

PBPK Modeling of Repurposed HIV Drugs in Prostate Cancer and the Influence of Patient Physiology

Mariana Pereira^{1,2,3 *}, Nuno Vale^{1,2,4}

¹ PerMed Research Group, RISE-Health, Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal
² RISE-Health, Department of Community Medicine, Health Information and Decision (MEDCIDS), Faculty of Medicine, University of Porto, Rua Doutor Plácido da Costa, 4200-450 Porto, Portugal
³ ICBAS—School of Medicine and Biomedical Sciences, University of Porto, Rua de Jorge Viterbo Ferreira 228, 4050-313 Porto, Portugal
⁴ Laboratory of Personalized Medicine, Department of Community Medicine, Health Information and Decision (MEDCIDS), Faculty of Medicine, University of Porto, Rua Doutor Plácido da Costa, 4200-450 Porto, Portugal

*mariana.m.pereira2097@gmail.com

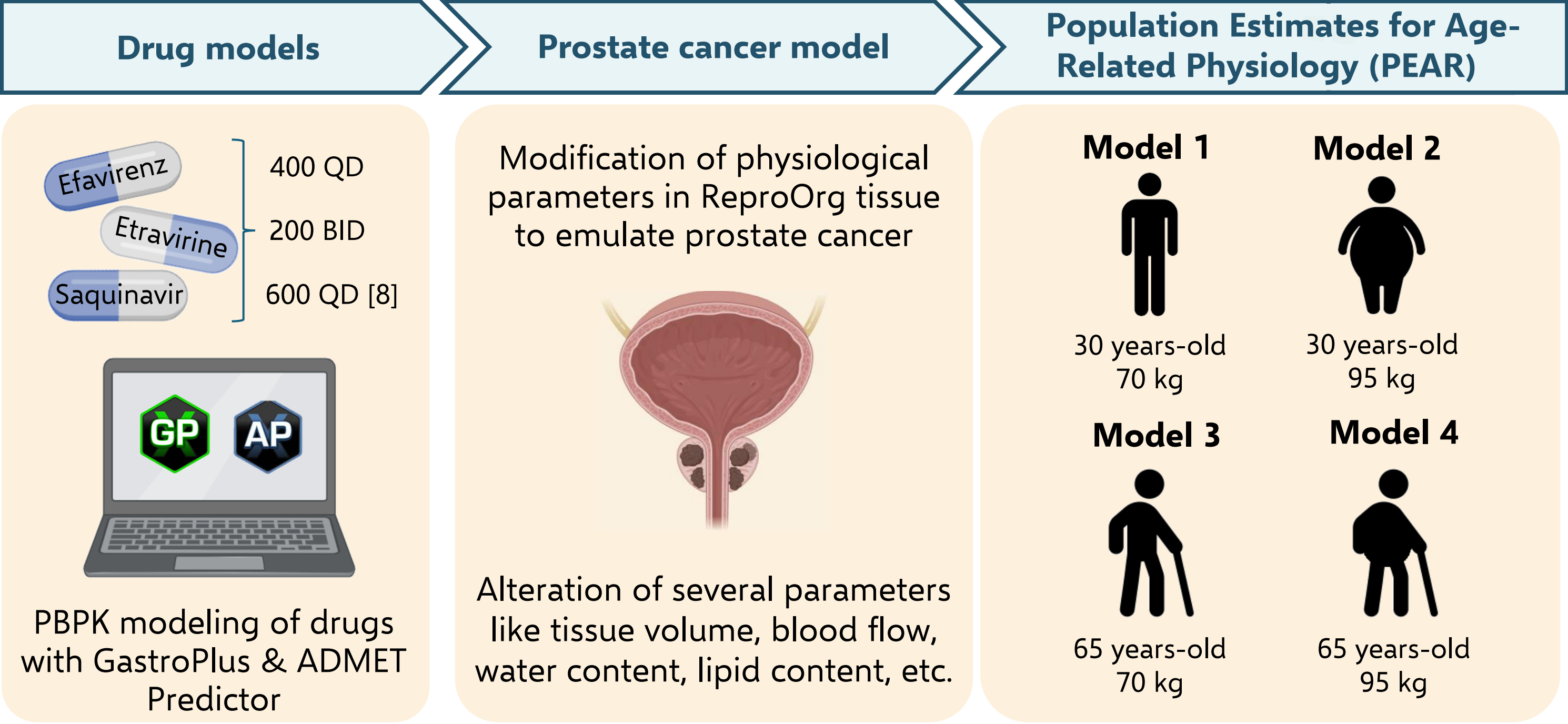


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Introduction

Drug repurposing is gaining traction as a strategic approach in cancer therapy development, leveraging the benefits of using safe drugs for human consumption. This approach accelerates the development process and significantly reduces costs [1]. **Efavirenz (EFV), etravirine (ETV), and saquinavir (SAQ)** are antiretroviral drugs approved for the treatment of human immunodeficiency virus (HIV) patients [2-4] and have been shown to have repurposing possibilities for other diseases [5]. Our group has published in vitro works demonstrating the potential of these drugs in various cancers [6,7]. This study aims to develop and compare physiologically based pharmacokinetic (PBPK) models for ETV, EFV, and SAQ in various scenarios simulating prostate cancer conditions. We will **create models representing normal and cancerous prostate tissue**. These models will be applied to diverse populations to **assess how age and weight influence drug pharmacokinetics in the context of prostate cancer**. The goal is to evaluate the impact of these conditions on the pharmacokinetic profiles of these drugs, providing insights into potential dosing adjustments and therapeutic strategies with these repurposed drugs for prostate cancer patients.

Workflow



Prostate Cancer Model Results

Table 1. GastroPlus® values of the normal and the altered cancerous ReproOrg/Prostate tissues for each model.

	Normal	Model 1/3	Model 2	Model 4
Kp (tissue-to-plasma partition coefficient)	1.5687 (1.9762) ^a	1.88	1.88	2.2
Fraction unbound (Fu) in tissue	0.0009	0.0015	0.0015	0.0015
Volume (mL)	47.18 (64.03) ^b	36	50	50
Blood flow (mL/s)	0.1615 (0.2241) ^b	0.3067	0.416	0.416
Lymph flow (%PF)	0.4	1	1	1
Volume fraction of neutral lipids (Vnt)	0.0207	0.027	0.027	0.027
Volume fraction of phospholipids (Vpht)	0.0162	0.019	0.019	0.019
Volume fraction of water (Vwt)	0.783	0.76	0.76	0.76
Concentration of acidic phospholipids (Capt)	5.03	6.5	6.5	6.5
Density (g/mL)	1	1.06	1.06	1.06
Fraction of tissue volume which is extracellular space (Fvec)	0.273	0.255	0.255	0.255
Lysosomal volume fraction (Vlys)	0.011	0.165	0.165	0.165
Lysosomal pH	5.1	5.4	5.4	5.4
Fraction of tissue volume which is endosomal space (Evendo)	0.005	0.0065	0.0065	0.0065
Leakage	1	0.8	0.8	0.8

^a Value for model 2; ^b Values for models 2 and 4.

Conclusions

These findings emphasize that while **prostate tissue-specific changes do not significantly affect the pharmacokinetics** of ETV, EFV, and SAQ, patient-specific characteristics such as **age and weight should be carefully considered** when repurposing these antiretroviral drugs for prostate cancer treatment. Older patients or those with obesity, factors often associated with prostate cancer, may require tailored dosing strategies to optimize therapeutic outcomes while minimizing toxicity.

References

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PEAR Model Results

Table 2. Pharmacokinetic parameters of a single 400 mg dose of EFV in the different physiological models.

EFV 400 mg once	30 yo – 70 kg	30 yo – 95 kg	65 yo – 70 kg	65 yo – 95 kg
C _{max} (µg/mL)	1.591	1.239	1.696	1.286
T _{max} (h)	2.72	2.56	2.8	2.64
AUC _{0-inf} (µg.h/mL)	59.206	56.404	53.934	54.643
AUC _{0-T} (µg.h/mL)	24.512	18.115	25.139	18.354

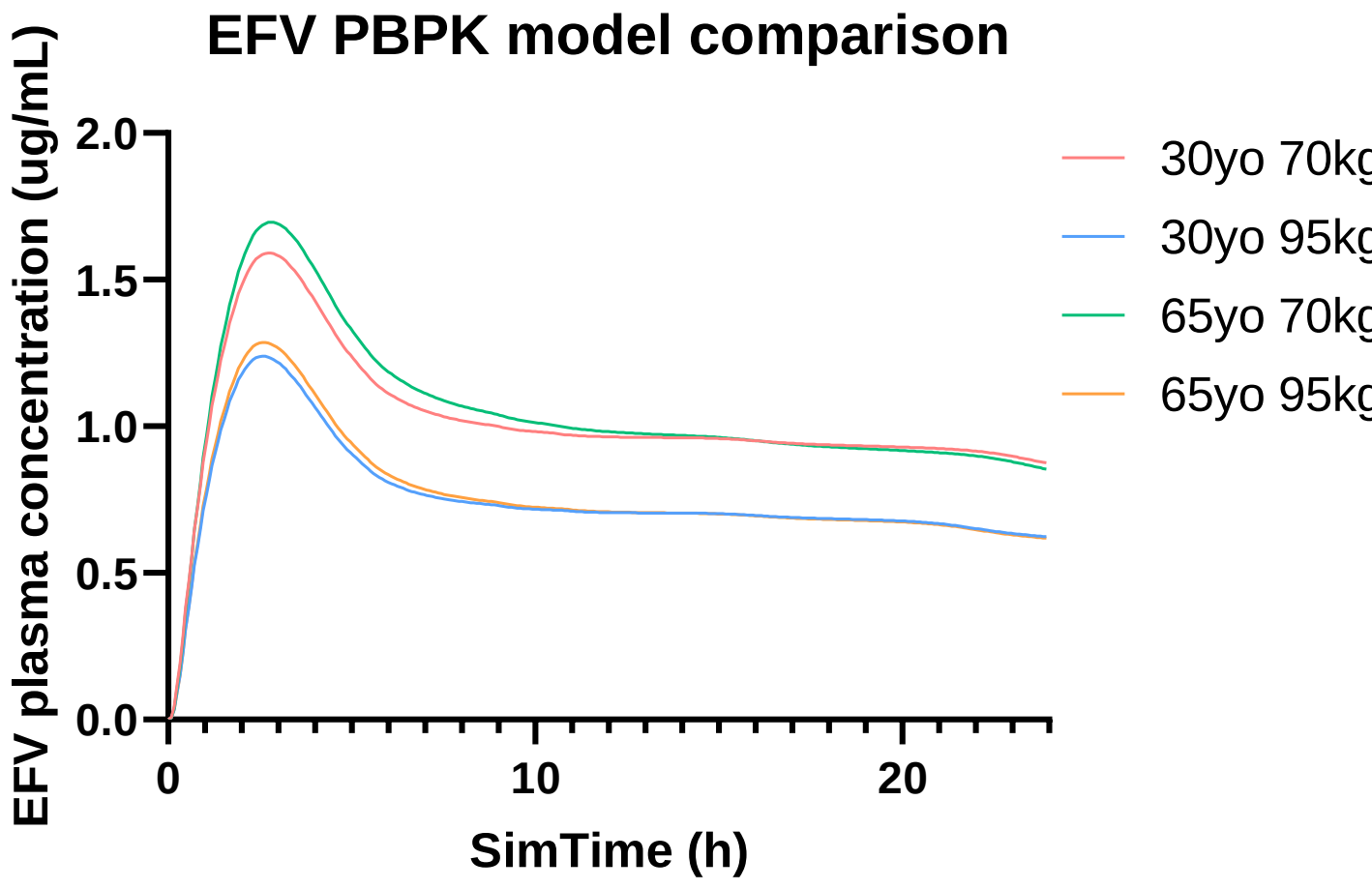


Figure 1. Time-plasma concentration curves of a single 400 mg dose of EFV in the different physiological models.

- **Older and lighter individuals exhibit higher plasma concentrations** of EFV
- Age and body weight significantly influence plasma EFV concentrations

Table 3. Pharmacokinetic parameters of a two 200 mg doses of ETV in the different physiological models.

ETV 200 mg twice	30 yo – 70 kg	30 yo – 95 kg	65 yo – 70 kg	65 yo – 95 kg
C _{max} (µg/mL)	0.310	0.255	0.328	0.262
T _{max} (h)	15.2	15.28	15.28	15.28
AUC _{0-inf} (µg.h/mL)	6.948	5.932	7.146	5.769
AUC _{0-T} (µg.h/mL)	4.142	3.348	4.406	3.453

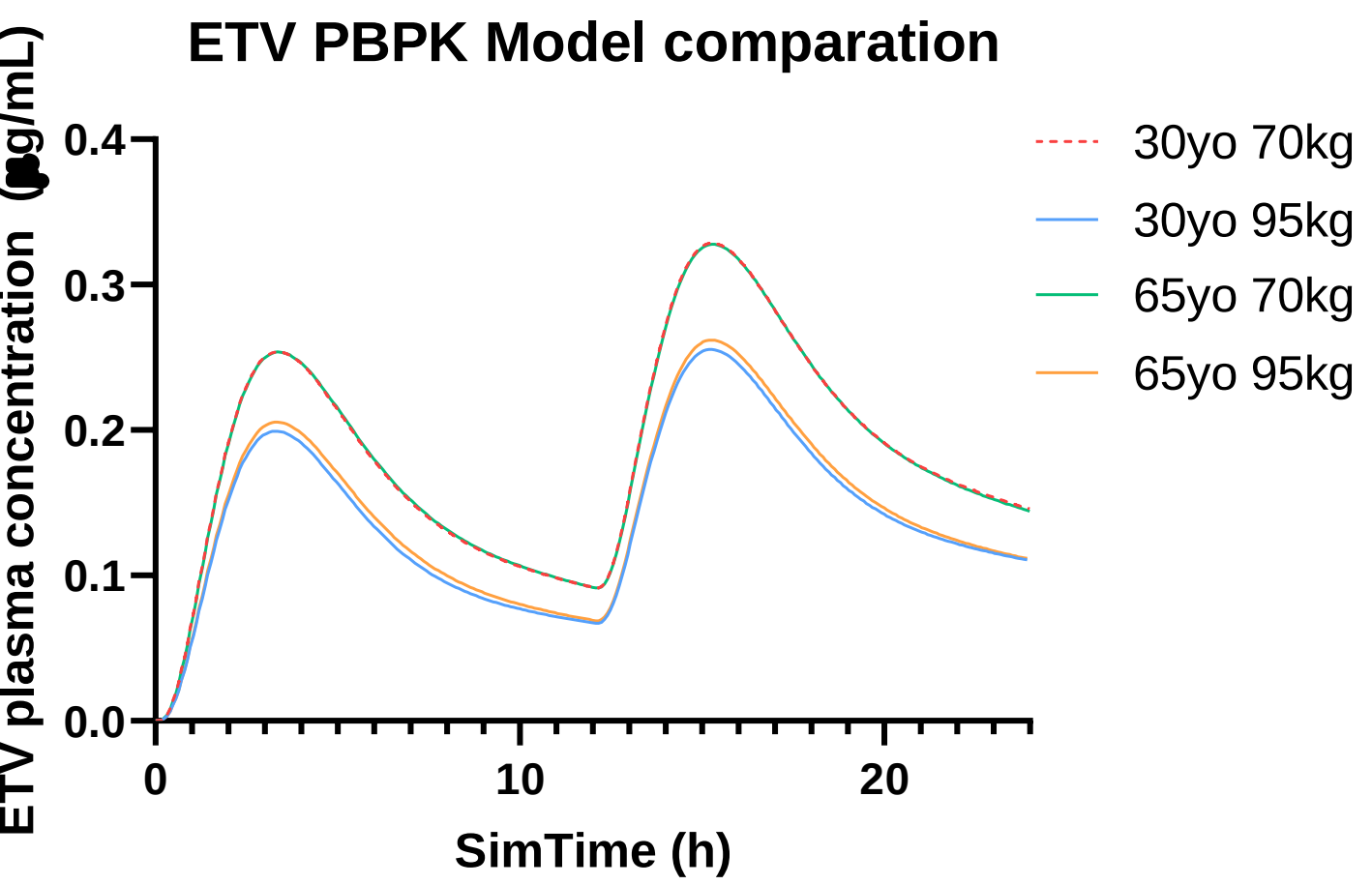


Figure 2. Time-plasma concentration curves of two 200 mg doses of ETV in the different physiological models.

- Individuals with **lower weight have the highest ETV C_{max}** independent of age
- For individuals with higher weight, older age is associated with a slightly higher ETV C_{max}

Table 4. Pharmacokinetic parameters of a single 600 mg dose of SAQ in the different physiological models.

SAQ 600 mg once	30 yo – 70 kg	30 yo – 95 kg	65 yo – 70 kg	65 yo – 95 kg
C _{max} (µg/mL)	12.489	10.173	11.727	11.546
T _{max} (h)	1.12	1.12	1.12	1.12
AUC _{0-inf} (µg.h/mL)	59.659	54.599	60.503	66.474
AUC _{0-T} (µg.h/mL)	56.844	50.447	56.862	60.145

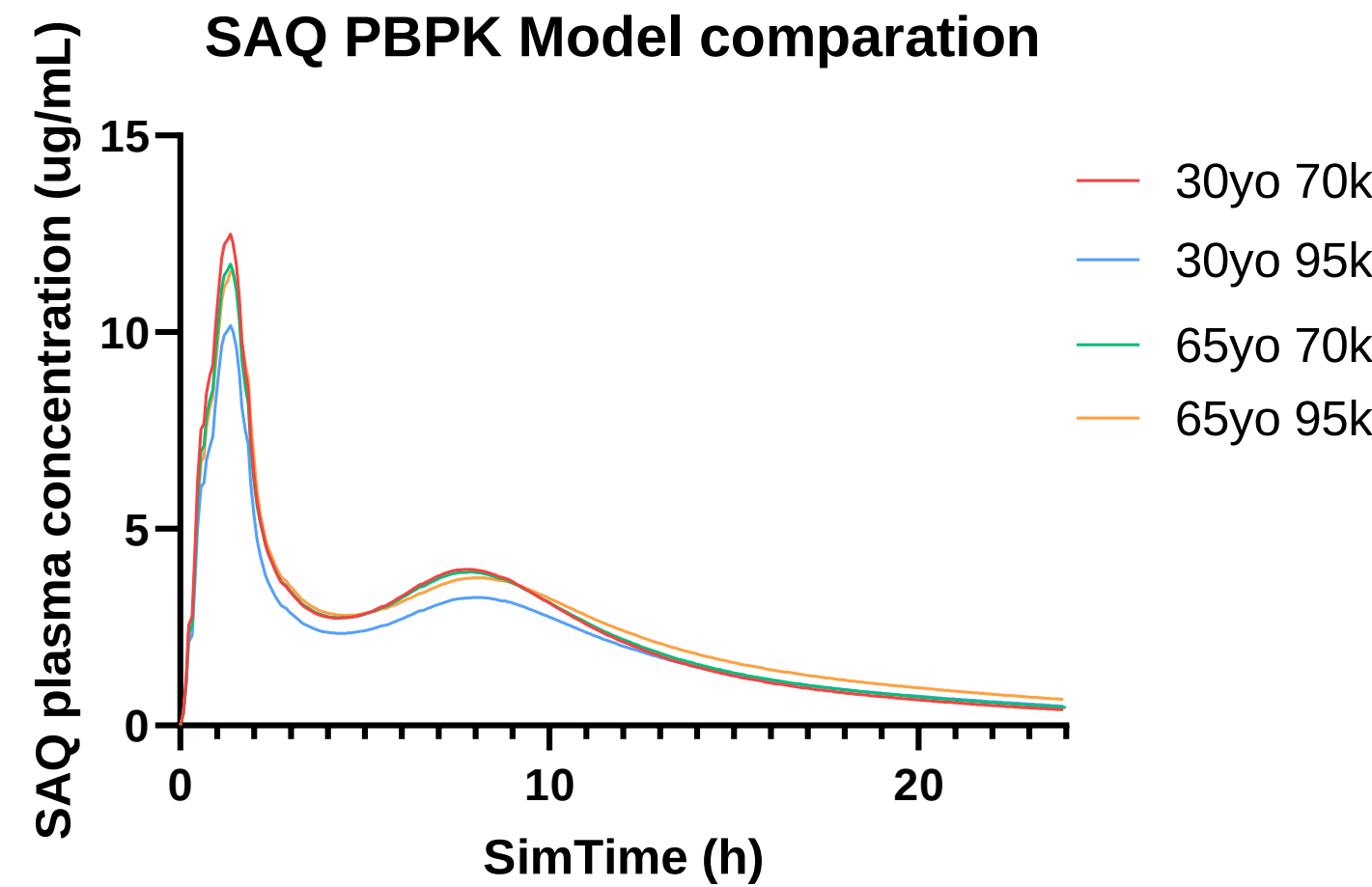
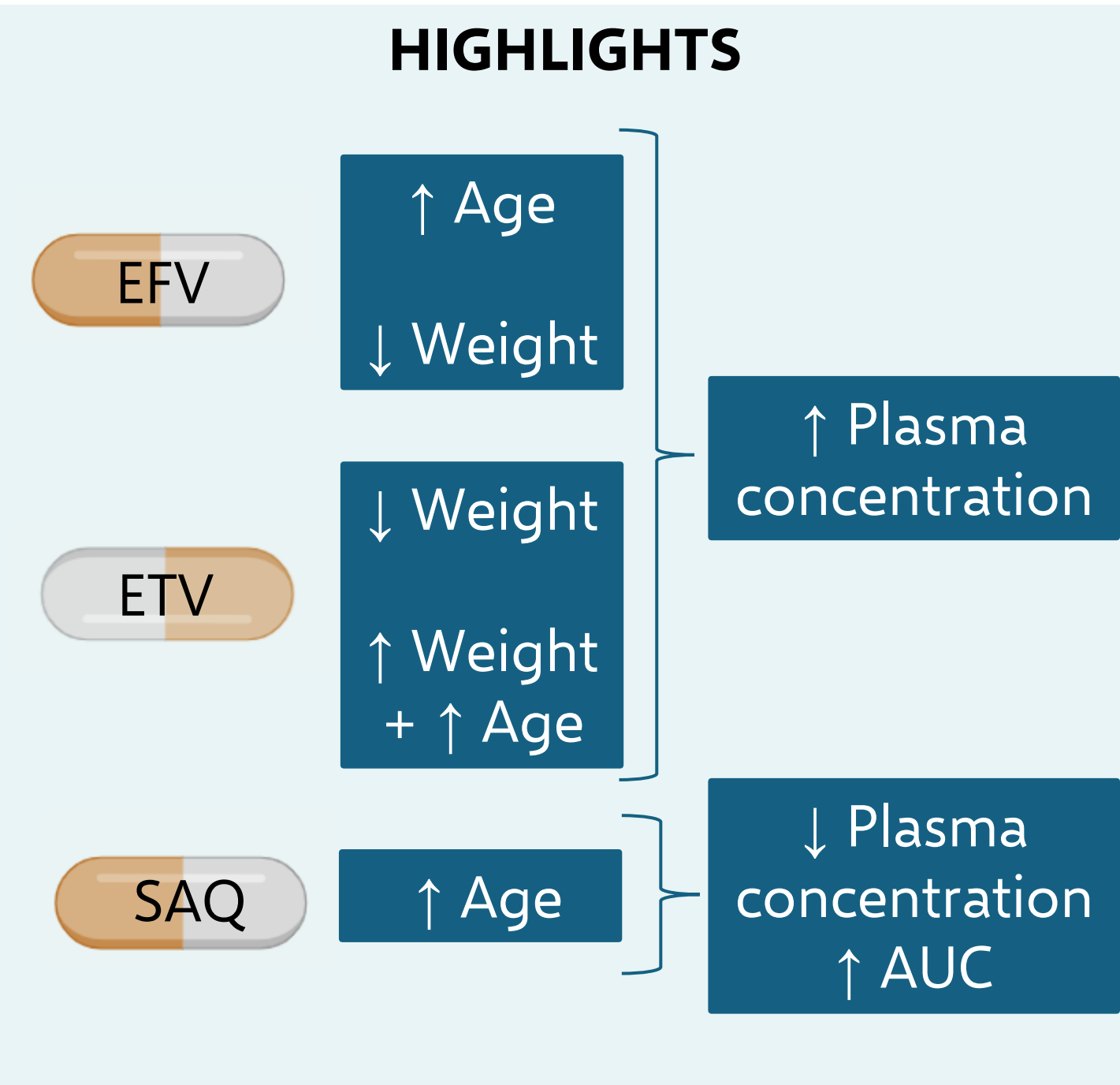


Figure 3. Time-plasma concentration curves of a single 600 mg dose of SAQ in the different physiological models.

- SAQ reaches a **higher C_{max} in younger individuals**, likely due to faster absorption and distribution
- **Younger individuals also clear the drug quickly**, leading to shorter overall exposure
- Older individuals show lower C_{max} but higher AUC_{0-T}, indicating **slower clearance and longer-lasting plasma levels**.
- Obesity affects SAQ concentrations, with differences observed between very obese and normal-weight patients.
- Age and body weight significantly influence SAQ pharmacokinetics, affecting both peak levels and duration of exposure.



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