Efavirenz (EFV) 400 versus 600 mg daily: Results of the ENCORE1 Intensive PK Sub-Study

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INTRODUCTION

- Efavirenz (EFV)-based combination therapy dosed 600 mg once daily is recommended as first-line treatment of HIV-infected treatment-naïve patients.[1]
- ENCORE1, an ongoing study in treatment-naïve HIV-infected adults assessing reduced dose EFV, recently showed virological non-inferiority of 400 mg EFV once daily compared to the standard dose of 600 mg at 48 weeks of therapy.[2]
- Efficacious dose reduction may provide added clinical benefit by reducing dose-related toxicities as well as decreasing treatment costs.

OBJECTIVES

- Determine and compare the pharmacokinetics (PK) of EFV dosed at 400 mg and 600 mg once daily in a sub-group of patients enrolled in ENCORE1.
- Evaluate the influence of patient demographics and *CYP2B6* 516G>T and 983T>C host genetics on EFV exposure.

METHODS

- ***Patients & PK Sampling:*** Consenting, HIV-infected, treatment-naïve adults were enrolled in the intensive PK sub-study of ENCORE1. Patients were randomised to receive 400 mg or 600 mg EFV once daily in combination with Truvada® (tenofovir disoproxil fumarate/emtricitabine, 300/200 mg once daily).
- Intensive PK sampling was undertaken at steady-state between 4-8 weeks of therapy, pre-dose (0 h), 2, 4, 8, 12,16 and 24 h post-dose.
- EFV plasma concentrations were quantified by a fully validated LC-MS/MS method with a lower and upper limit of quantification of 0.025 and 10 mg/L, respectively.[3]
- ***Genotyping:*** Total genomic DNA was extracted from whole blood and samples quantified and normalised to 20 ng/µL.
- Genotyping for *CYP2B6* 516G>T (rs3745274) and *CYP2B6* 983T>C (rs28399499) was performed using TaqMan assays and identified by real time PCR-based allelic discrimination.
- ***Data Analysis:*** EFV PK parameters (apparent oral clearance, CL/F; area under the concentration-time curve over 24h, $AUC_{0\text{-}24}$; maximum concentration, C_{max}; representation of mid-dose interval, C_{12}; trough concentration 24h post-dose, C_{24}) were calculated by non-compartmental methods using WinNonlin™.
- To assess differences between doses and genotypes, geometric mean ratios (GMR) and 90% CI were calculated using log-transformed data then expressed as linear values. The primary endpoint was GMR EFV $AUC_{0\text{-}24}$ for comparison of randomised doses. Changes were considered significant if the CI did not cross 1 (primary analysis).
- As log transformation did not correct for non-normality in PK parameters when comparing doses and genotypes a post-hoc, non-parametric analysis was performed (Mann-Whitney U test, $p<0.05$ considered significant).
- Multivariate linear regression was carried out to evaluate the influence of patient weight, age, sex, *CYP2B6* 516G>T and EFV dose on EFV $logAUC_{0\text{-}24}$ and $logC_{24}$.

Figure 1. Efavirenz concentrations over 24h following 400 mg and 600 mg once daily dosing (n=46). Black dashed lines (- - - -) show the previously calculated minimum effective concentration, MEC (1.0 mg/L) and toxicity cut-off (4.0 mg/L).[4]

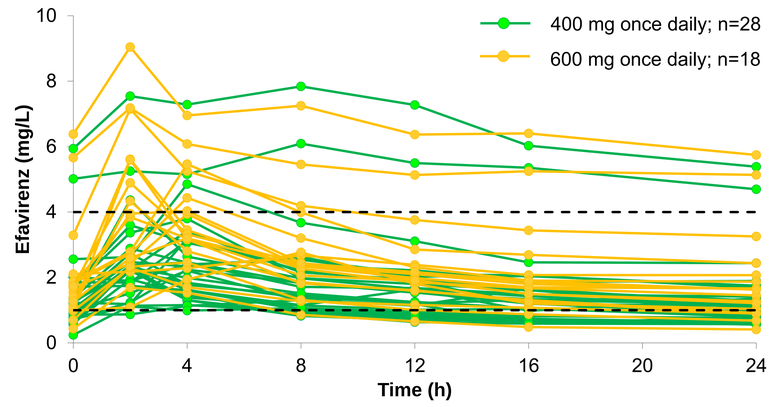
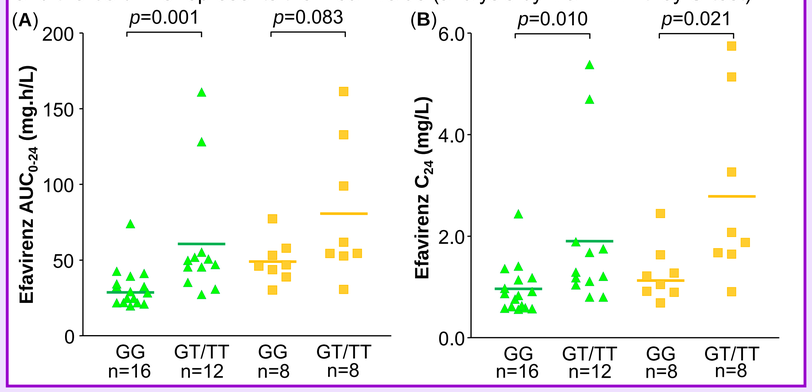


Table 1. Efavirenz PK parameters stratified by dose and associated statistical analyses (n=46).

Parameter	400 mg	600 mg	GMR (90% CI)*	p†
$AUC_{0\text{-}24}$ (mg.h/L)				
Geometric mean (90% CI)	38.0 (34.4-54.0)	54.2 (47.8-75.8)	0.70 (0.54-0.91)	
Median (IQR)	34.8 (26.0-48.4)	53.6 (43.5-61.6)	-	0.007
CL/F(L/h)				
Geometric mean (90% CI)	10.5 (10.2-13.2)	11.1 (9.96-15.0)	0.95 (0.73-1.23)	
Median (IQR)	11.5 (8.27-15.4)	11.2 (9.75-13.8)	-	0.857
C_{max} (mg/L)				
Geometric mean (90% CI)	2.65 (2.46-3.36)	4.09 (3.72-5.23)	0.65 (0.52-0.81)	
Median (IQR)	2.43 (2.21-3.30)	4.18 (2.77-5.60)	-	0.002
C_{12} (mg/L)				
Geometric mean (90% CI)	1.50 (1.36-2.25)	2.05 (1.81-2.92)	0.73 (0.55-0.97)	
Median (IQR)	1.54 (0.98-1.95)	1.95 (1.61-2.39)	-	0.029
C_{24} (mg/L)				
Geometric mean (90% CI)	1.12 (1.01-1.72)	1.52 (1.33-2.47)	0.73 (0.54-1.01)	
Median (IQR)	1.08 (0.78-1.39)	1.54 (0.91-2.07)	-	0.065

* efavirenz 400 mg/efavirenz 600 mg
† *p* values obtained by Mann-Whitney U test

Figure 2. Scatter plots of efavirenz (**A**) $AUC_{0\text{-}24}$ and (**B**) C_{24} for 400 mg (▲) and 600 mg (■) comparing *CYP2B6* 516G>T genotype. Each point is an individual patient and the **bold** line represents the mean value (analysis by Mann-Whitney U-test).



RESULTS

- ***Patients:*** 46 patients (400 mg n=28, 600 mg n=18) participated in the PK sub-study at sites in South Africa, Thailand, UK and Argentina (n=15 female; 37% African, 22% Asian, 41% Caucasian). Mean (s.d.) age, weight and baseline CD4 count were 36 years (10), 71 kg (16) and 269 (95) cell/mm^3, respectively.
- ***PK:*** EFV concentrations over the 24h dosing interval and PK parameters stratified by dose are presented (Figure 1; Table 1).
- EFV $AUC_{0\text{-}24}$, C_{max} and C_{12} were significantly lower in the 400 mg dosing group (Table 1). C_{12} and C_{24} were below the suggested MEC (1.0 mg/L) in 25 and 46% and 6 and 28% of patients receiving 400 mg and 600 mg EFV, respectively.
- ***Genotyping:*** Genotype data were available for 44/46 patients. Genotype frequencies were 52, 35 and 9% for *CYP2B6* 516GG, GT and TT, respectively and 93, 2 and 0% for *CYP2B6* 983TT, TC, CC, respectively and were in Hardy-Weinberg equilibrium.
- Patients who were *CYP2B6* 516G>T wild-type (GG; n=24) had significantly lower $AUC_{0\text{-}24}$, C_{max}, C_{12} and C_{24} and higher CL/F than carriers of the mutant allele (GT /TT; n=20; $p\leq0.018$ for all comparisons, Mann-Whitney U test).
- Stratified for dose, significant differences remained for 400 mg EFV but only C_{24} was significantly lower for GG (n=8) *vs.* GT/TT (n=8) for 600 mg EFV (Figure 2). *CYP2B6* 983T>C was not assessed given that 43/44 were wild-type (TT).
- Multivariate analysis revealed CYP2B6 516G>T, EFV dose and weight were independently associated with $logAUC_{0\text{-}24}$ (r^2=0.44, $logAUC_{0\text{-}24}$=1.79+(0.16*dose)+(0.22*G516T)-(0.004*weight); p=0.0001) and *CYP2B6* 516G>T and dose with $logC_{24}$ (r^2=0.35, $logC_{24}$=-0.11+(0.31*G516T)+(0.15*dose); p=0.0001).
- Overall 78% of patients achieved viral load <50 copies/mL at 48 weeks (missing viral load tests were classified as detectable).
- Due to small sample size, a formal PK-pharmacodynamic (PD) analysis was not possible. At week 48, 5/28 (18%) had detectable viral loads (≥50 copies/mL) for 400 mg EFV, 2 of which were <1.0 mg/L (MEC) for C_{12} and C_{24}. For 600 mg EFV, 5/18 (28%) had viral loads ≥50 copies/mL; 1 was below the MEC at C_{24}.

CONCLUSIONS

- Patients receiving 400 mg EFV had comparable viral suppression to 600 mg once daily (consistent with main ENCORE1 findings[2]) despite significantly lower EFV exposure and higher proportions of C_{12} and C_{24} below the suggested MEC at PK sampling.
- These data challenge the currently defined PK targets for therapeutic success.
- *CYP2B6* 516G>T genotype and weight were independently associated with EFV PK ($AUC_{0\text{-}24}$, C_{24}), which is consistent with previous reports.
- PK-PD modelling of the data obtained in ENCORE1 is currently ongoing to elucidate predictors of EFV PK and response in a heterogeneous HIV-infected patient population naïve to antiretroviral therapy.

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