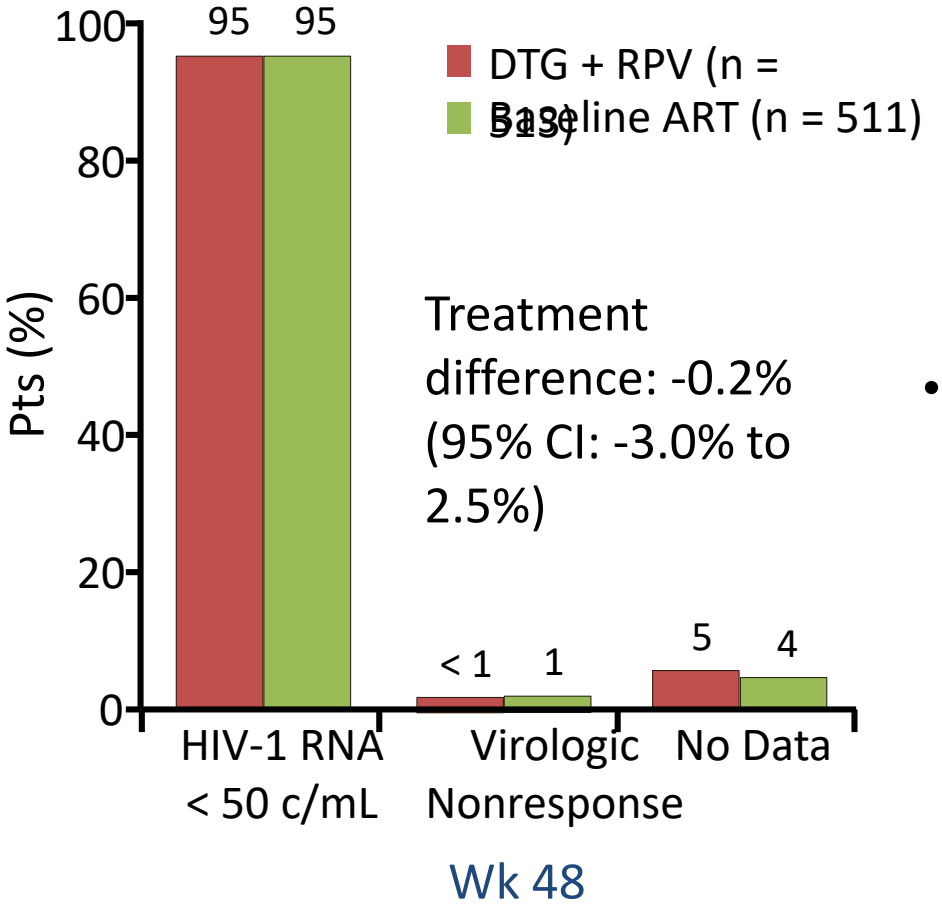
- Randomized, open-label, multicenter phase III trials
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (ITT-E snapshot
- 70% to 73% of pts receiving TDF at baseline

HIV-infected pts with HIV-1 RNA < 50 c/mL for ≥ 12 mos while receiving first-line or second-line ART with 2 NRTIs + INSTI, NNRTI, or PI; no previous VF; HBV negative (N = 1024)



Llibre JM, et al. CROI 2017. Abstract 44LB.

Switch From Suppressive ART to DTG + RPV Noninferior to Continued Baseline ART at Wk 48



- 1 pt with confirmed criteria for virologic withdrawal at Wk 36 in DTG + RPV arm had K101K/E (1.2-fold RPV change)
  - Resuppressed with continued DTG + RPV
  - No INSTI resistance
- AE rates generally similar between treatment arms through Wk 52
  - Numerically higher rate of drug-related grade 1/2 AEs with switch: 17% vs 2%
  - Numerically higher rate of withdrawal for AEs with switch: 4% vs < 1%

Llibre JM, et al. CROI 2017. Abstract 44LB.

Switch to DTG + RPV in Suppressed Pts With Multiple Previous Treatment Failures

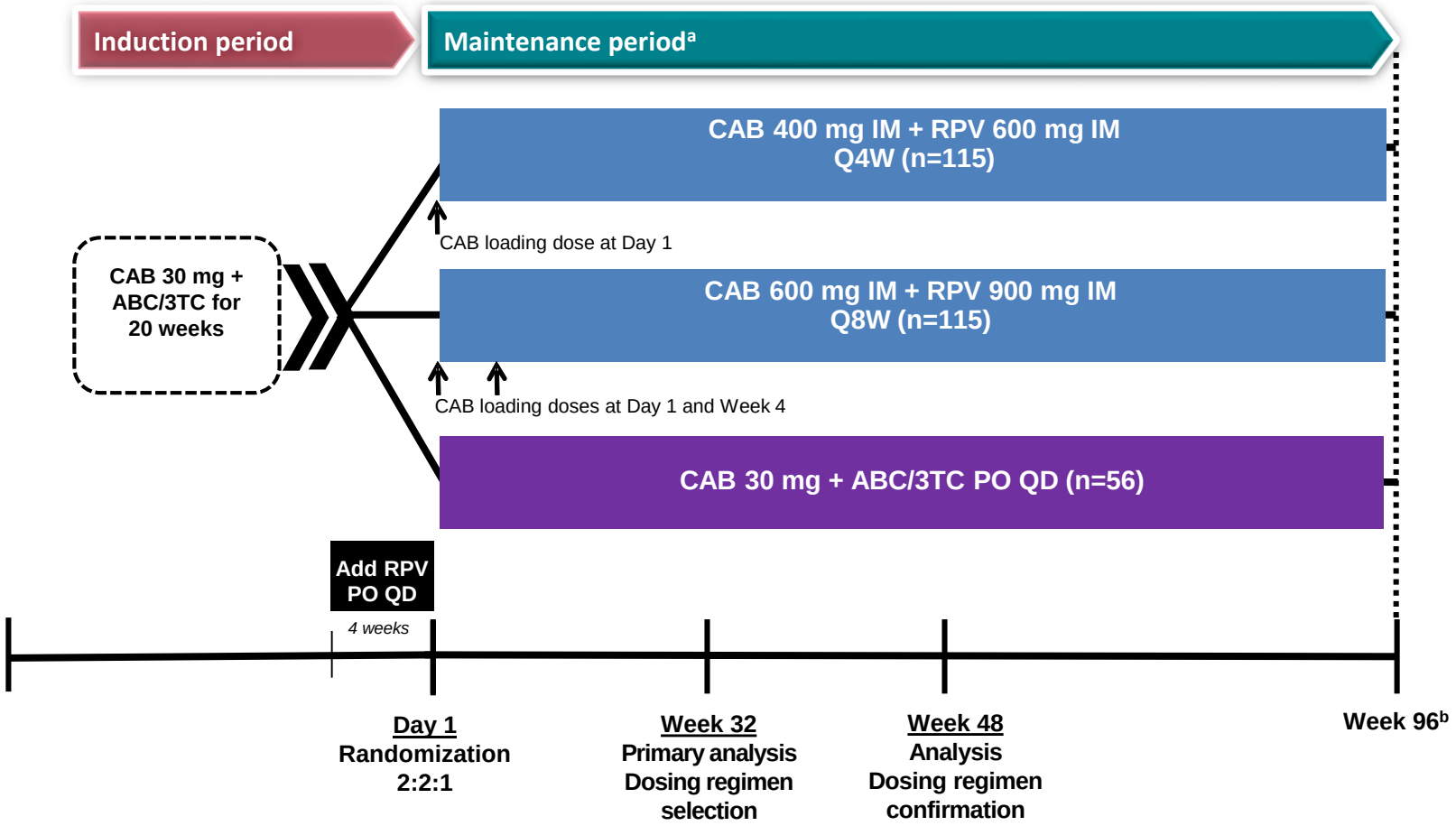
- Open-label cohort study based in clinical practice setting (N = 38)
  - DTG 50 mg/day + RPV 25 mg/day for pts with long-term virologic suppression but virologic failure on > 1 previous ART regimens

Baseline Characteristic , %	Switch to DTG + RPV (N = 38)	
Regimen at time of switch	▪ NRTI + NNRTI + PI	85
	▪ NRTI + NNRTI + PI + INSTI	53
Reasons for switch to DTG + RPV	▪ Drug–drug interaction	38
	▪ Toxicity	33
	▪ Simplification	25
Pre-existing resistance mutations	▪ NRTI: 65; NNRTI: 37; PI: 32; INSTI: NA	

- HIV-1 RNA suppressed to < 35 copies/mL in 92% (35/38) at Wk 48
  - No virologic failures; 3 pts d/c (GI toxicity, DDI, physician decision, n = 1)
- DTG + RPV associated with improved liver function tests, improved lipid profile, and stable kidney function at Wk 48

Díaz A, et al. AIDS 2016. Abstract TUPDB0106.

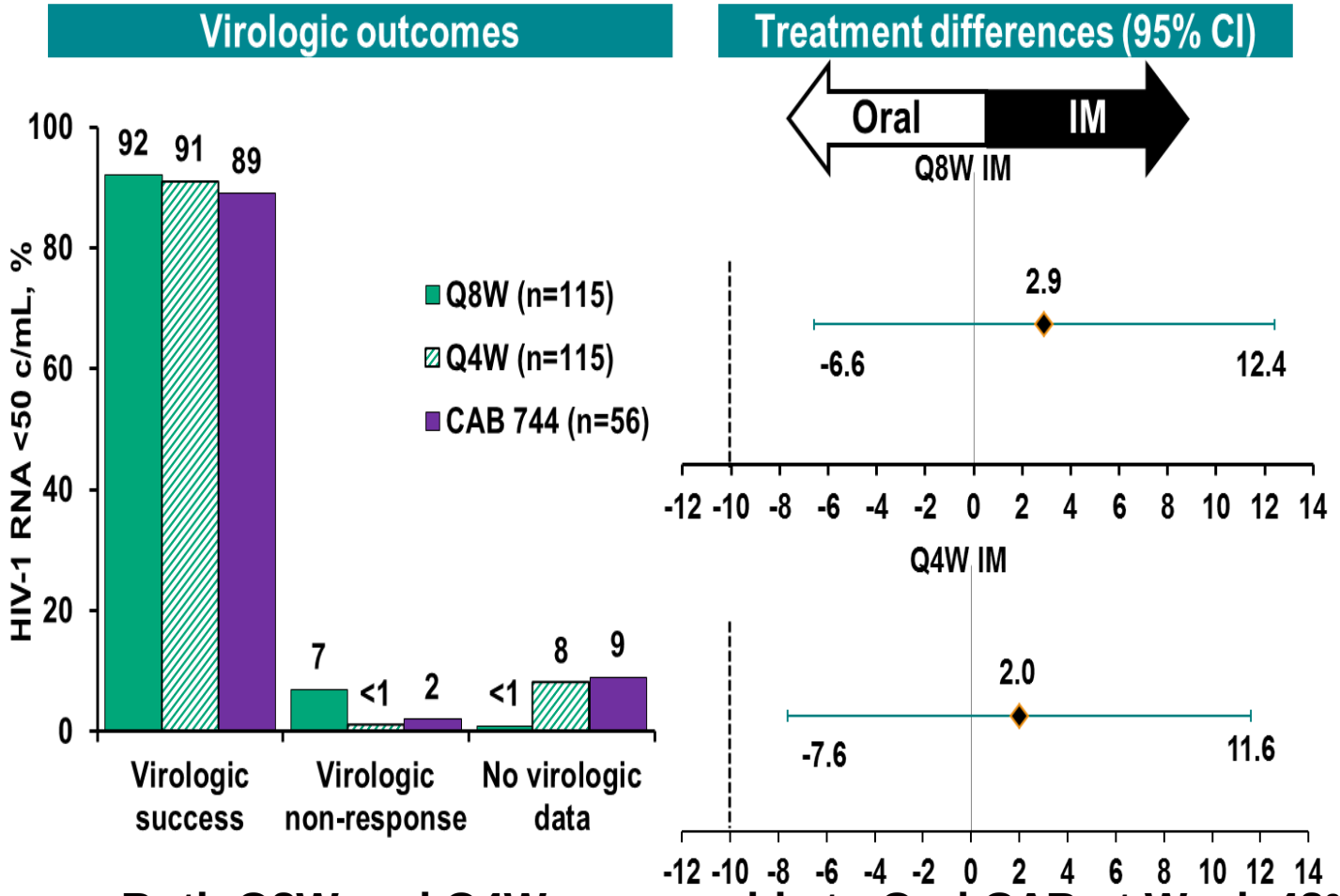
Switch to Long acting Injectables
LATTE-2



ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; QD, once daily; Q4W, every 4 weeks; Q8W, every 8 weeks; ULN, upper limit of normal. [a]Subjects who withdrew after at least 1 IM dose entered the long-term follow-up period. [b]Subjects can elect to enter Q4W and Q8W LA Extension Phase beyond Week 96.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

HIV-1 RNA <50 c/mL at Week 48: ITT-ME (Snapshot)



Both Q8W and Q4W comparable to Oral CAB at Week 48[a]

[a]Met prespecified threshold for concluding IM regimen is comparable to oral regimen (Bayesian Posterior Probability >90% that true IM response rate is no worse than -10% compared to the oral regimen). Observed Bayesian Probabilities: Q8W vs Oral = 99.7%; Q4W vs Oral = 99.4%.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

Protocol-Defined Virologic Failure (PDVF)

Maintenance period[a]	Q8W IM (n=115)	Q4W IM (n=115)	Oral CAB (n=56)
Subjects with PDVF	2 (1%)[b]	0	1 (2%)
INI-r mutations	1[c]	0	0
NRTI-r mutations	0	0	0
NNRTI-r mutations	1[c]	0	0

- NNRTI—**K103N, E138G, and K238T** (FC RPV=3.3; Etravirine=1.9); INI—**Q148R** (FC CAB=5.1; Dolutegravir=1.38)[c]
- No additional PDVFs beyond W48 on any arm (all subjects through W72)[d]

PDVF: <1.0 $\log_{10}$ c/mL decrease in plasma HIV-1 RNA by Week 4, OR confirmed HIV-1 RNA ≥200 c/mL after prior suppression to <200 c/mL, OR >0.5 $\log_{10}$ c/mL increase from nadir HIV-1 RNA value ≥200 c/mL. [a]One additional PDVF without treatment-emergent resistance occurred during oral Induction Period due to oral medication non-adherence. [b]One PDVF at Week 4: no detectable RPV at Week 4 and Week 8, suggesting maladministration. [c]One PDVF at Week 48 at HIV-1 RNA 463 c/mL (confirmed at 205 c/mL). [d]Contains data beyond W48.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

2 drugs

Health Warning!

Not in Hepatitis B co-infected

? Pregnancy

?TB

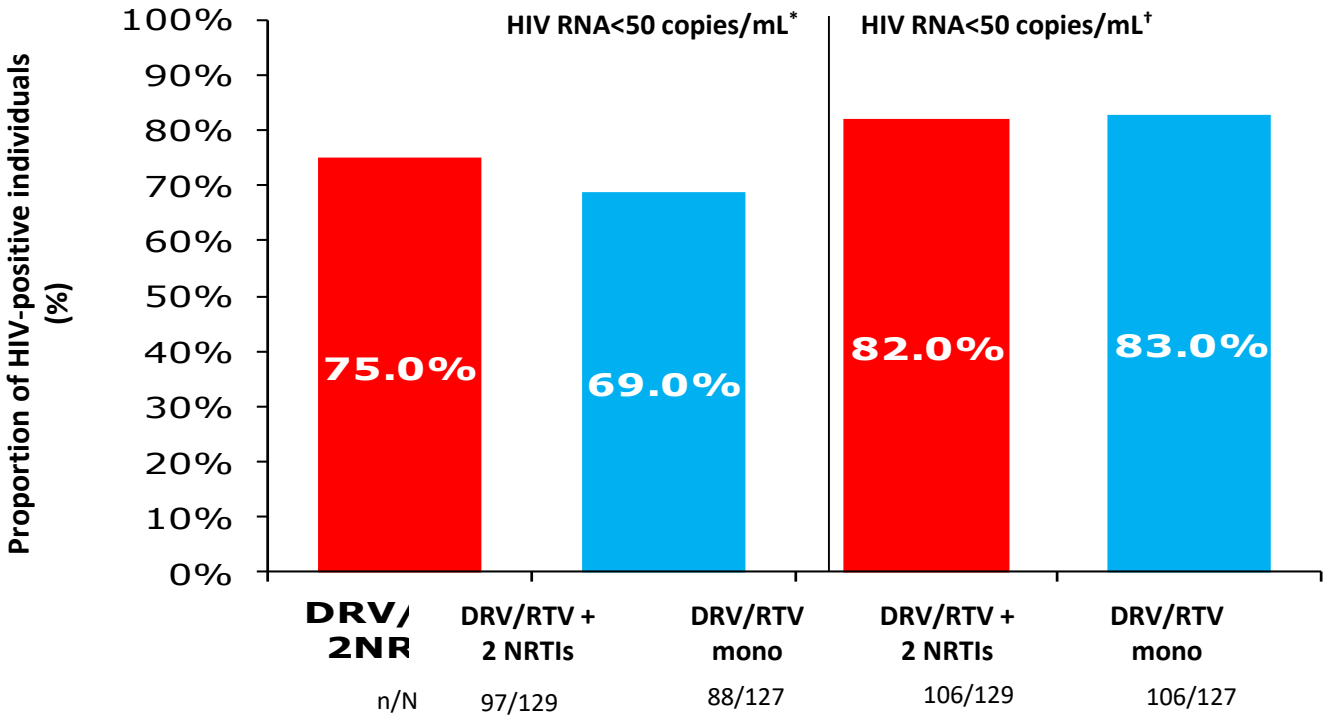
1

PI monotherapy

MONET: Switch to DRV/RTV vs DRV/RTV + 2 NRTIs

Primary endpoint: HIV-1 RNA<50 copies/mL

Proportion of subjects with HIV-1 RNA<50copies/mL by Week 144



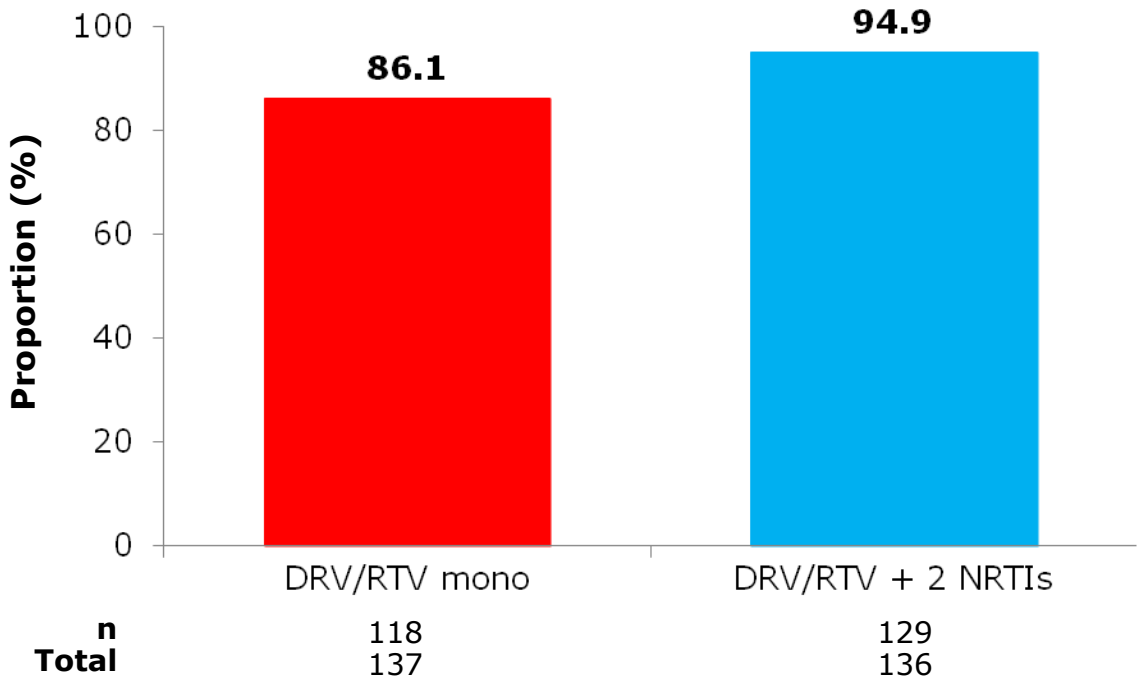
- **For patients with HIV RNA < 50 mL/min at baseline, switching to DRV/RTV monotherapy did not show noninferior efficacy to DRV/RTV plus two NRTIs in an ITT/TLOVR analysis, but not in a strict ITT analysis (switches not considered failures)**

* Intent to treat (ITT), TLOVR, switch = failure method; † strict ITT analysis (switches not considered failures)
DRV, darunavir; ITT, intent–to-treat; NRTI, nucleoside reverse transcriptase inhibitors; RTV, ritonavir
Arribas et al, HIV Medicine 2012;13:398–405

PROTEA: Switch to DRV/RTV or DRV/RTV + 2 N(t)RTIs

Primary endpoint: HIV-1 RNA<50 copies/mL

Proportion of subjects in ITT population with HIV-1 RNA<50copies/mL by Week 48

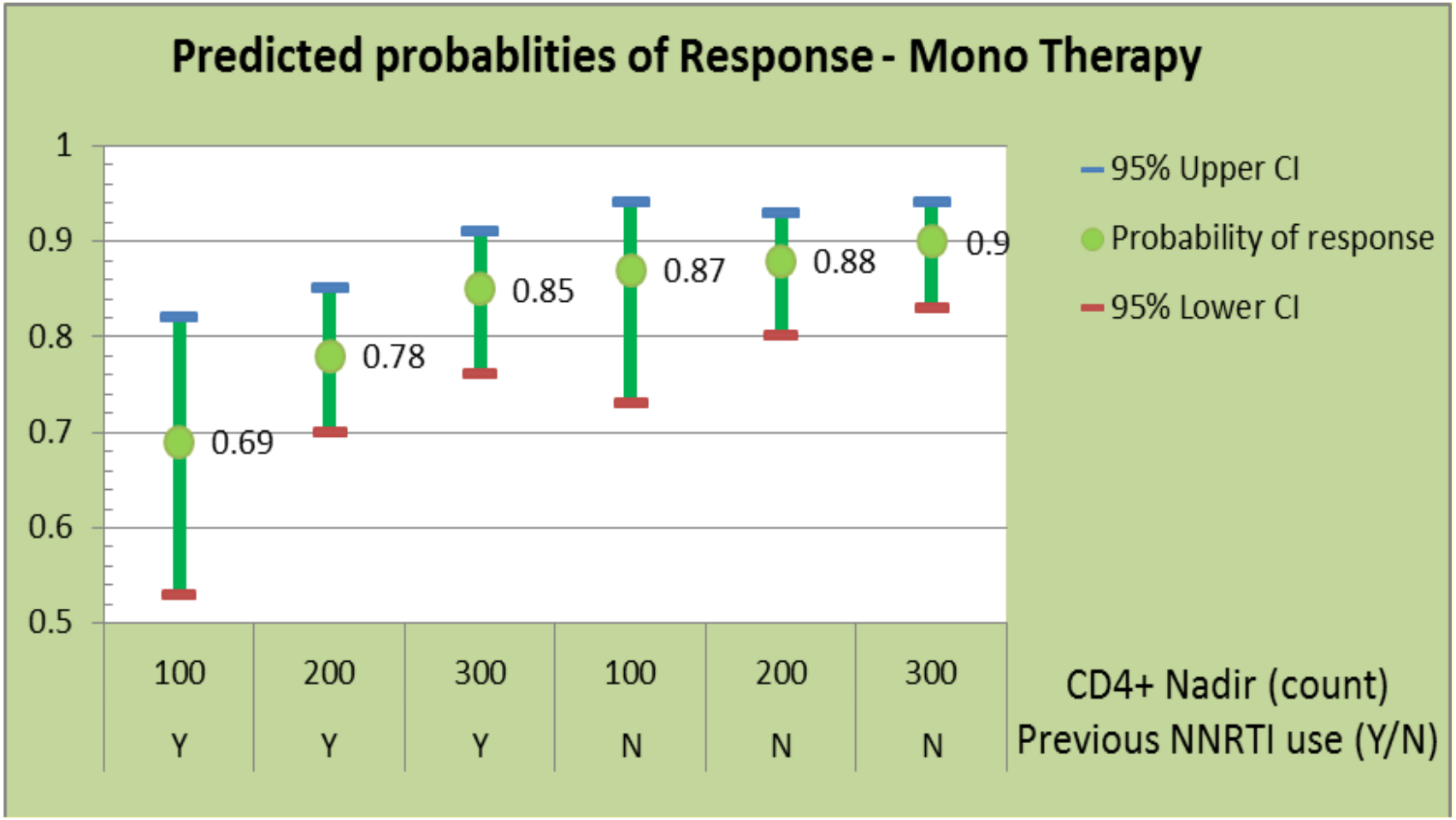


- **Switching to DRV/RTV monotherapy showed lower efficacy vs triple antiretroviral therapy at Week 48 in the primary switch equals failure analysis (difference -8.8%, 95% CI: −15.5 to −1.8)**
- **There was no evidence of PI resistance**

CI, confidence interval; DRV, darunavir; ITT, intent–to-treat; N(t)RTI, nucleo(t)side reverse transcriptase inhibitor; PI, protease inhibitor; RTV, ritonavir

Antinori A et al. HIV12 2014; Glasgow, Scotland. #O423A

PI Monotherapy- predictors of response



Ripamonti et al CROI 2015 poster 551

INSTI monotherapy

Methods DOMONO

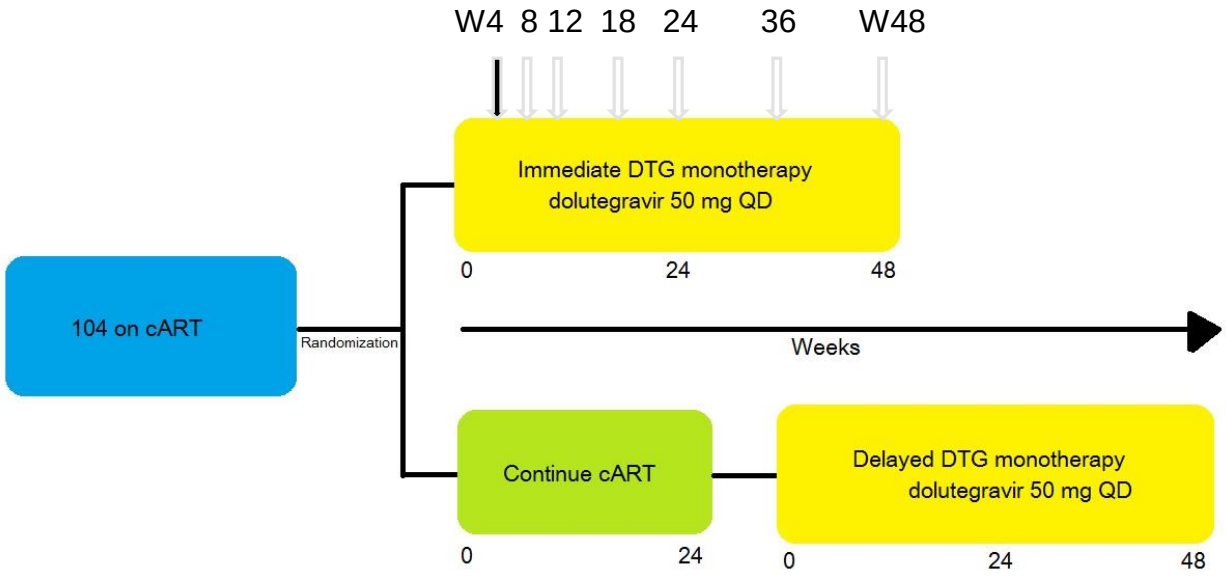
Randomized open label multicenter

Dolutegravir monotherapy 50 mg for 48 weeks with or without a meal

If HIV-RNA becomes detectable (any level >20c/ml) the patient is instructed to take DTG with a meal

Key inclusion:

- HIV-RNA < 1,0E5
- CD4-nadir ≥ 200
- HIV-RNA <50 ≥24w
- Never failed
- No resistance
- HBV immune
- >95% estimated compliance



Results secondary endpoint 1: Week 24 <50 c/ml DTG monotherapy versus cART

DTG n=46/50 (92%)
cART n=53/53 (100%)
} p=0.052

Delta 8% (95% C.I. -1% to +19%) (*)

Emergent INSTI Resistance After Switch to DTG Monotherapy

- International, multicenter retrospective study
  - Evaluated virologically suppressed pts switched to DTG 50 mg QD monotherapy
  - Pts with history of VF on INSTI and INSTI resistance excluded
- 11 of 122 pts switched to DTG monotherapy experienced VF
  - 9 of 11 had genotypic INSTI resistance at VF

- INSTI resistance pathways varied

INSTI Resistance at VF
92Q/155H (n = 1)
97A/155H (n = 1)
155H/148R (n = 1)
118R (n = 2)
148K (n = 1)
148H (n = 2)
148R (n = 1)

Blanco JL, et al. CROI 2017. Abstract 42.

LESS

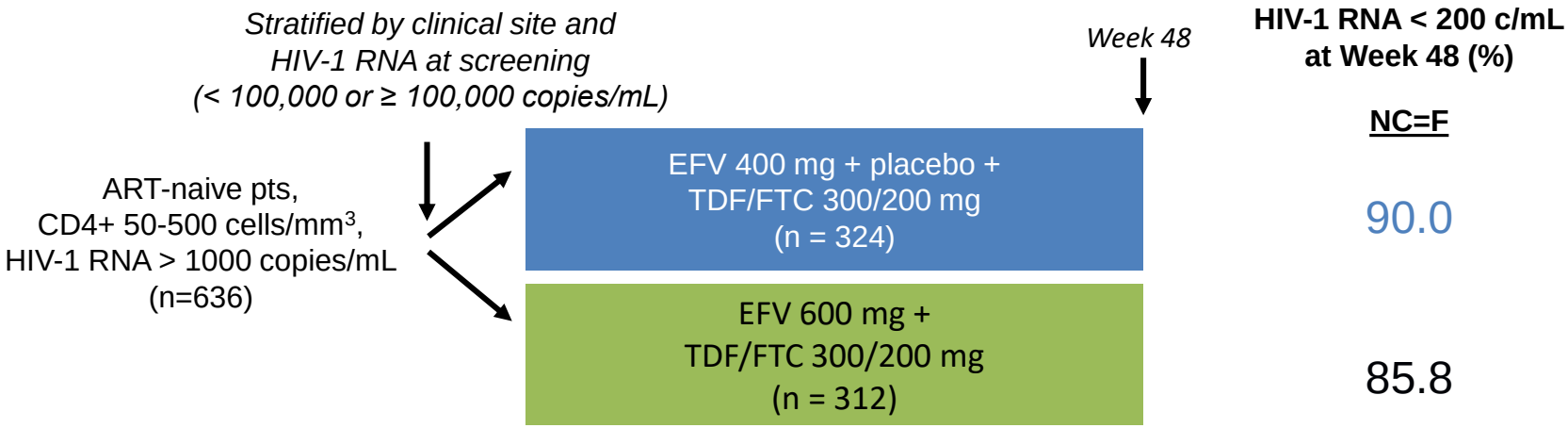
Lower doses

Can we Save EFV?

Dose Reduction of EFV

ENCORE1: 400-mg EFV non-inferior to 600-mg EFV With TDF/FTC for Initial ART

- Randomized, double-blind, placebo-controlled, non-inferiority phase III trial
  - Part of ongoing effort to identify ARVs effective at lower doses (and cost)



- **No significant difference in SAEs between treatment arms**
- More pts with study drug-related AEs for EFV 600 mg vs EFV 400 mg (47.2% vs 36.8%; p=0.008)
- **More pts discontinued EFV 600 mg** due to AE vs EFV 400 mg (1.9% vs 5.8%; p=0.010)

Puls, R et al. IAS 2013. Abstract WELBB01

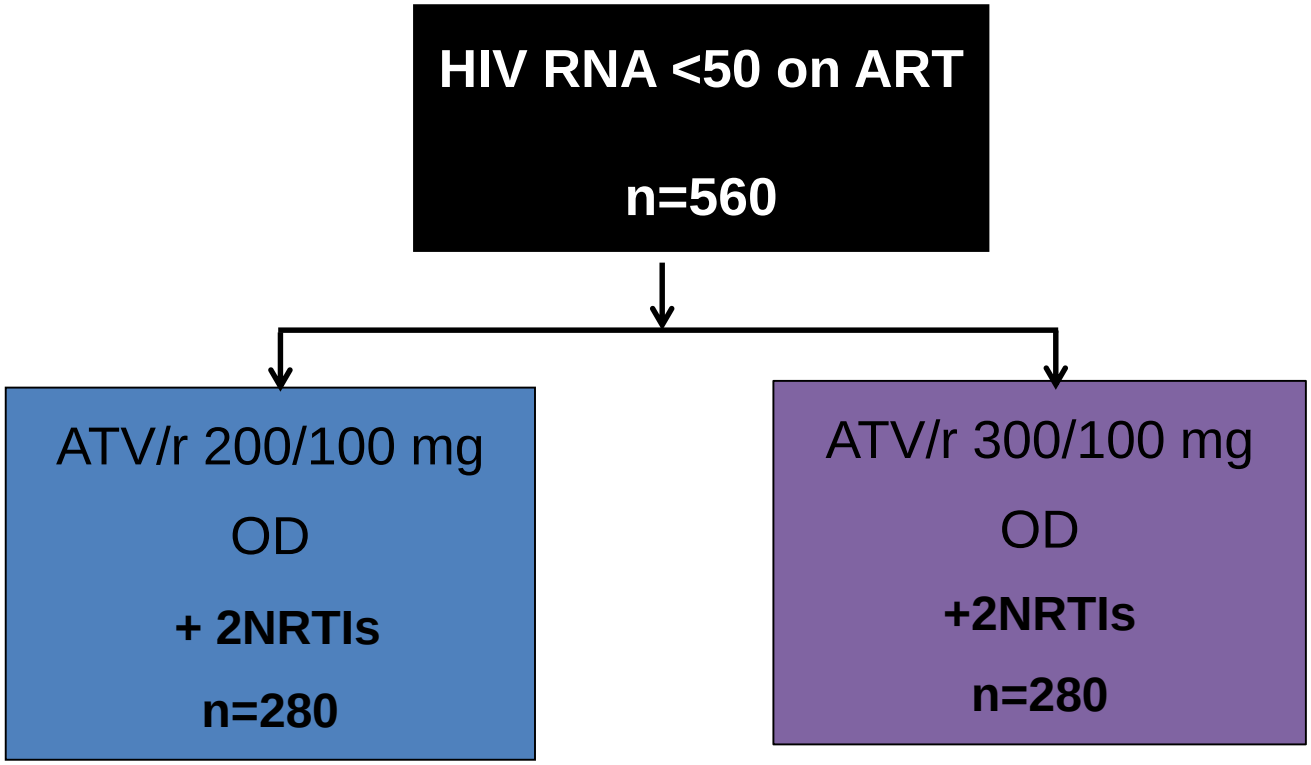
PI dose optimisation

Atazanavir/r: 200/100 mg OD dose?

Darunavir/r: 400/100 OD dose?

Cobicistat as alternative to ritonavir?

LASA trial:Maintenance trial, primary analysis at Week 48



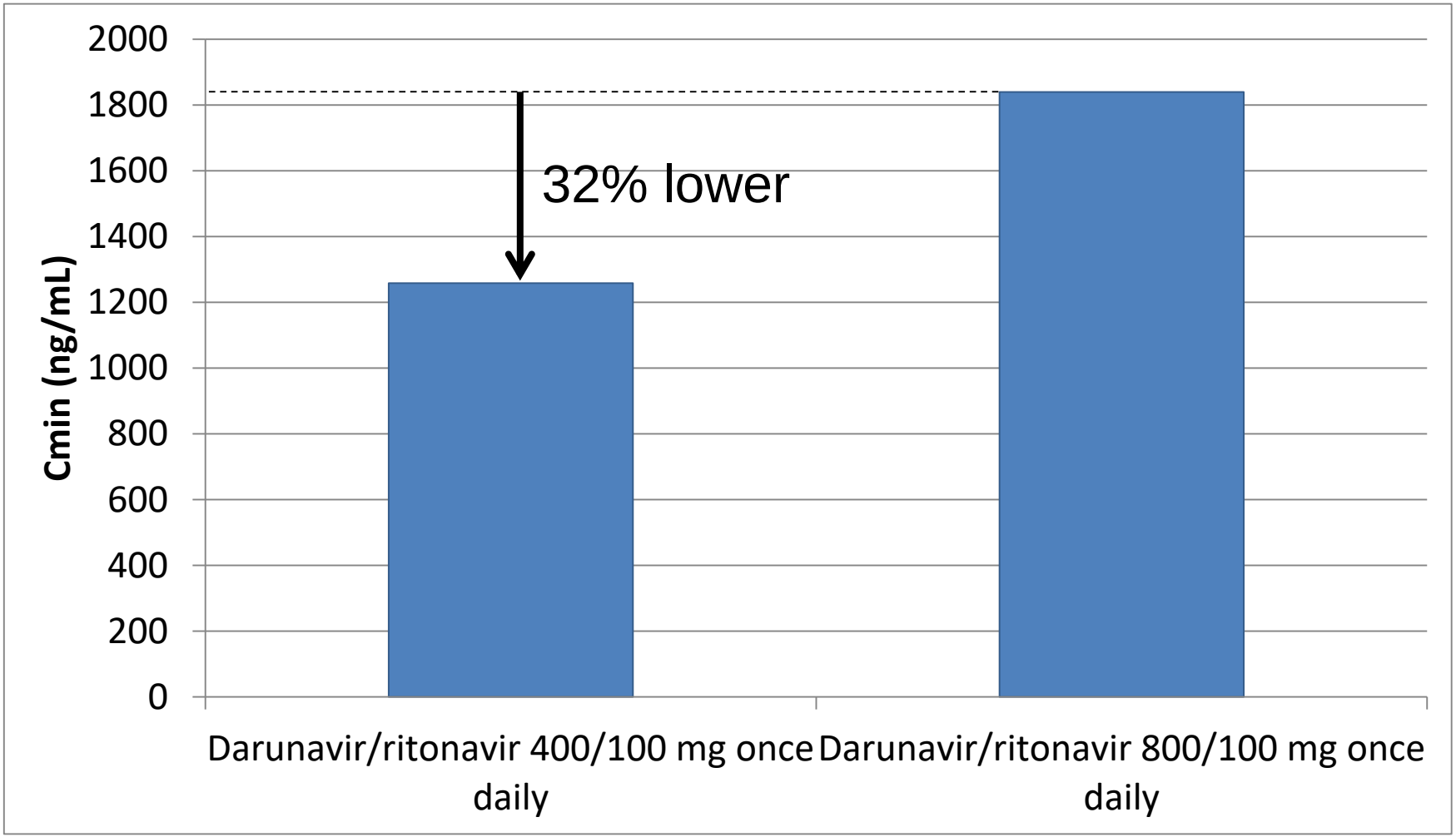
<50 copies/mL were: 93.4% vs 91.7% (95% CI: 1.71, -2.67 to 6.09).

Patients enrolled in Thailand. (HIV RNA suppression endpoint)

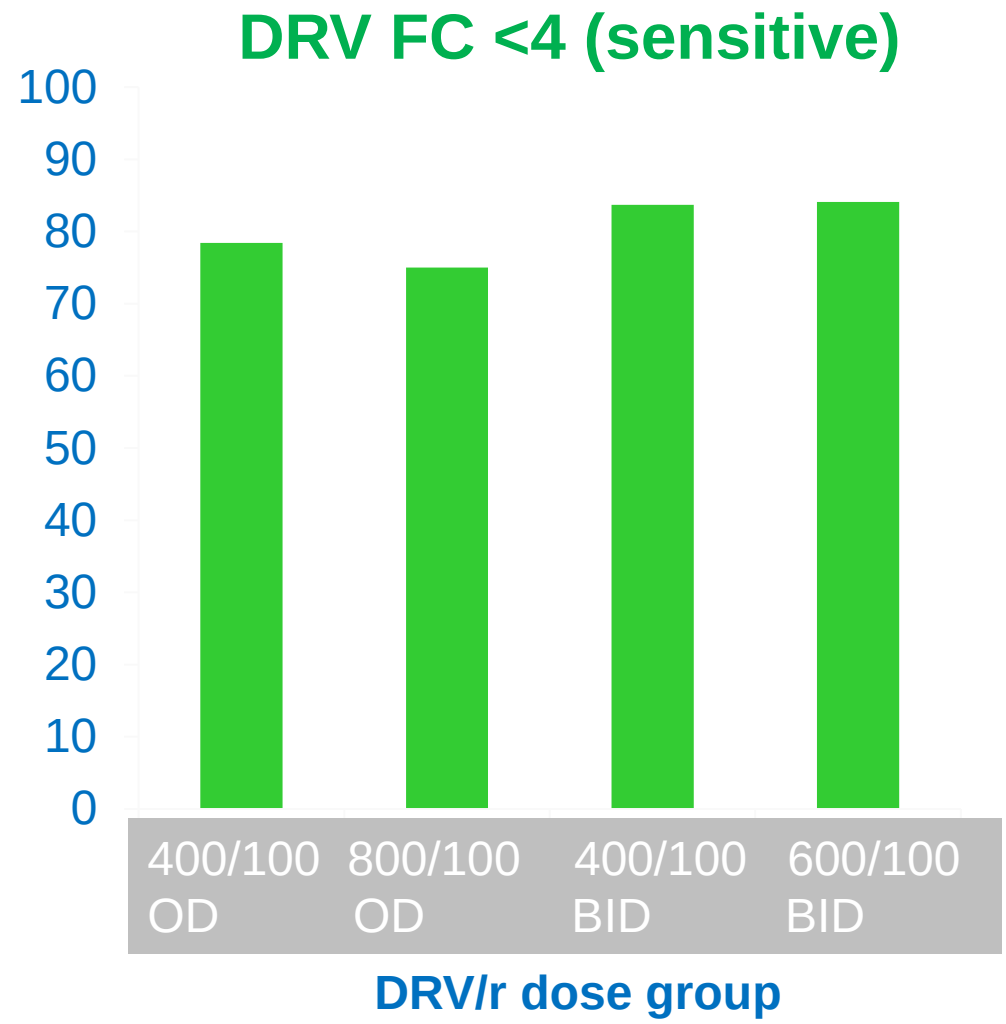
DRV/r: can we switch to a 400/100 OD dose?

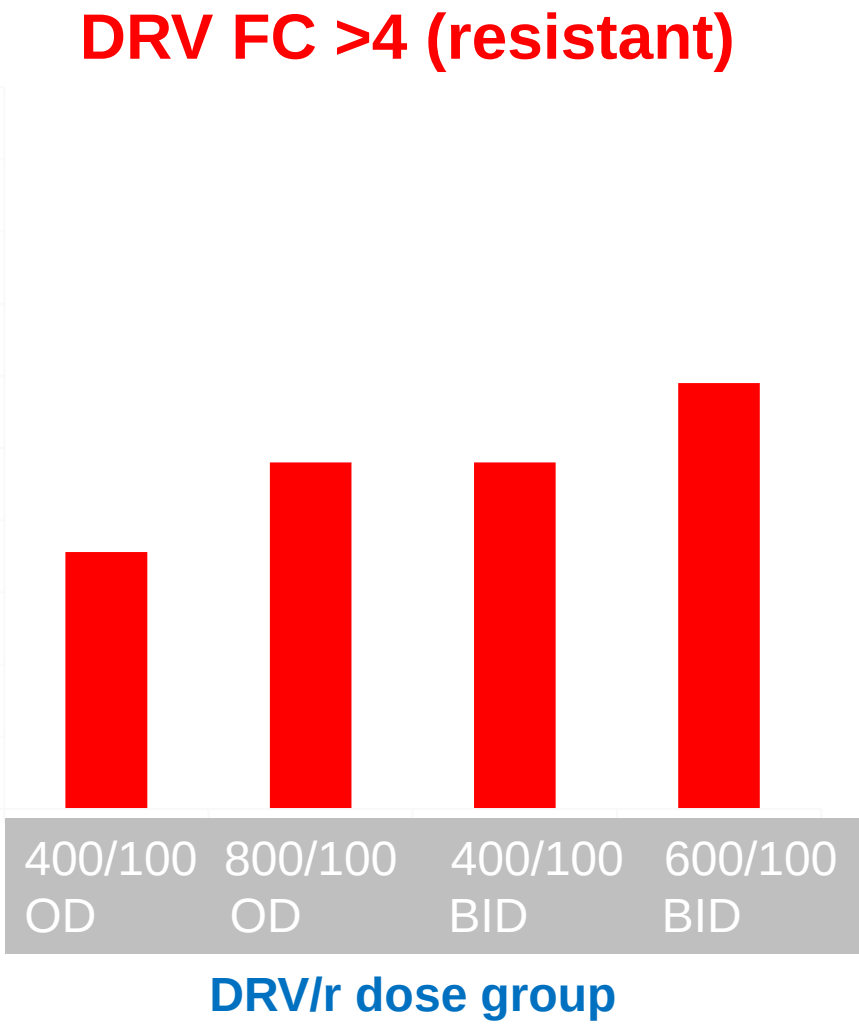
- Approved dose is 600/100 mg BID for PI pre-treated patients,
  800/100 OD for PI naïve patients

Cmin for DRV/r 400/100 versus 800/100 OD POWER 1 and 2 trials: Cmin 32% lower for 400/100 OD versus 800/100 dose



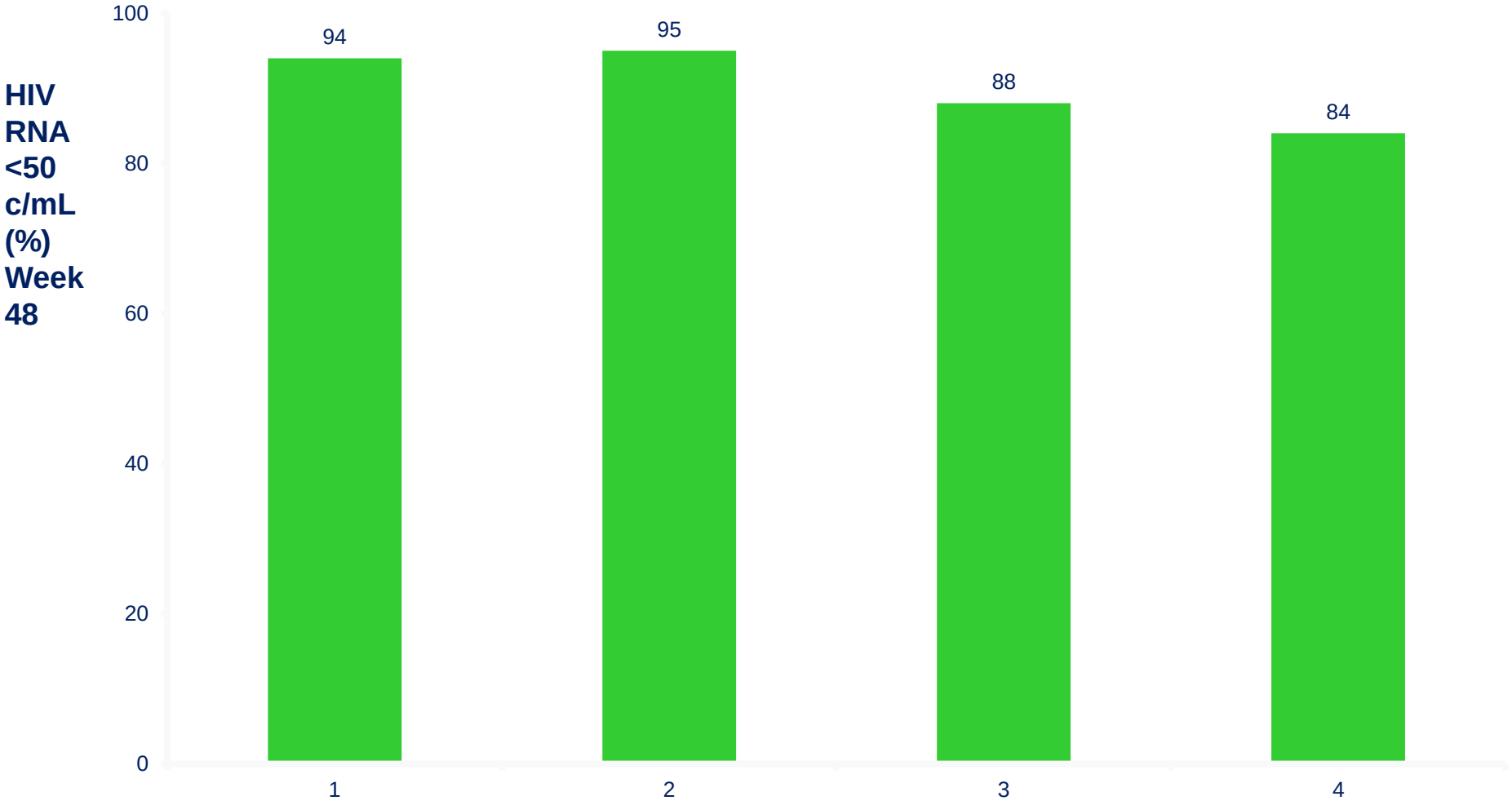
POWER trials: %HIV RNA >1 log reduction at Week 24, by dose and baseline DRV resistance





Katlama C et al AIDS 2007, 21: 395-402
Haubrich et al AIDS 2007, 21: F11-F18

TITAN trial: HIV RNA <50 copies/mL at Week 48, Treatment experienced, PI sensitive patients, DRV/r 600/100 mg BID +2NRTIs, by DRV Cmin



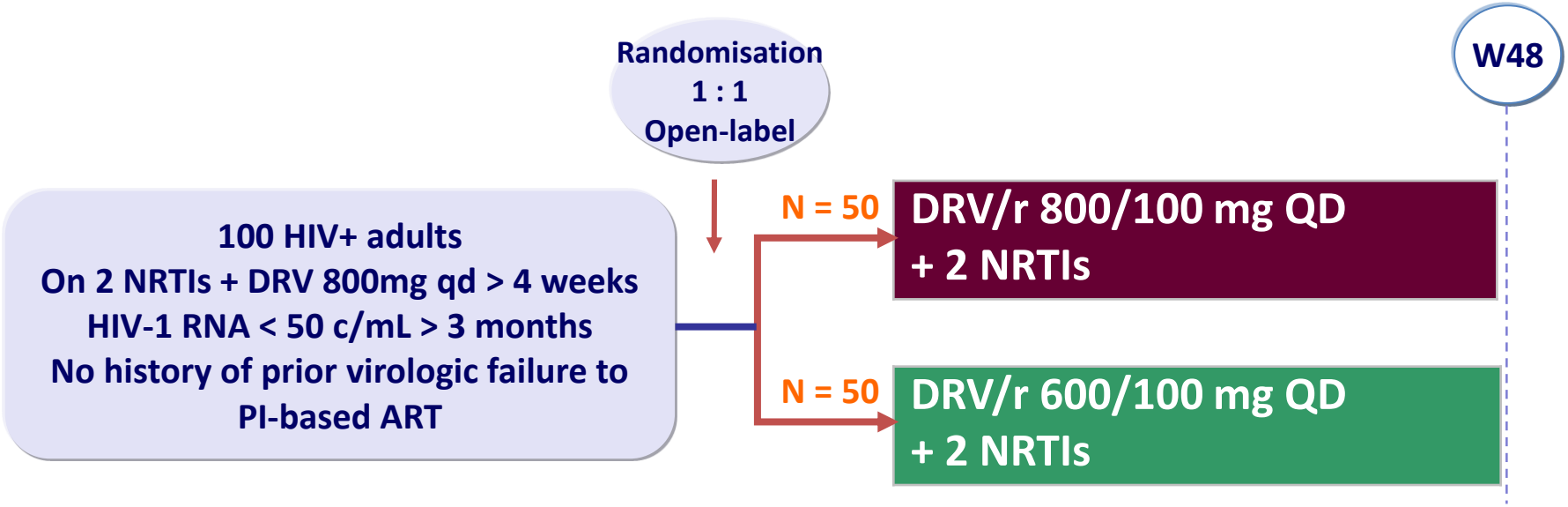
Sekar et al, EACS, Madrid 2007 [abstr P4.1/10

ODIN trial – safety results to Week 48
DRV/r 800/100 OD versus 600/100 BID

Safety parameter	800/100 OD n=294	600/100 BID n=296	p value
≥1 Grade 3 or 4 AE	23 (8%)	45 (15%)	p<0.05
D/C for adverse events	10 (3%)	14 (5%)	n.s.
Triglycerides ≥500mg/dL	15 (5%)	31 (11%)	p<0.05
Total cholesterol ≥240mg/dL	29 (10%)	58 (21%)	p<0.05
LDL cholesterol ≥160mg/dL	28 (10%)	47 (17%)	p<0.05

No other significant differences in lab parameters or individual clinical adverse events

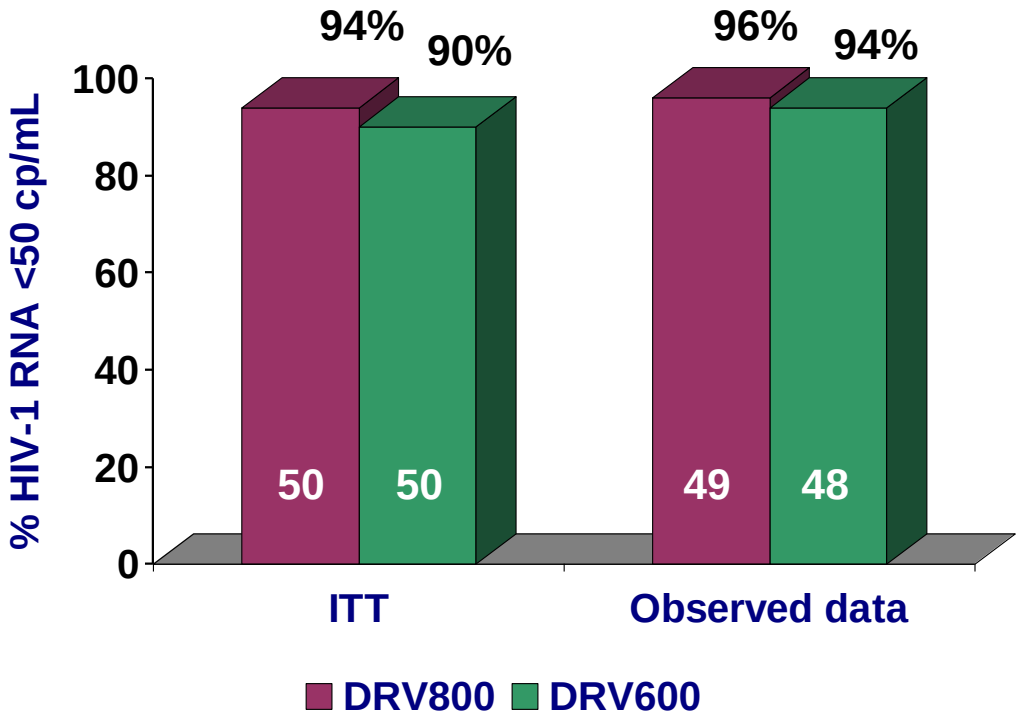
DRV600. Study Design

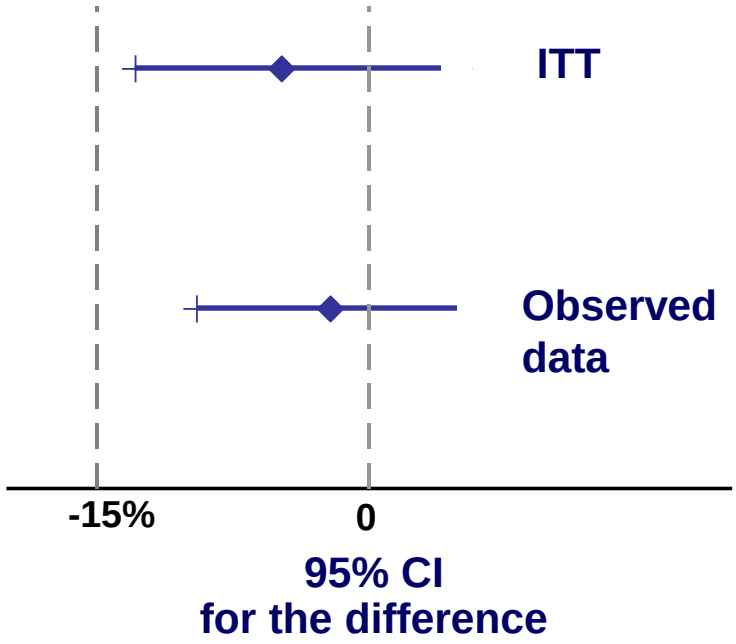


- **Study endpoints**
  - The proportion of patients with HIV-1 RNA <50 c/mL at w48 (ITT).
    Non inferiority if lower limit of the 95% CI for δ < -15%, 80% power
  - Changes in CD4+ T cell count
  - Changes in DRV C_{trough} in plasma
  - The proportion of patients with AEs during follow-up
  - The economic cost derived from ARV drugs

DRV600. Results at w48

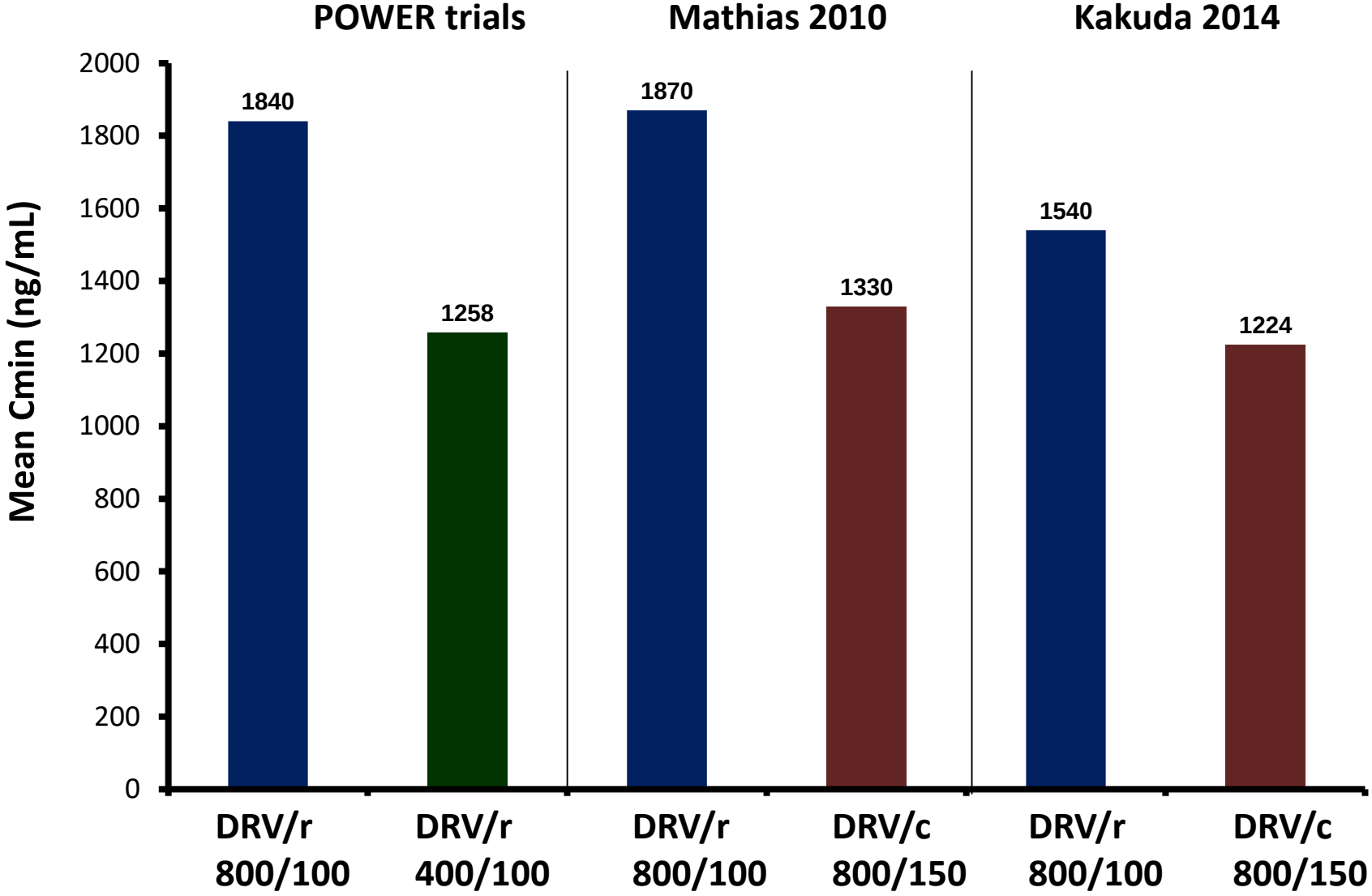
Non inferiority of DRV/r 600/100 mg QD





ITT	-4.0 (-12.9; 4.9)
Observed data	-2,2 (-9.6; 5.2)

Similar to Cobi?
DRV/r 400/100 OD versus DRV/c 800/150 OD



Conclusion

1. **No clinical advantage of 4 drugs-even in low CD4 and high VL.**
2. **Need RT inhibitors plus high barrier to resistance in 2 drug Rx**
3. **Dual therapy Regimen in naïve or switch-some data evolving**
4. **Monotherapy is a niche area but only with boosted Pis not InSTIs**
5. **Stay with the data use triple therapy and wait for trials to report.**
6. **Low dose EFV approved by the FDA**
7. **? move to low dose DRV**