Reduced Darunavir Dose Is as Effective in Maintaining HIV Suppression as the Standard Dose in Virologically Suppressed HIV-Infected Patients. The DRV600 Study.

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Background

- Current aim is to increase substantially the number of HIV+ patients on ART during the next decade.
- Meeting this goal in the setting of limited resources is challenging.
- Strategies aimed at maximizing ART efficiency
  - Use of generic drugs
  - Use of antiretrovirals which are cheaper to make
  - Improve synthesis of antiretrovirals
  - **Dose optimization**

Adapted from Hill et al

HIV-dose selection

- For several HIV-drugs, Phase 2 data showed no difference in efficacy between doses
- Trend to select higher doses for Phase 3 and registration

Pros

- Maximize efficacy
- Drug-drug interactions

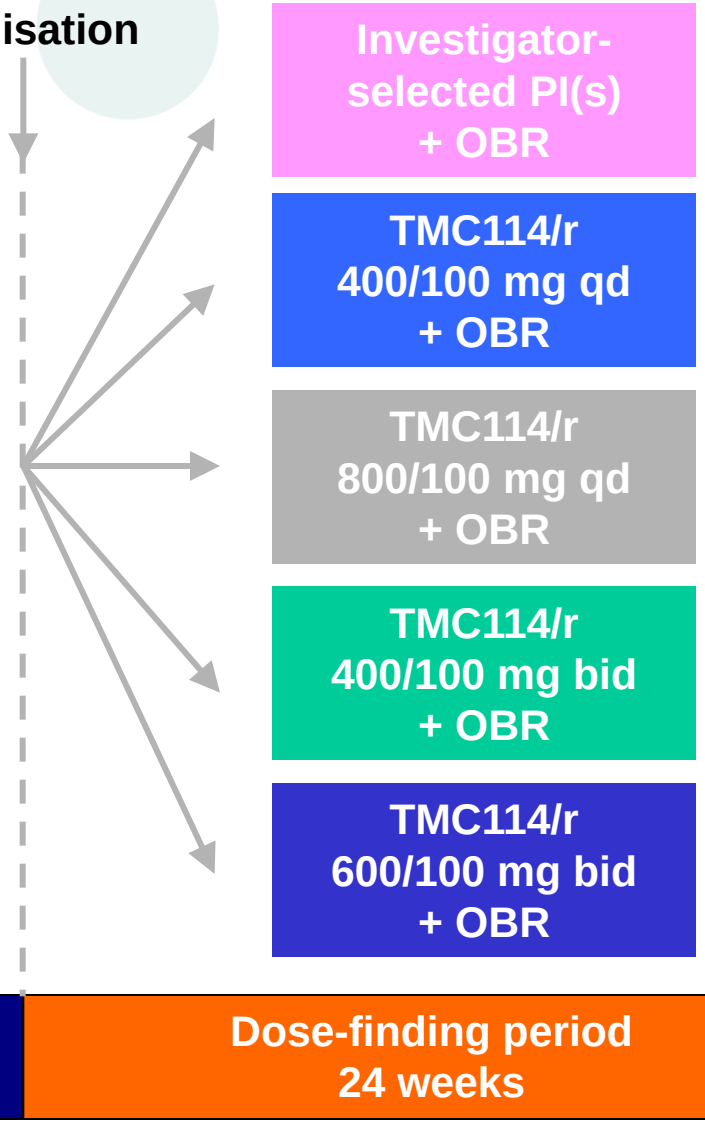
Cons

- Safety (i.e. AZT, ddI, d4T)
- Cost

Adapted from Hill et al

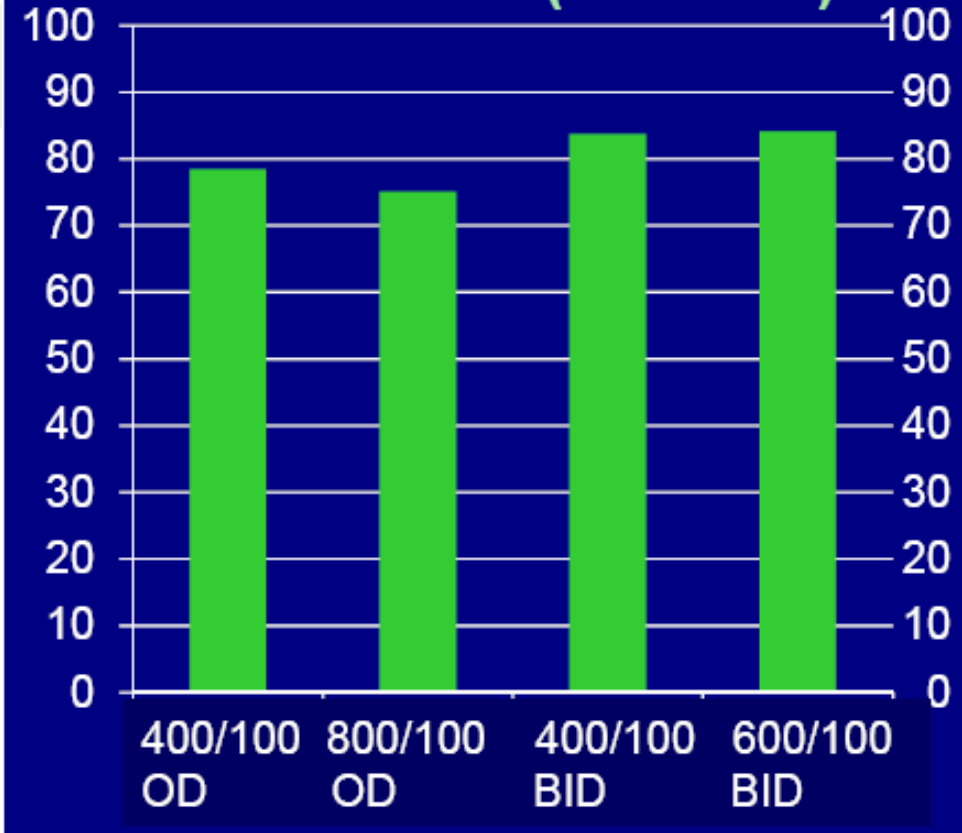
DRV/r dose-selection. POWER 1 & 2

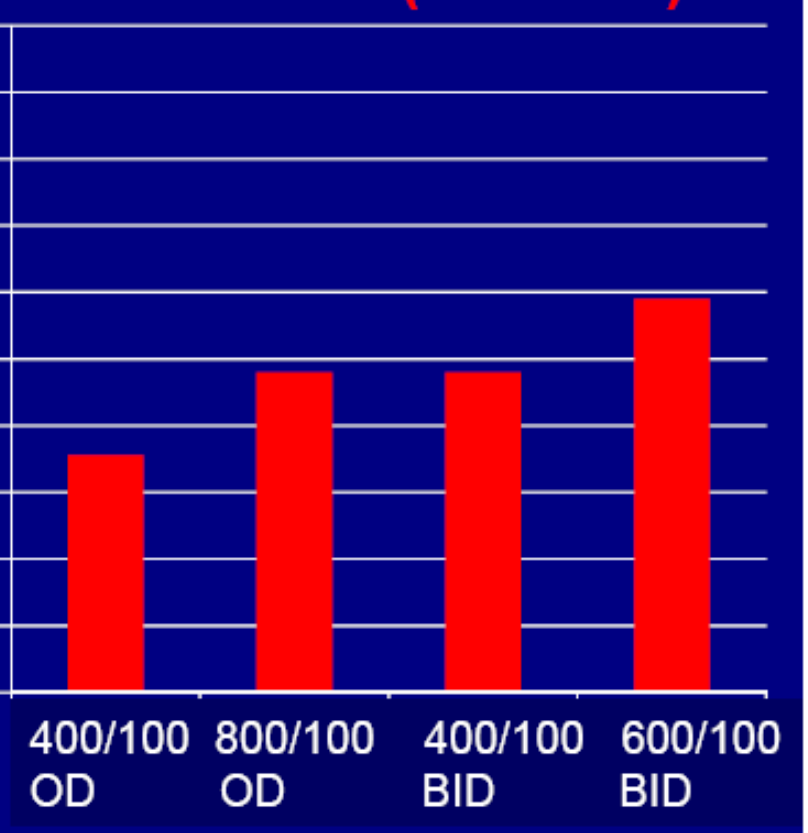
- 3-class experienced
- ≥ 1 PI mutation
- VL > 1000 copies/mL
- Investigator-selected PI(s) plus OBR (NRTIs ± ENF)



Haubrich R, et al. AIDS 2007

DRV/r Phase 2 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

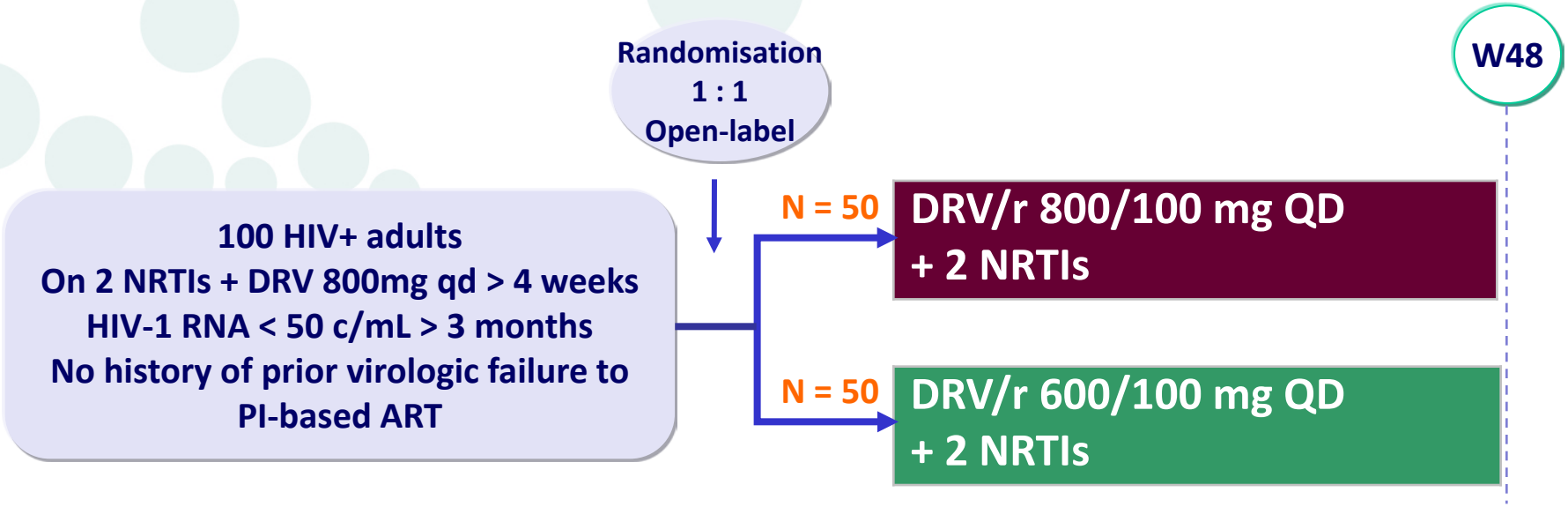
Presented at the 12th Int. Workshop on Clin. Pharmacology of HIV Therapy, 13-15 April 2011, Miami, FI, USA

The DRV600 Study. Hypothesis & Objectives

- **Hypothesis:** Lowering DRV daily-dose from 800 to 600mg QD in HIV+ patients with undetectable VL and no DRV RAM would maintain viral suppression while reducing costs associated with ART.

- **Objective:** To assess the efficacy, safety and economic impact of reducing DRV dose from 800mg to 600mg QD in virologicaly suppressed HIV-infected patients without evidence of PI resistance.
  - **PK sub-study ……** 14th IWCPHT 2013; P_25
  - **CSF sub-study……** 15th IWCPHT 2014; P_46

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

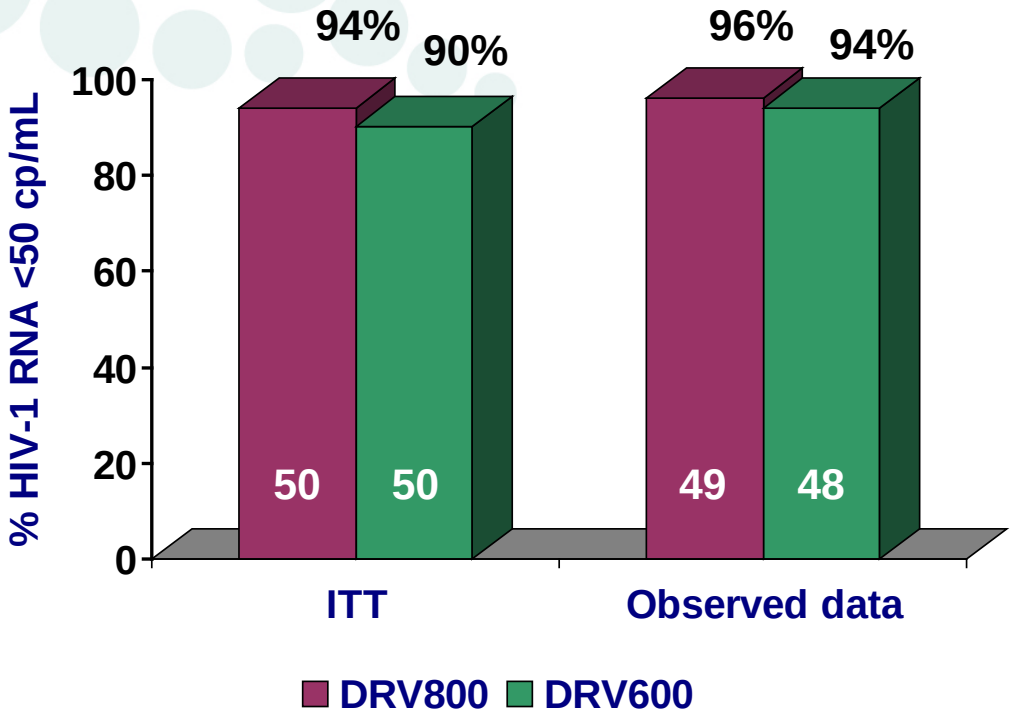
Baseline characteristics & patient disposition

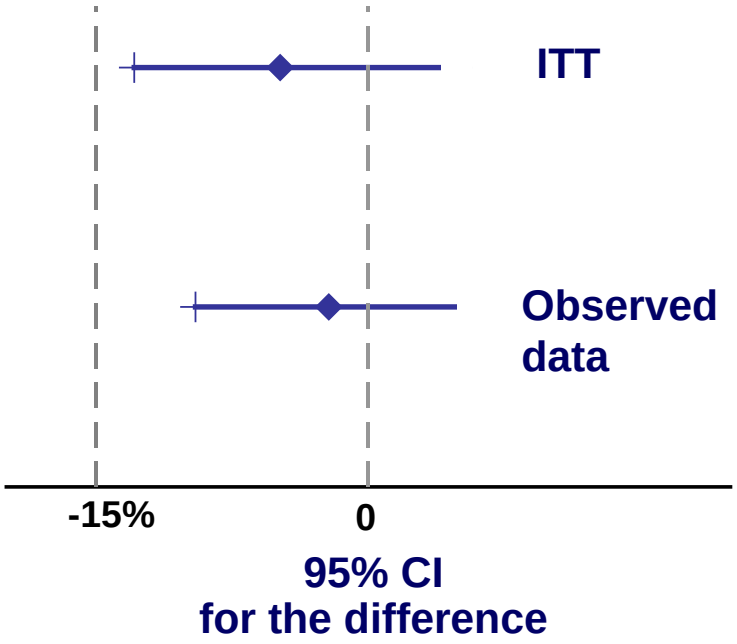
	DRV 800 n=50	DRV 600 n=50
Age, years	44.8 (10.5)	45.6 (10.8)
Sex, male	41 (82%)	40 (80%)
BMI, kg/m^2	24.9 (3.5)	25.3 (3.4)
HCV antibody positive	7 (14%)	13 (26%)
CD4 cell count, $cells/mm^3$	591 (272)	523 (331)
NRTIs		
TDF/FTC	34 (68%)	32 (64%)
ABC/3TC	16 (32%)	17 (34%)
Protocol defined treatment failure at w48, n (%)	3 (6%)	5 (10%)
Confirmed HIV RNA elevation	2	3
Lost to follow-up	1	1
Exitus	-	1*

*Liver cirrhoses. Septic shock.

Results w48

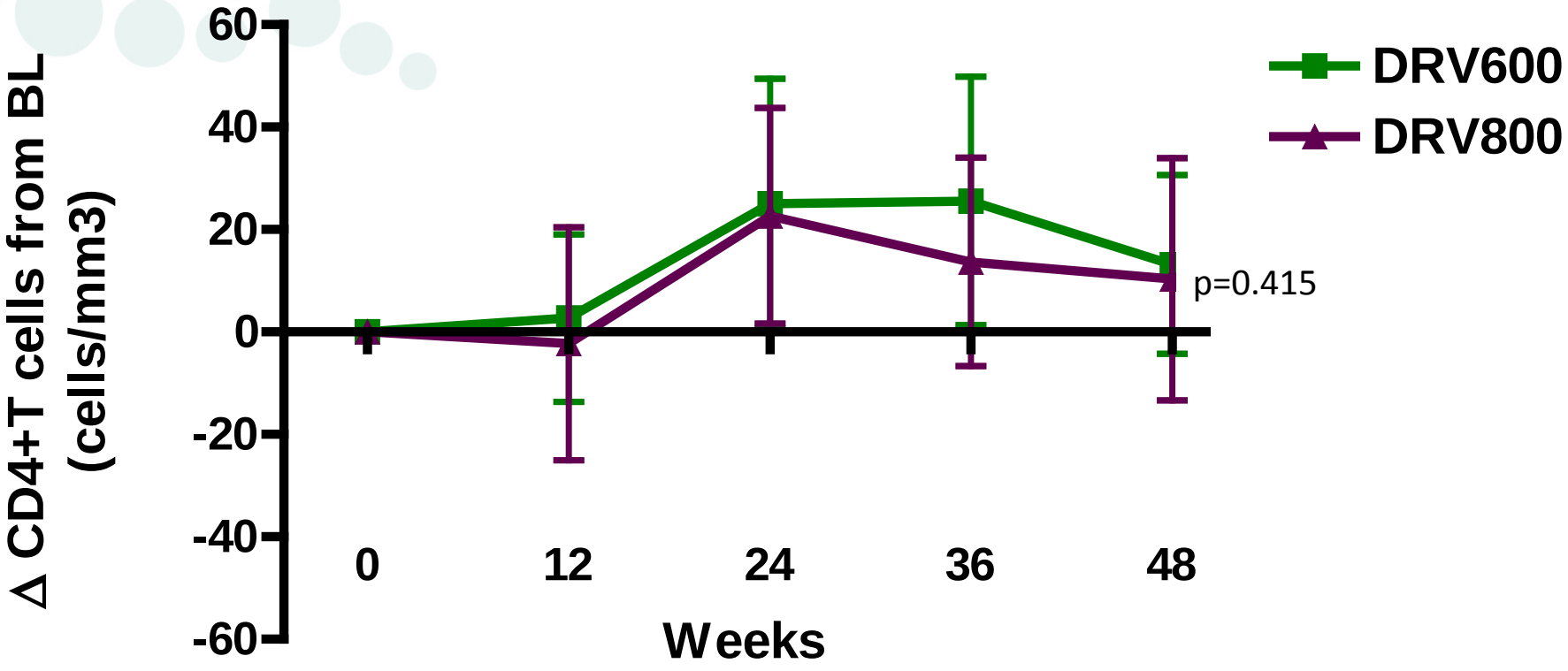
Non inferiority of DRV/r 600/100 mg QD



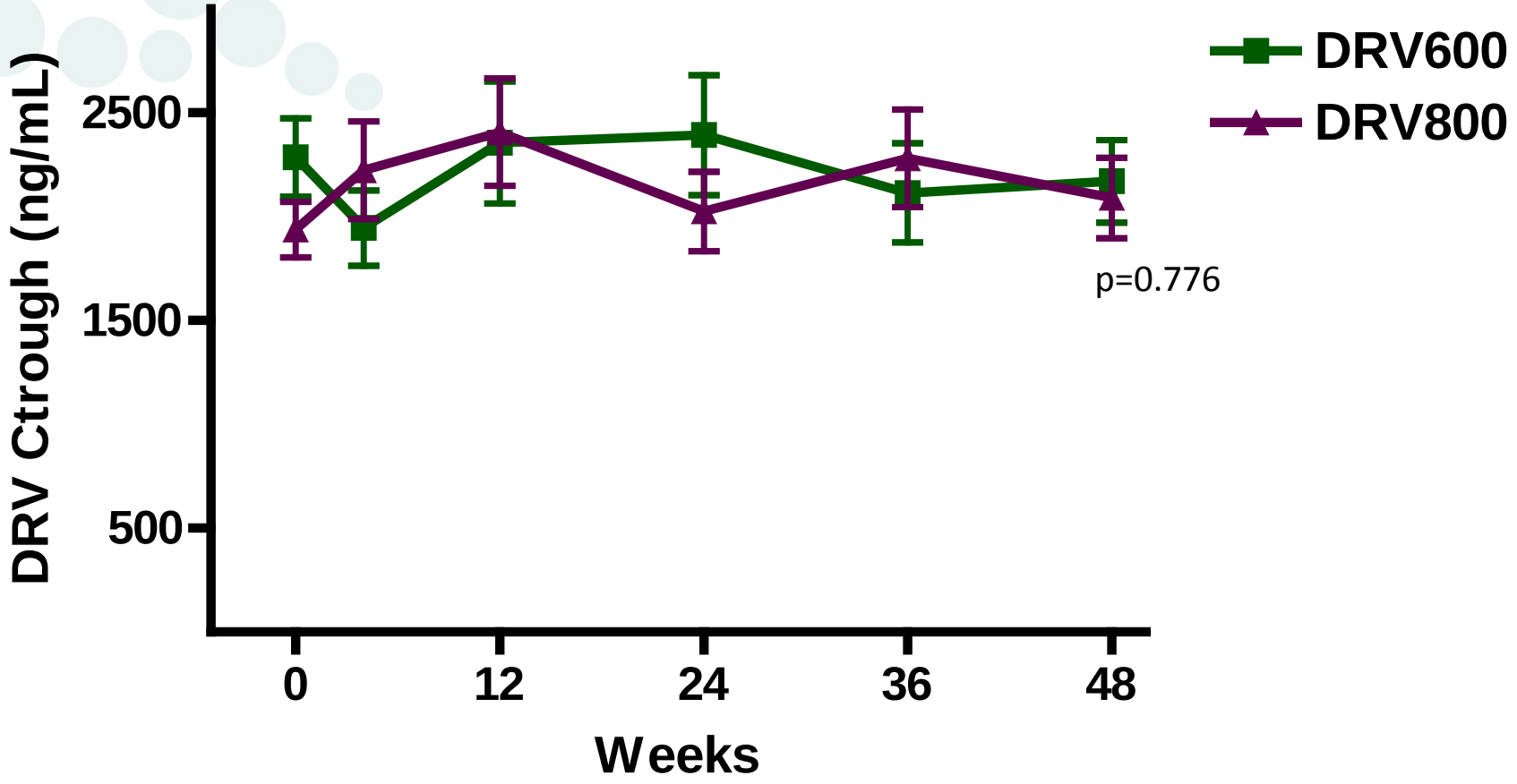


ITT	-4.0 (-12.9; 4.9)
Observed data	-2,2 (-9.6; 5.2)

Change in CD4+ T cell count from baseline

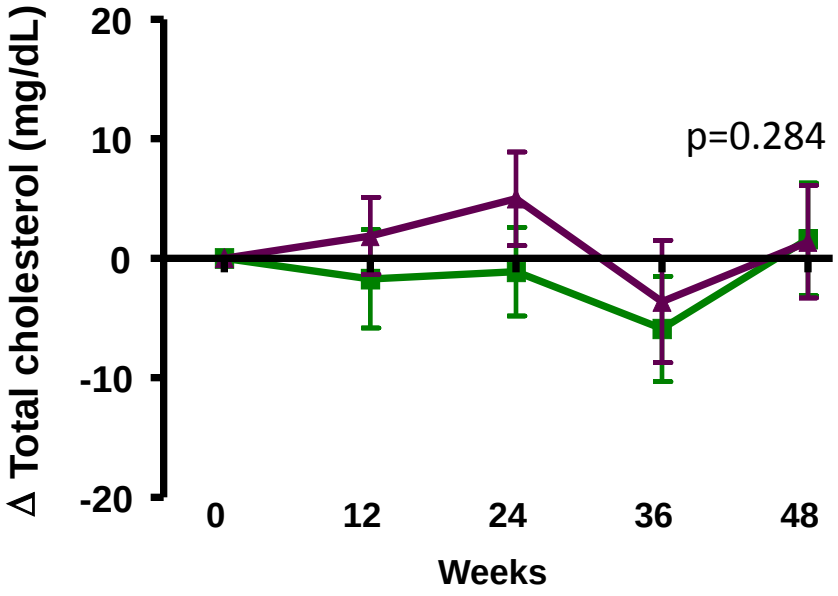


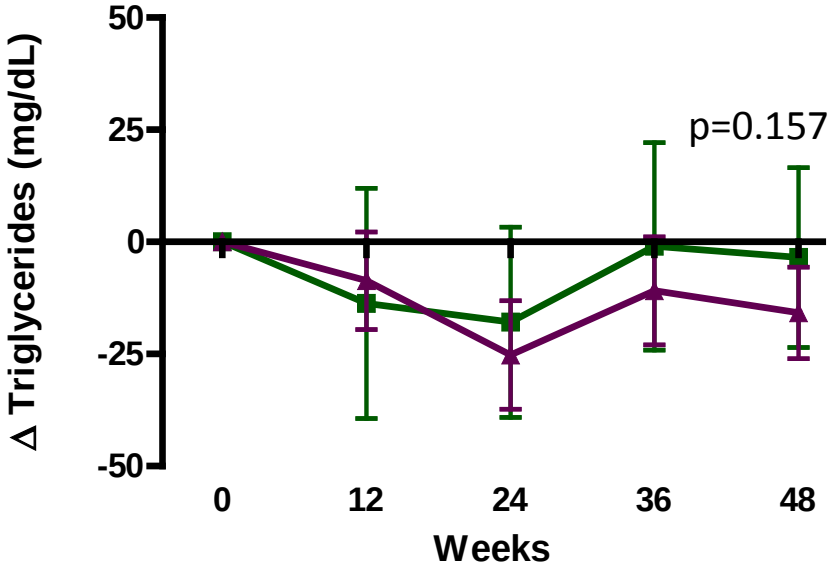
Pharmacokinetics. DRV C_{trough}



Safety

Drug-related AEs	DRV 800 n=12	DRV 600 n=7
Gastrointestinal disturbances	6	4
Dislipidemia	5	-
Other <5%	1	3





DRV800 DRV600

Cost-efficacy analysis

	Annual DRV cost per patient	Virologic response w48 (ITT)	Average annual DRV cost per patient with virologic response	Incremental cost per patient successfully treated	Patients successfully treated with DRV600 to have one free DRV600 a year
Base case					
DRV800	4,389 €	0.94	4,669 €	1,011 €	4
DRV600	3,292 €	0.9	3,658 €		
Best scenario					
DRV800	4,389 €	0.94	4,669 €	1,341 €	3
DRV600	3,292 €	0.989	3,329 €		
Worst scenario					
DRV800	4,389 €	0.94	4,669 €	610 €	6
DRV600	3,292 €	0.811	4,059 €		

Conclusions

- Compared with standard dose of 800mg QD, a DRV dose reduction to 600mg QD:
  - Provided **non-inferior efficacy** at w48 in suppressed HIV+ patients.
  - Resulted in **comparable darunavir PK** parameters
    - C_{trough} well above the protein binding adjusted DRV IC_{90} for wt strains
  - Had **comparable exposure/efficacy in CSF**
  - **Cost saving approx 1,000 € /pt-yr**
    - 4 pts on DRV600 qd = 1 free DRV600 qd

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