

Etravirine's Pharmacokinetics Explored: PBPK Modeling and DDI Analysis with Efavirenz for Cancer Treatment

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Introduction

Drug repurposing is an emerging strategy in the quest for new cancer therapies, offering distinct advantages such as leveraging drugs already deemed safe for human use, accelerating the drug development process, and reducing costs [1]. Efavirenz (EFV) and etravirine (ETV) are first and second-generation non-nucleoside reverse transcriptase inhibitors that are approved for the treatment of human immunodeficiency virus (HIV) patients [2,3] and have been shown to have repurposing possibilities for other diseases [4]. Our group has recently published an in vitro work demonstrating the potential of ETV repurposing in bladder cancer treatment [5]. Combining repurposed drugs, either with each other or with traditional anticancer medications, can enhance their efficacy, reduce individual dosages, minimize side effects, and even overcome drug resistance [6]. A combination of ETV and EFV can emerge as a new cancer treatment regimen, but their drug-drug interaction (DDI) needs to be studied to guarantee the safety of this combination before repurposing.

Methods

Literature and ADMET Predictor® (version 11) data of ETV were used in combination to develop a PBPK model using GastroPlus® software (version 9.8.3) from Simulation Plus (Simulation Plus Inc., Lancaster, CA, USA). The model was constructed using a fed state and based on the physiology of a male American of 30 years old and 70 kg. Tablets were used as dosage form and two dosage regimens were tested, 100 mg once and two 200 mg doses 12 h apart. Pharmacokinetic values were obtained and compared with the literature [7,8]. Afterward, the DDI module of GastroPlus was used to make dynamic simulations of interactions between ETV (200 mg two times a day) and EFV at a single dose of both 400 mg and 600 mg, using a PBPK model already validated and included in the software.

Results

For 100 mg single dose the maximum plasma concentration (C_{max}), the time required to maximum plasma concentration (T_{max}), and the area under the curve from administration to the last time point with a measurable concentration after dosing (AUC_{0-T}) for a 96 h simulation where of 0.131 $\mu\text{g/mL}$, 3.28 h and 2.592 $\mu\text{g.h/mL}$, respectively. These values fit with the ones obtained in literature in the same conditions ($0.129 \pm 0.064 \mu\text{g/mL}$, 4 h and $1.417 \pm 1.140 \mu\text{g.h/mL}$) [7]. Further validation of the model was obtained with a 24 h simulation of 200 mg ETV every 12 h, with a simulated C_{max} of 0.329 vs $0.363 \pm 0.207 \mu\text{g/mL}$ and a simulated AUC_{0-T} of 4.374 $\mu\text{g.h/mL}$ vs $4.005 \pm 2.346 \mu\text{g.h/mL}$ in the literature [8] (table 1).

Table 1. Pharmacokinetic parameters from two case studies and those estimated in the present study using GastroPlus.

Parameters	Study 1 [7]		Study 2 [8]	
	Estimated value	Literature value	Estimated value	Literature value
Fa %	48.236	n.d	44.397	n.d
FDp %	41.369	n.d	39.715	n.d
F %	35.342	n.d	33.931	n.d
C _{max} (μg/mL)	0.131	0.129 ± 0.064	0.329	0.363 ± 0.207
T _{max} (h)	3.280	4 (2.0-6.0)	15.28	n.d
AUC _{0-T} (ng.h/mL)	2.592	1.417 ± 1.140	4.374	4.005 ± 2.346
AUC _{0-∞} (ng.h/mL)	3.6436	n.d	7.277	n.d

After this was obtained, the DDI study was performed with ETV as a victim and EFV as the perpetrator, with induction kinetic constants of its CYP enzymes 3A4 and 2B6 already integrated into the GastroPlus-validated EFV model. Ratios between ETV/EFV alone (baseline) and in combination for fraction absorbed (Fa), fraction of the drug concentration in the portal vein (FDp), fraction of the drug concentration in blood (F), C_{max} , T_{max} , AUC_{0-T} , and area under the curve extrapolated to infinity ($AUC_{0-∞}$) were obtained. For 400 mg of EFV, the ratios were mostly around the 0.9-1 mark, with the lowest being for ETV C_{max} at a ratio of 0.878, which translates to a decrease of C_{max} from 0.329 to 0.289 $\mu\text{g/mL}$, and $AUC_{0-∞}$ of EFV with 0.773, which is a decrease from 97600 to 75400 $\mu\text{g.h/mL}$. However, none of these values are significant decreases (table 2).

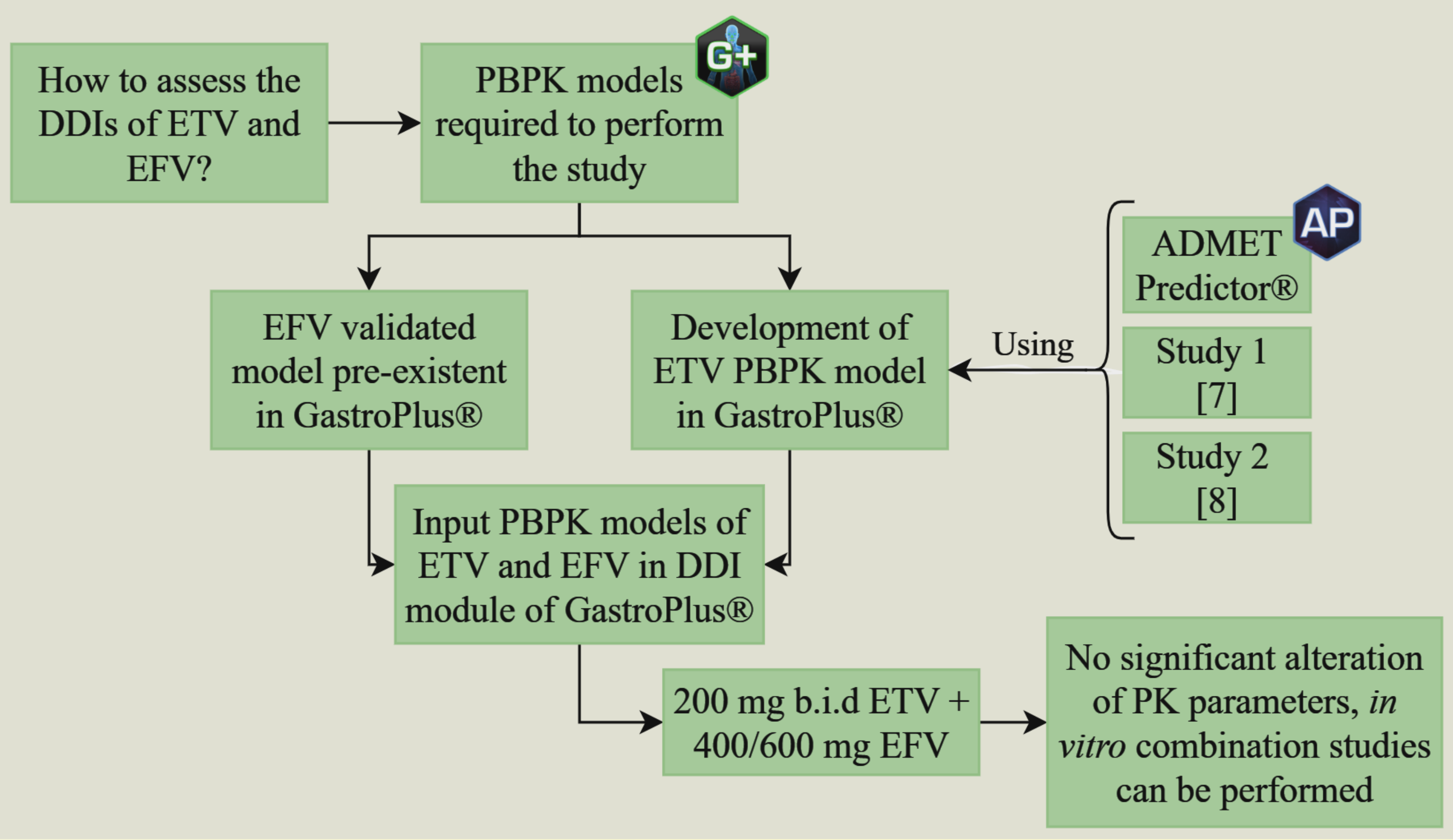
Conclusion

This study demonstrates a successful attempt at creating a PBPK model of ETV with pharmacokinetic values comparable to those obtained previously in literature. It also demonstrates that there is no drug-drug interaction between ETV and EFV, two potential repurposing drugs that have shown potential for cancer treatment, which indicates that this is a viable combination to start performing in vitro testing and possibly develop a new anticancer therapy.

Objectives

The objective of this work was to develop a Physiologically Based Pharmacokinetic (PBPK) model of ETV, using literature and computational data, and perform DDI studies between ETV and EFV at relevant concentrations.

Figure 1. Schematic of workflow and broad results from the present study.

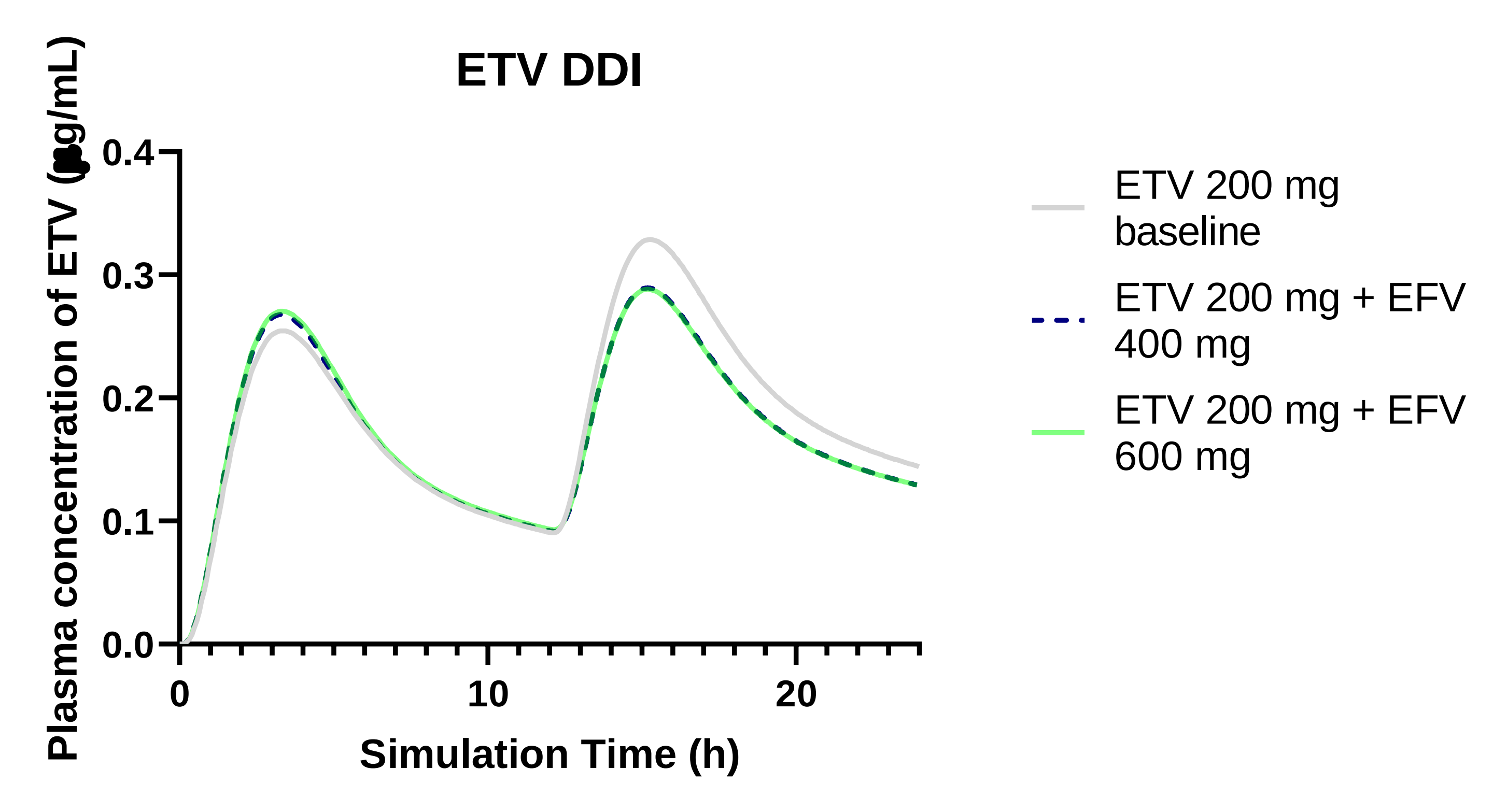


For 600 mg EFV the situation was comparable, with the same not significant decreases noted in ETV C_{max} (ratio 0.875, 0.329 to 0.288 $\mu\text{g/mL}$) and EFV $AUC_{0-∞}$ (ratio 0.72, 150000 vs 108000 $\mu\text{g.h/mL}$). It is also important to note that there were no significant changes between the pharmacokinetic parameters of the same concentration of ETV when compared between combinations with 400 mg or 600 mg of EFV (figure 2).

Table 2. Pharmacokinetic parameters of 200 mg of ETV alone b.i.d (baseline) and in combination with a single dose of either 400 or 600 mg of EFV, with the ratio between the baseline and each condition.

Compounds	Fa (%)	FDp (%)	F (%)	C _{max} (μg/mL)	T _{max} (h)	AUC _{0-t} (ng.h/mL)	AUC _{0-∞} (ng.h/mL)
ETV baseline	44.4	39.72	33.93	0.329	15.28	4373.6	7277
ETV 200 mg b.i.d + EFV 400 mg	44.52	36.67	31.32	0.289	15.2	4125	6833
Ratio	1.003	0.923	0.923	0.878	0.995	0.943	0.939
ETV 200 mg b.i.d + EFV 600 mg	44.52	36.8	31.43	0.288	15.2	4146.4	6862.8
Ratio	1.003	0.926	0.926	0.875	0.995	0.948	0.943

Figure 2. Simulation time-plasma concentration curve of ETV baseline (gray line), ETV with EFV 400 mg (dotted line), or EFV 600 mg (green line).



References

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