O-01

Population PK-PD Analysis of 400 mg *vs.* 600 mg Efavirenz Once Daily in Treatment-Naïve HIV Patients at 48 Weeks: Results of the ENCORE1 Study

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encore1

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Background

- The WHO/PEPFAR/GFATM aim to expand antiretroviral coverage to 15 million worldwide by 2015[1]
- Although antiretroviral costs have reduced, current funds are unlikely to cover the expansion
- Other cost-reduction schemes need to be explored to reach treatment goals
- Dose reduction strategies that maintain therapeutic success may reduce medication costs but also reduce drug-related adverse events

[1] WHO 2010; http://www.who.int/hiv/pub/progress_report2011/global_facts/en/

Background

- The WHO recommends an efavirenz (EFV)-based regimen for first-line treatment of therapy naïve patients:
  - EFV + TDF/FTC (600/300/200 mg once daily)
  - EFV + TDF/3TC (600/300/300 mg once daily)
- An early phase II dose ranging study (DMP 266-005) suggested comparable efficacy of lower EFV doses[2]

	Proportion HIV-RNA <400 copies/mL (%)	
EFV Dose (mg)*	Week 16	Week 24
200	96	96
400	85	91
600	88	100
EFZ placebo	48	65

* EFV + ZDV/3TC

[2] Haas *et al*. International Conference on AIDS, 1998; **Abstract 22334**

ENCORE1

- ENCORE1 is a randomised, double-bind, placebo-controlled trial comparing reduced dose EFV (400 mg once daily) with the standard dose (600 mg once daily) in treatment-naïve, HIV-infected adults over 96 weeks

- Dose reduction to 400 mg was non-inferior to 600 mg EFV once daily at 48 weeks of treatment (plasma HIV-RNA <200 copies/mL: 94% *vs.* 92%, respectively; modified ITT)[3]

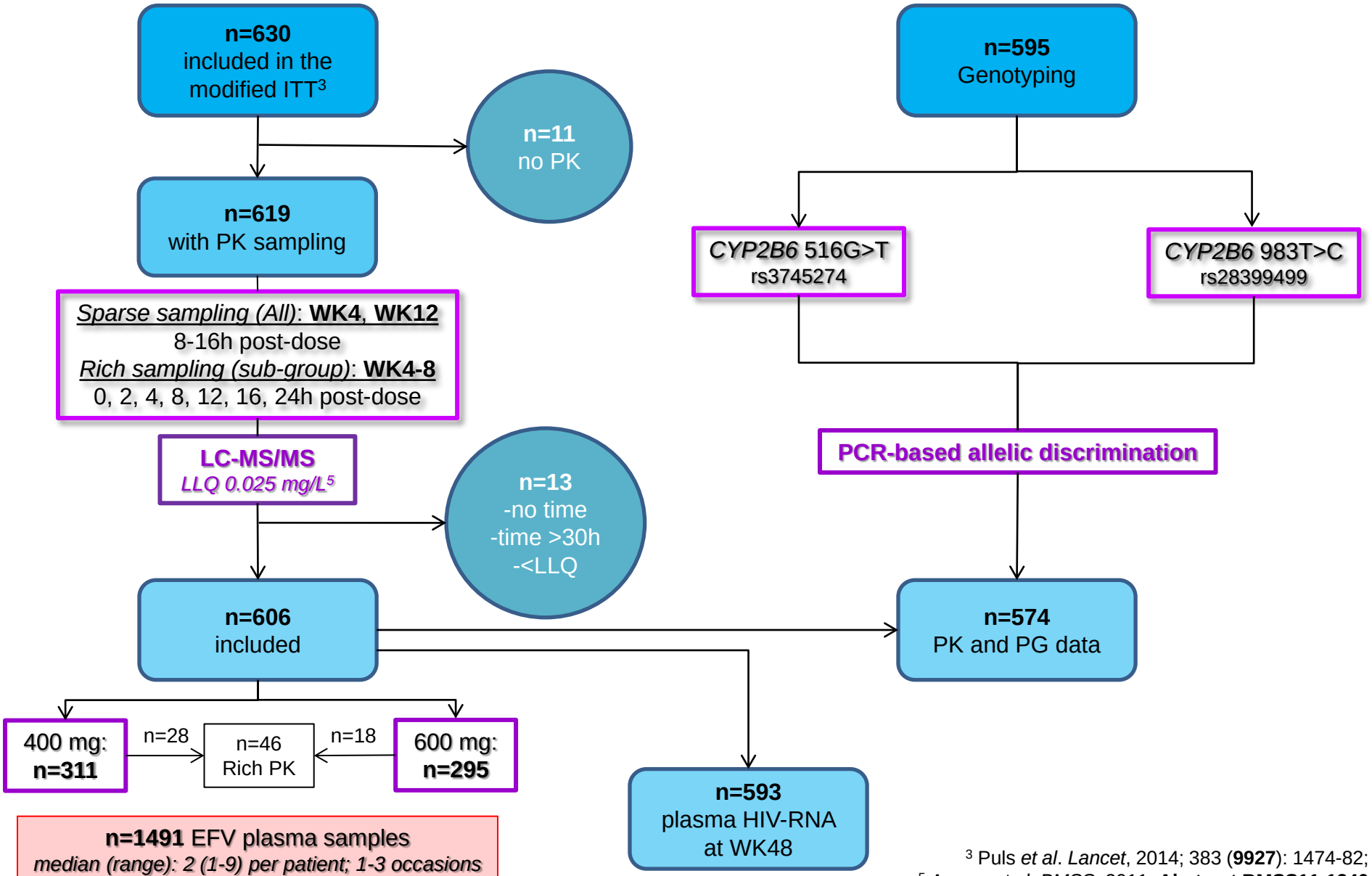
- PK sub-studies: EFV plasma/CSF
  Dried-blood spots (Else et al, O-16)
  EFV PK modelling and PK-PD

***AIM*: Evaluate EFV PK-PD and the putative minimum effective concentration (1.0 mg/L at mid-dose interval)[4] in patients enrolled in ENCORE1**

[3] Puls *et al*. *Lancet*, 2014; 383 (**9927**): 1474-82; [4] Marzolini *et al*. *AIDS* 2001; 15 (**1**): 71-5

Methods

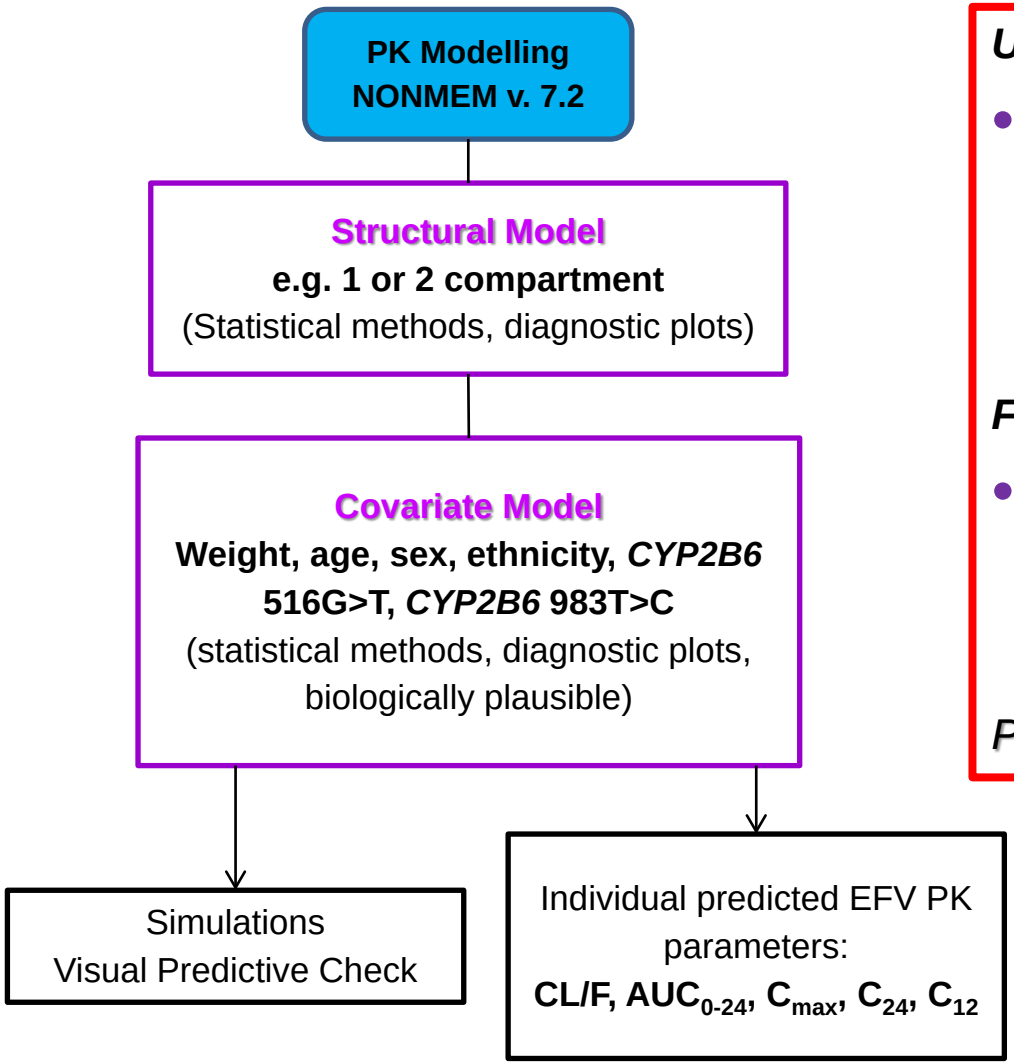
PK Sampling & Genetics



[3] Puls *et al*. *Lancet*, 2014; 383 (**9927**): 1474-82;
[5] Amara *et al*. *BMSS*, 2011; **Abstract BMSS11-1240**

PK Modelling & PK-PD Analysis

Rich & sparse concentration-time data were modelled to derive individual predicted EFV PK parameters for each patient on each occasion (n=606 patients, n=1491 concentrations) and the mean of these parameters per patient used to investigate EFV PK-PD.



Univariate logistic regression

- Assess association between log-transformed mean individual predicted EFV PK parameters [CL/F, $AUC_{0\text{-}24}$, C_{max}, C_{24}, C_{12} (representing mid-dose interval)] and HIV-RNA <200 copies/mL at WK48

Fisher's exact test

- Assess associations between EFV dose, genotype, screening HIV-RNA (≤/>100,000 copies/mL and HIV-RNA <200 copies/mL at WK48

Patients with missing viral load excluded

Multivariate analysis

Results

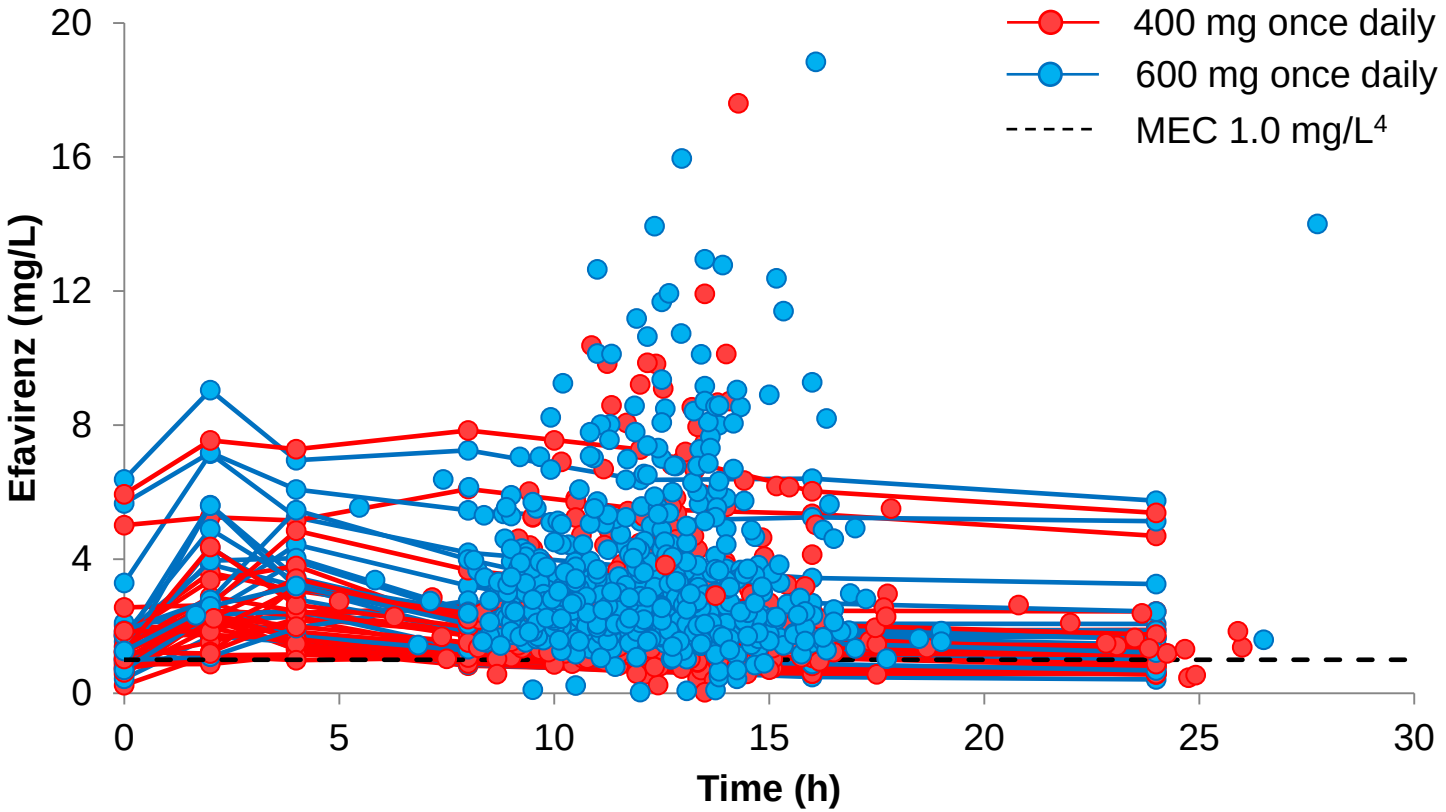
Patient Demographics

Parameter	Median (range) *
Female [n (%)]	191 (32)
Age (years)	35 (18-69)
Weight (kg)	65 (39-148)
Height (m)	1.68 (1.44-1.90)
BMI (kg/m^2)	23 (15-50)
CD4 cell count (cells/mm^3)	270 (40-679)
Screening HIV RNA ≤100,000 copies/mL [n (%)]	375 (62)
HIV RNA at week 0 (copies/mL)	56803 (162-10000000)
HIV RNA <200 copies/mL at 48 weeks† [n (%)]	577 (97)
Regimen [n (%)]	
400 mg once daily	311 (51)
600 mg once daily	295 (49)
Ethnicity [n (%)]	
Caucasian	76 (13)
Asian	201 (33)
African	226 (37)
Hispanic	102 (17)
Aboriginal	1 (0.2)

* *Unless stated otherwise*

† n=593 available viral load measurements at week 48 (13/606 missing)

Pharmacokinetic Profiles

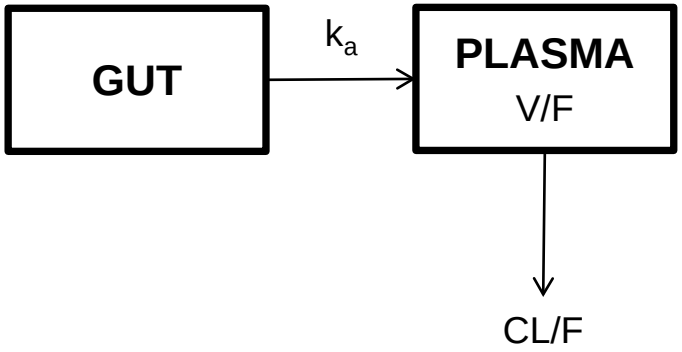


n=606 patients; n=1491 EFV concentrations

	Rich samples		WK4 samples		WK12 samples	
Dose	***n***	***Time (h)***	***n***	***Time (h)***	***n***	***Time (h)***
400 mg	196	0-24	300	5.0-26.0	301	2.1-25.9
600 mg	126	0-24	292	1.7-19.0	276	5.8-27.8

[4] Marzolini *et al*. *AIDS* 2001; 15 (**1**): 71-5

EFV PK Model



- 1 compartment, 1st order absorption (k_a fixed to 0.6 h^{-1})[6]
- Significant covariates:
  - Composite ***CYP2B6* 516G>T/983T>C genotype** on EFV CL/F
  - **Weight** on EFV CL/F and V/F (allometric scaling)
- Interindividual variability of CL/F reduced by **14%** following addition of genotype
- In comparison to reference genotype (516GG/983TT), EFV CL/F decreased by 34%, 27%, 71%, 65% for 516GG/983TC or CC, GT/TT, GT/TC or CC, TT/TT, respectively

Parameter	Estimate	RSE (%)
CL/F GG/TT (L/h)	11.9	2.4
V/F (L)	283	5.1
k_a (h^{-1})	0.6 (fix)	-
Random effects		
Interindivdual variability CL/F (%)	37.9	11.0
Interoccasion variability CL/F (%)	21.1	27.9
Covariates		
CL/F GG/TC or CC (L/h)	7.9	16.1
CL/F GT/TT (L/h)	8.7	2.4
CL/F GT/TC or CC (L/h)	3.5	18.0
CL/F TT/TT (L/h)	4.2	7.0
CL/F MISS (L/h)	8.5	8.3
θ_{Weight} CL/F	0.75 (fix)	-
θ_{Weight} V/F	1.00 (fix)	-
Residual error		
Proportional (%)	20.0	8.6

RSE: relative standard error, $RSE=SE_{ESTIMATE}/ESTIMATE*100$

$\theta_{genotype}$: relative changes in EFV CL/F for a specific composite CYP2B6 G516T/T983C genotype compared to reference genotype GG/TT

[6] Arab-Alameddine *et al*. *Clin Pharmacol Ther*, 2009; 85 (**5**): 485-94

PK-PD Analysis (I)

- Of the available viral load measurements at 48 weeks **97%** and **98%** were <200 copies/mL for EFV 400 mg and 600 mg once daily, respectively (97% overall)

- Due to the small proportion of patients with viral load ≥200 copies/mL at 48 weeks (3%) a multivariate analysis was not feasible

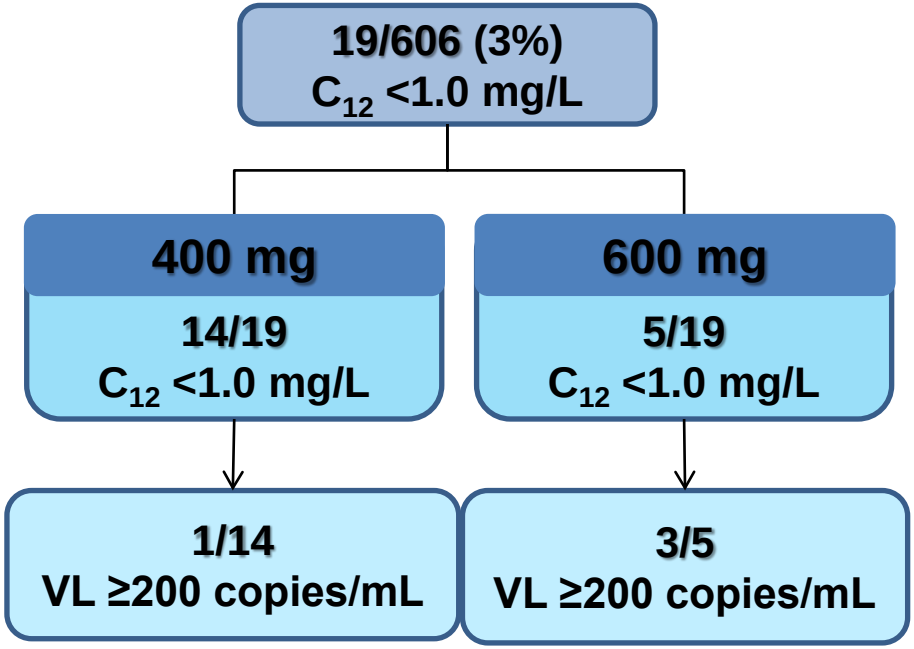
- Dose, genotype and viral loads at screening were ***not significant*** in the univariate analysis (p>0.05, all comparisons; Fisher's exact test)

- Mean individual predicted EFV $\log C_{24}$ was significantly associated with achieving viral load <200copies/mL at week 48 (odds ratio, 95% CI: **3.8, 2.0-7.0; *p*=0.0001**)

PK-PD Analysis (II)

- Given the small proportion of viral load (VL) ≥200 copies/mL at 48 weeks (3%) a robust reassessment of the MEC could not be made

- Based on the recommended MEC of 1.0 mg/L[4] and mean individual predicted EFV C_{12} (approximating mid-dose interval):



Proportion of patients with VL ≥200 copies/mL is higher in those with C_{12} <1.0 mg/L

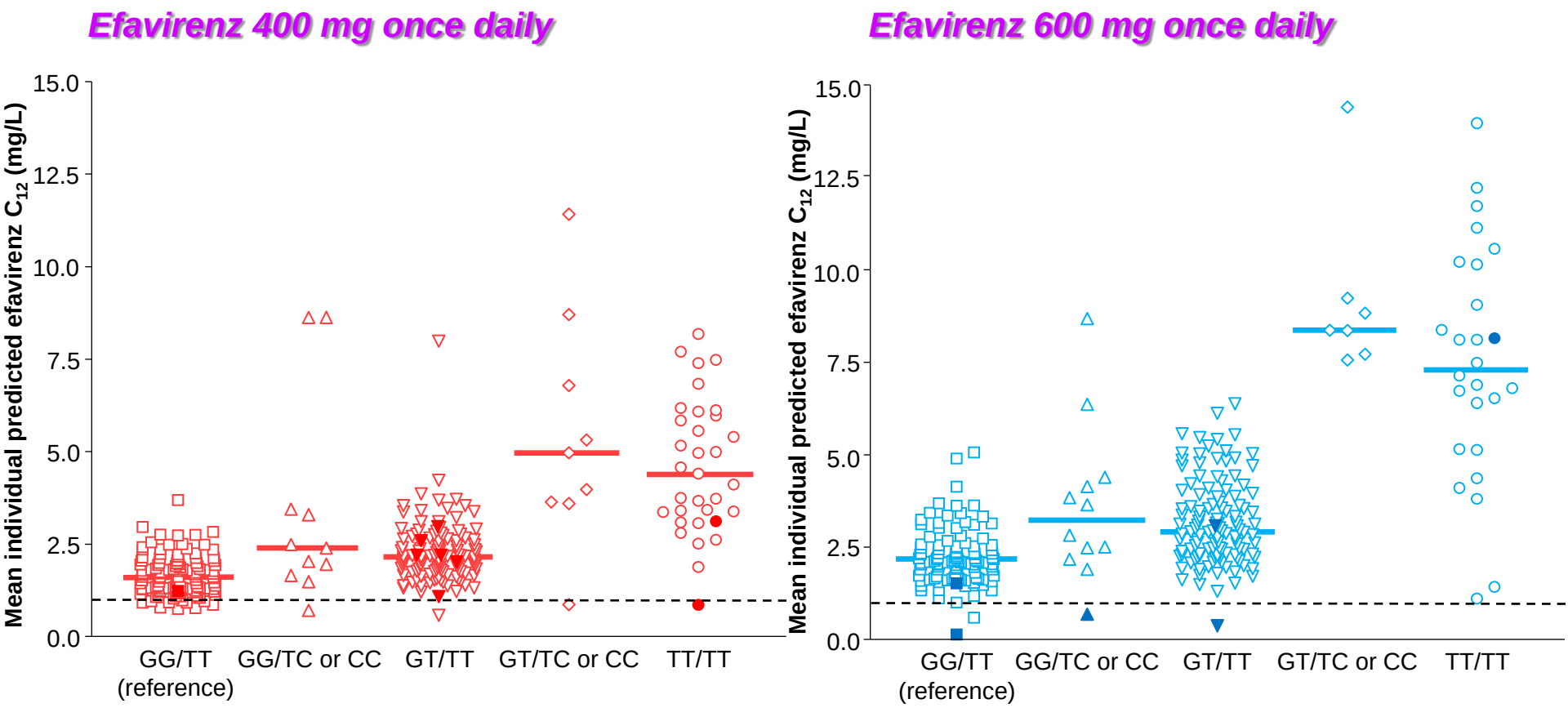
	VL ≥200 copies/mL [% (n/N)]	*p* value*
C_{12} <1.0 mg/L	21 (4/19)	0.001
C_{12} ≥1.0 mg/L	2 (12/574)	

* Fisher's exact test

[4] Marzolini *et al*. *AIDS* 2001; 15 (**1**): 71-5

PK-PD Analysis

Mean individual predicted EFV C_{12} stratified for dose and composite *CYP2B6* 516G>T/983T>C genotype. Filled shapes represent detectable viral loads (≥200 copies/mL at 48 weeks). Dashed line (– – – ·) represents 1.0 mg/L[4]



[4] Marzolini *et al*. *AIDS* 2001; 15 (**1**): 71-5

Conclusions

- ENCORE1 showed no difference in virological response between the two EFV dosing arms
- As expected, lower EFV exposures were observed with EFV 400 mg once daily compared to the standard dose (600 mg once daily)
- Relationships between EFV PK with weight and *CYP2B6* polymorphisms consistent with previous reports (analysis of *CYP2B6* 15582C>T is currently underway[7])
- Factors other than the covariates explored in this analysis may explain poorer outcome (HIV-RNA ≥200 copies/mL at 48 weeks) observed in a small proportion of patients receiving 400 mg or 600 mg EFV once daily.

[7] Holzinger *et al*. *Pharmacogenet Genomics*, 2012; 22 (**12**): 858-67

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