

Joint pharmacogenetic model of tenofovir and emtricitabine and their active intracellular metabolites in HIV Patients

Julie Bertrand (1), Aurélie Barrail-Tran (2), Rada Savic (3), Céline Verstyuyft (4) and the ANRS 134 COPHAR3 trial group

(1) UMR 1137 IAME INSERM Université Paris Diderot, (2) AP-HP, Hôpital Bicêtre, Pharmacie Clinique ; Université Paris Sud ; INSERM UMR 1184, Center for Immunology of Viral Infections and Autoimmune Diseases (3) Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, (4) Service de génétique moléculaire et pharmacogénétique, hôpital Bicêtre, AP-HP; Université Paris Sud; INSERM UMR 1184, Center for Immunology of Viral Infections and Autoimmune Diseases

Introduction

Background

- Tenofovir (TFV) and emtricitabine (FTC) are part of the recommended antiretroviral therapy (ART) regimen for naïve HIV patients and since 2012, the WHO recommends offering oral PrEP containing TFV.
- Their active intracellular forms: TFV-diphosphate (TFV-DP) and FTC-triphosphate (FTC-TP) hinder the activity of HIV reverse transcriptase and prevent the production of new virion.
- Despite several PK studies, large inter-individual variability in TFV, TFV-DP, FTC and FTC-TP PK parameters is still unexplained.

Objectives

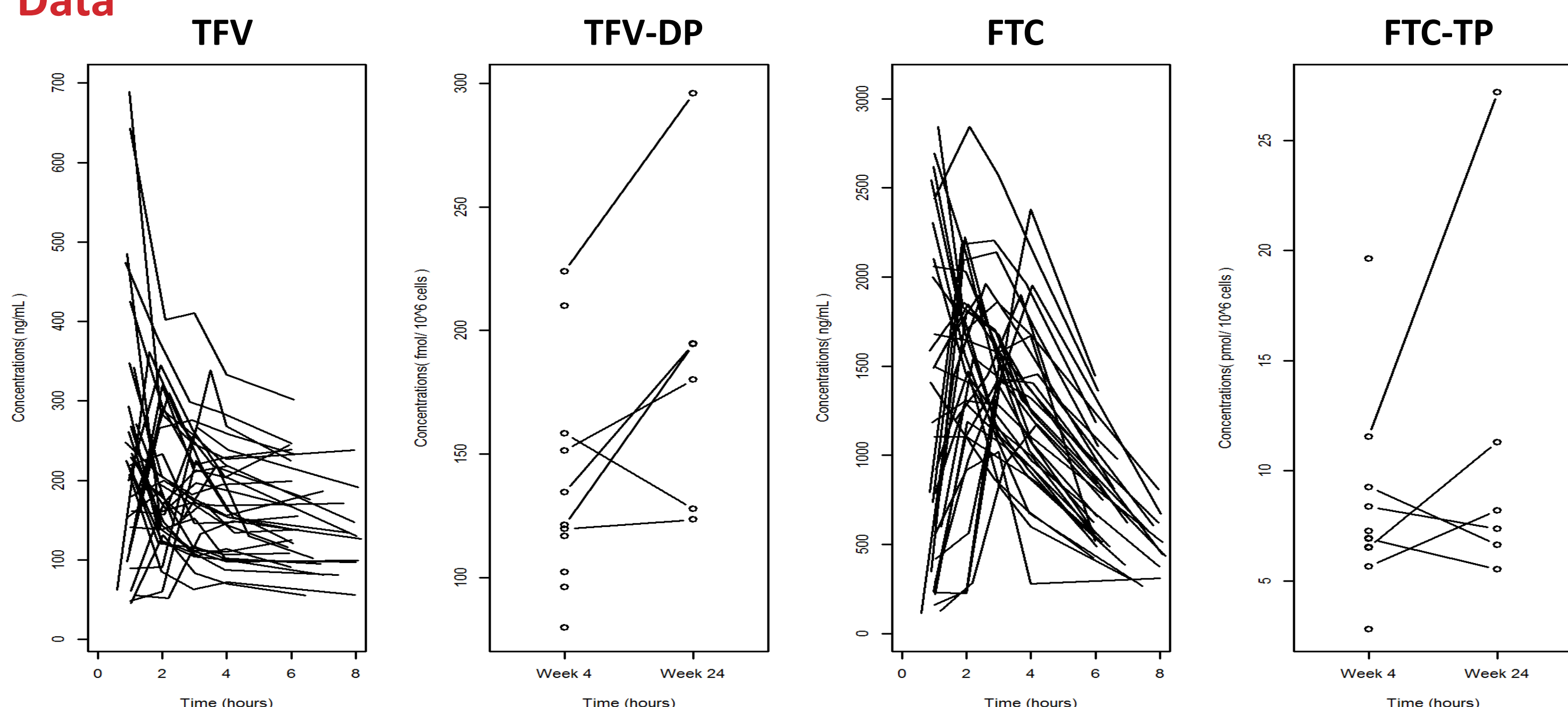
- We performed a joint population pharmacogenetic analysis of TFV, TFV-DP, FTC and FTC-TP concentrations and genetic variants collected in the ANRS 134 COPHAR3 trial [1].
- A simulation study was performed to predict concentrations following different dosing regimen.

Methods

Study design

- 35 treatment naïve patients starting on a treatment containing
 - 300 mg of atazanavir + 100 mg ritonavir
 - fixed-dose combination of 300 mg of TFV + 200 mg FTC.
- PK sample collection:
 - TFV/FTC: pre-dose and 1, 2, 3, 4 and 8h post-dose on W4 and pre-dose on W24
 - TFV-DP/FTC-TP: pre-dose on W4 and W24
- MEMS-capped bottle record of exact time of each opening

Data



Population analysis

- Adherence "gold standard analysis": dosing information history from MEMS cross-validated with self reported time of dos intake preceding PK visit [1].
- Data were analysed using the nonlinear mixed-effects approach available in Monolix 2016 R1 [2].
- A covariate analysis was performed, using a forward stepwise selection procedure alternating screening on empirical Bayes estimates (with shrinkage <50%) at 5% and population covariate model selection on Wald test at 1%.
 - Gender, weight, age, race, creatinine and atazanavir clearance
 - MRP2, MRP4, MDR1.

Predictions

- Plasma and intracellular mean (C_{mean} and $C_{mean,intra}$), min and max concentrations at steady state as well as mean metabolite ratio (MMR) = $C_{mean,intra}/C_{mean}$
- Following a seven-days-a-week (7D, ANRS 134 COPHAR 3) and a four-days-a-week (4D, ANRS 162-4D trial [3]) regimen.

Conclusions

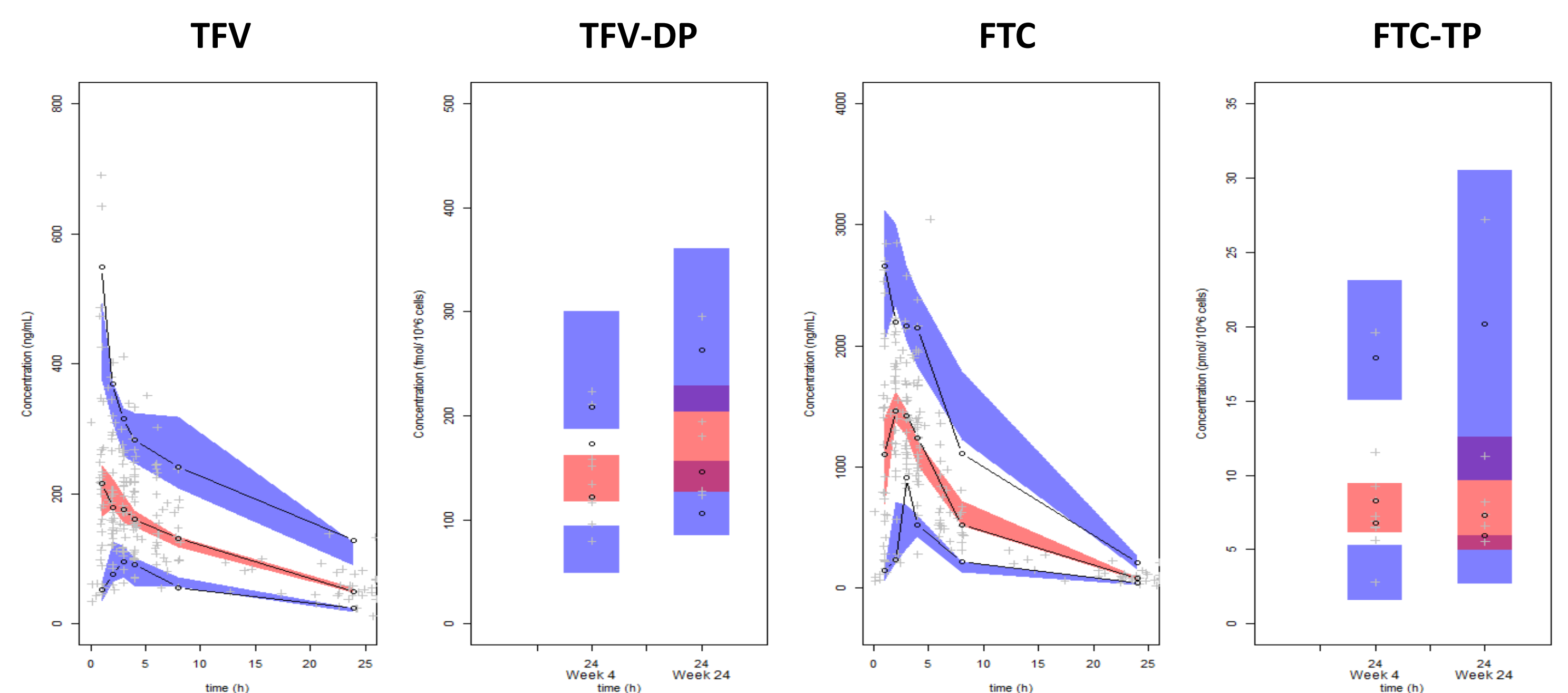
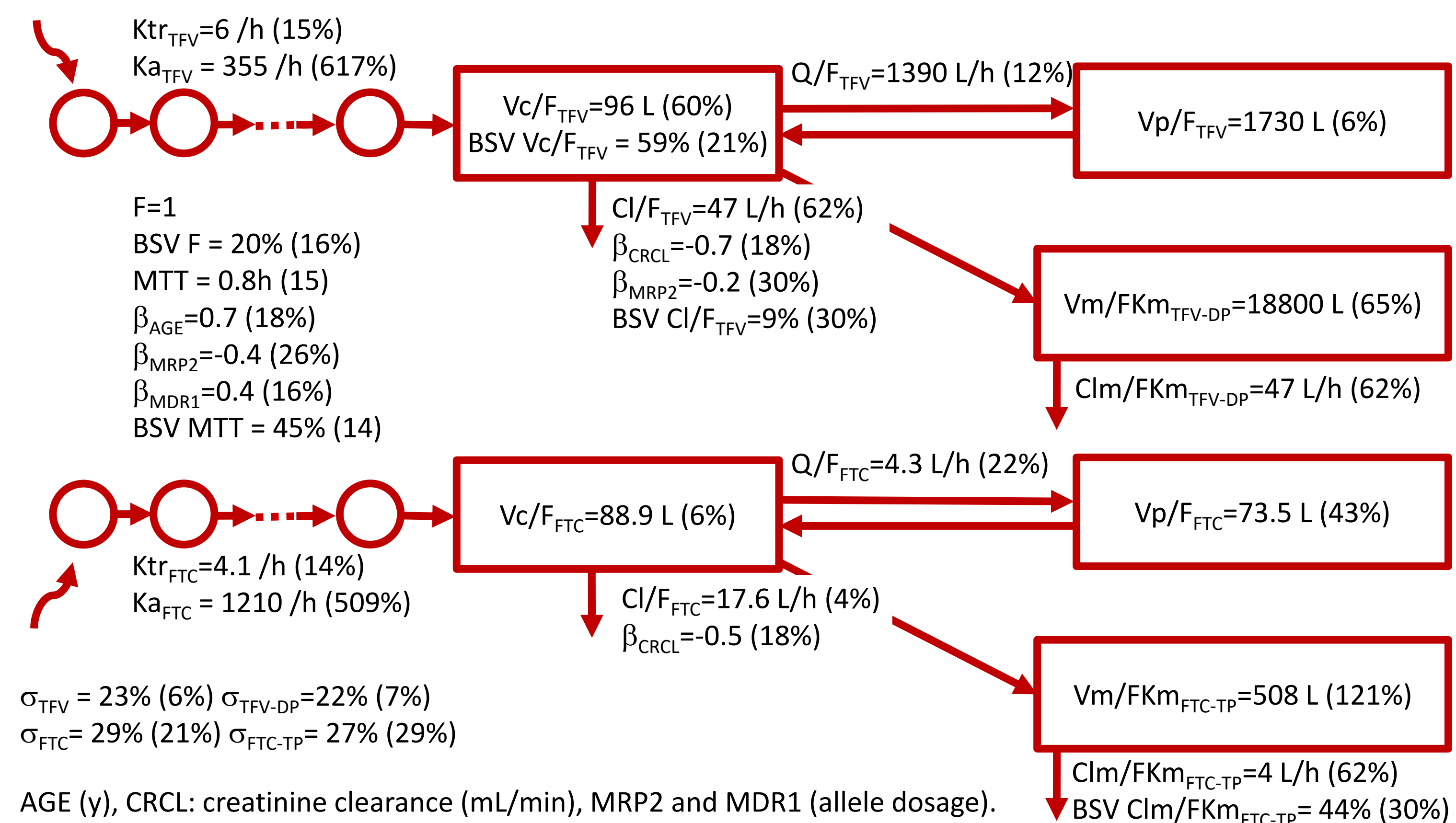
- Parameter estimates were in accordance with the literature except for Q/F_{TFV} (twice the highest reported value) and $t_{1/2}$ for TFV-DP and FTC-TP (60% longer)
- MRP2 effect on CL/FTFV coherent with an endogenous substrate of MRP2 competing with TFV for excretion by MRP4 [6]
- Low model predicted concentrations in the cells with regard to the drugs efficacy levels assessed from simulations and in vivo studies, yet clinical success reported in ANRS 162-4D trial

References

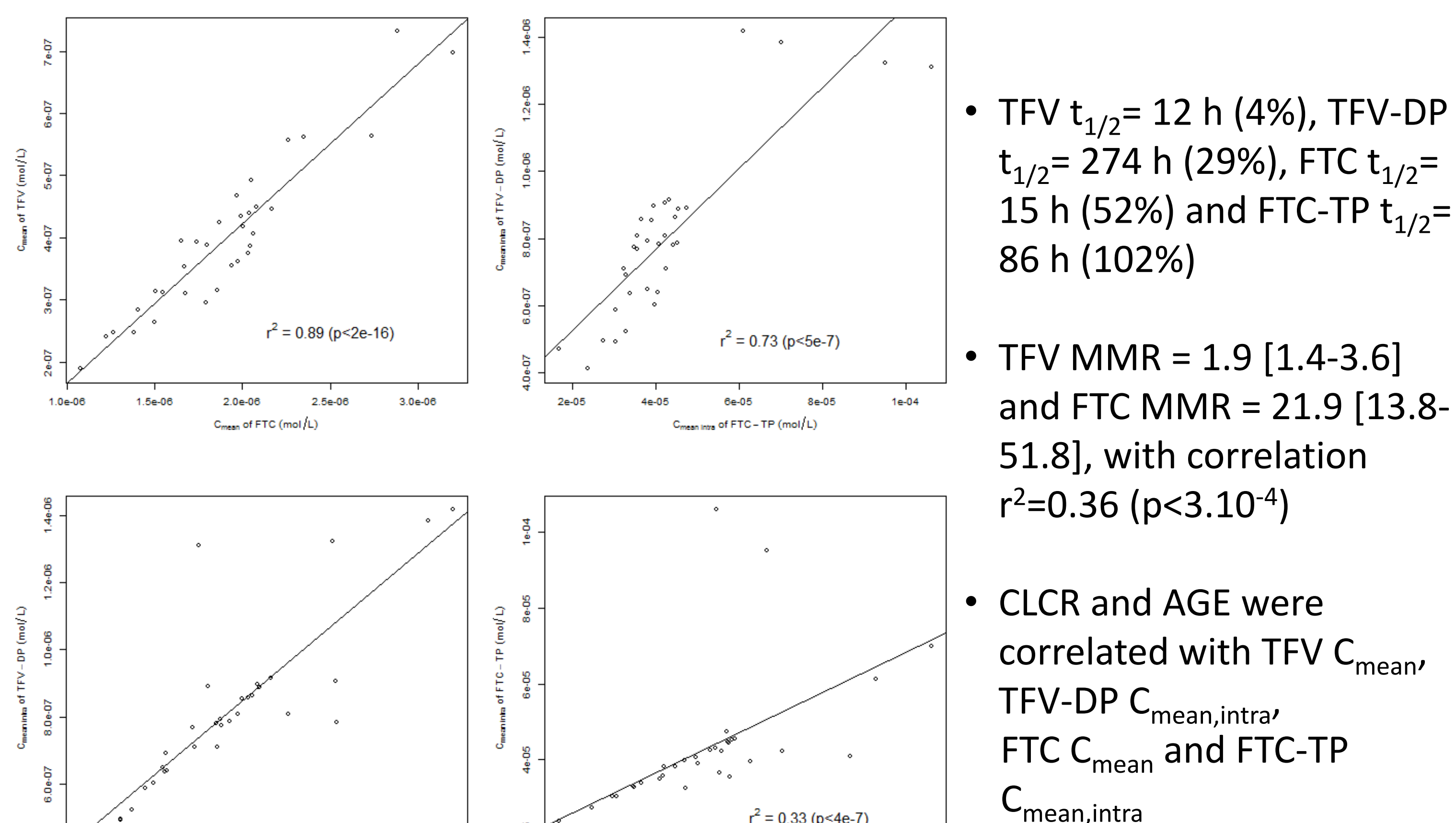
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Results

Final joint covariate model parameter estimates and relative standard errors



Relationships between TFV, TFV-DP, FTC, FTC-TP concentrations, and covariates



Model predicted concentrations for seven- and four-days-a-week regimen

