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## Introduction

Sexual transmission of human immunodeficiency virus (HIV) is the main way of HIV infection spreading, with semen being one of the most important sources of HIV infections. The use of combined antiretroviral treatments (cART) resulted into significant decrease in blood plasma (BP) HIV load. A parallel decay in HIV-RNA levels both in plasma and seminal plasma (SP) has been reported in numerous studies. However, other studies have described discordance between BP HIV load and SP HIV load (spVL). Thus, despite a suppressed BP HIV load, spVL could be detectable for some patients receiving cART (~ 10 %). One determinant of HIV shedding in the male genital tract could be the penetration of antiretroviral drugs in this compartment. Available data on FTC and TFV seminal plasma concentrations are sparse, despite these drugs are recommended in first-line regimen for HIV treatment and are intended to be used as a pre- and post-exposure prophylaxis agents.

The aims of this study were: (i) to describe FTC and TFV blood plasma and seminal plasma pharmacokinetics in a large population of HIV-1 infected men; (ii) to evaluate FTC and TFV penetration in the male genital tract by SP-to-BP exposures ratios at steady state; and (iii) to assess the impact of FTC and/or TFV seminal plasma exposures on the seminal plasma HIV load.

## Methods

### Patients, treatments, sampling

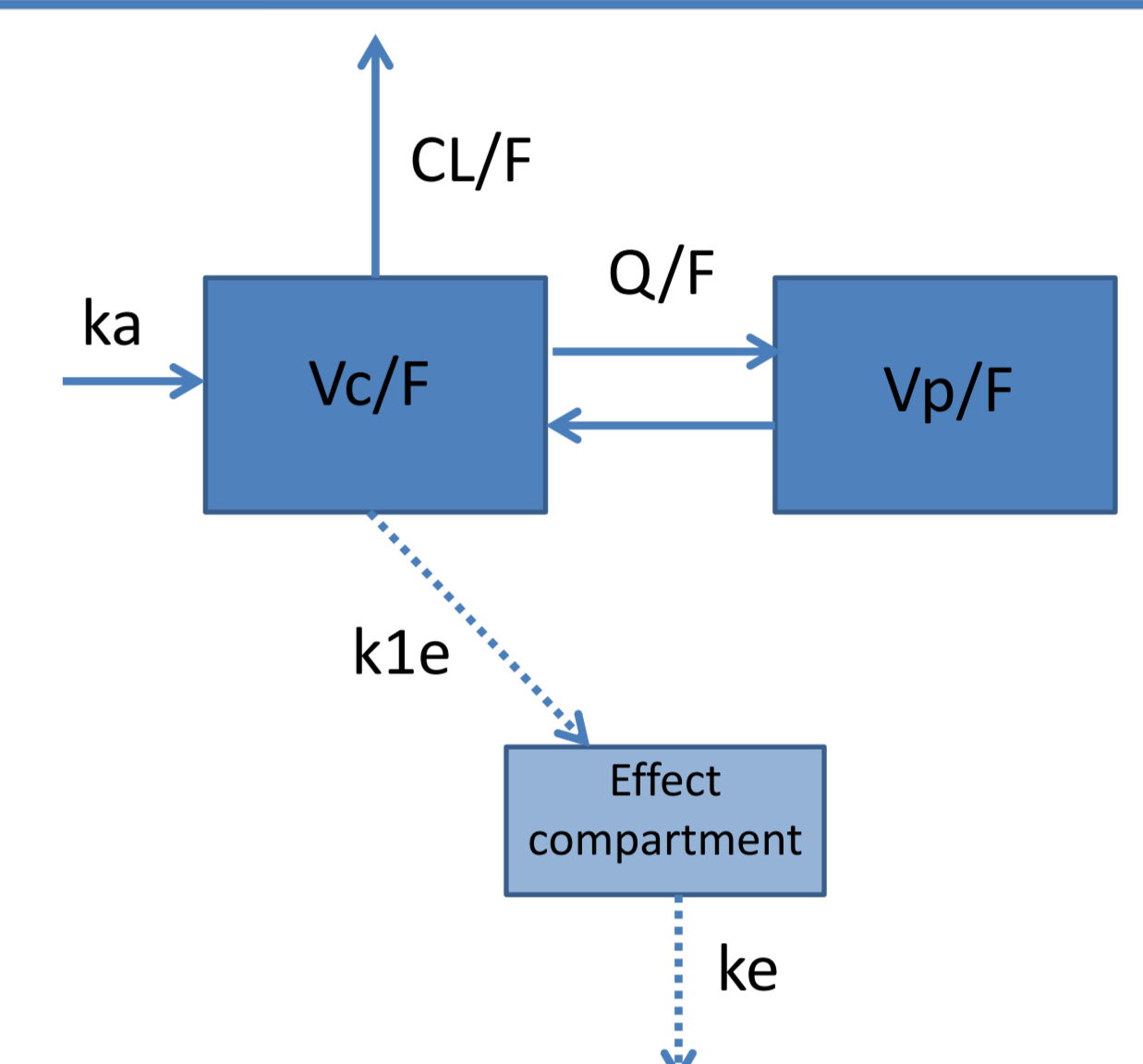
Our study populations included HIV-1 infected men having sex with men from the EVARIST ANRS-EP 49 study. These men received stable cART and had a suppressed BP HIV load for at least 6 months. FTC and TFV BP and SP concentrations were measured using a validated high-performance liquid chromatography tandem mass spectrometry method. For FTC, 122 and 117 men were included for the BP and SP analyzes respectively. A total of 236 BP concentrations and 209 SP concentrations were available. For TFV, 129 and 123 men were included for BP and SP analyzes respectively. A total of 248 BP concentrations and 217 SP concentrations were available.

### Modeling

Data were analyzed by a population approach, using the software program Monolix version 4.1.4. Parameters were estimated using the stochastic approximation expectation maximization (SAEM) algorithm. FTC and TFV BP pharmacokinetics were described by two-compartment models. Addition of an effect compartment with different input and output constants was used to describe FTC and TFV SP pharmacokinetics.

### Statistical Analysis

Mixed effects logistic regressions with random effect on individuals were performed with R software in order to evaluate the impact of FTC and/or TFV seminal plasma exposures on the spVL detectability.



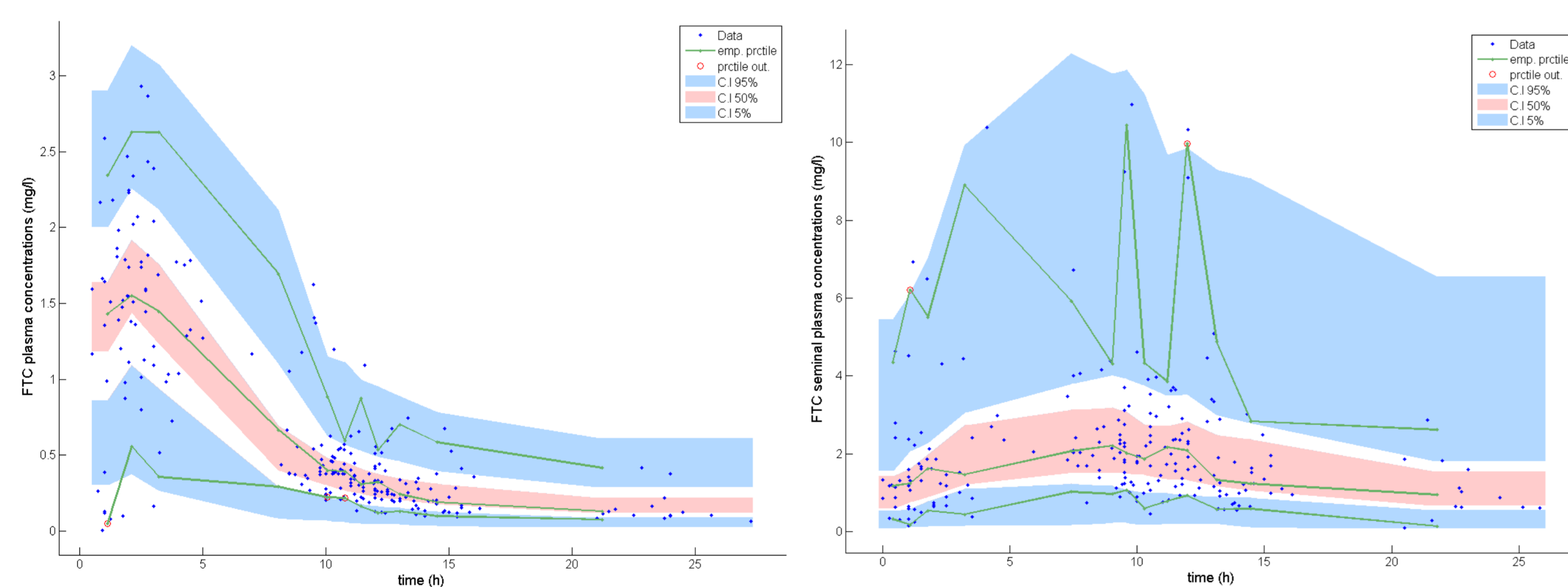
Population pharmacokinetic model for FTC and TFV in BP and SP. Parameters are: absorption rate constant ( $k_a$ ), apparent elimination clearance ( $CL/F$ ), central volume of distribution ( $V_c/F$ ), intercompartmental clearance ( $Q/F$ ), peripheral volume of distribution ( $V_p/F$ ), blood plasma-to-seminal plasma transfer ( $k_{1e}$ ) and seminal plasma elimination rate constants ( $k_e$ ),  $F$  being the unknown bioavailability.

## Results

### FTC Results

Parameter	Estimate	RSE (%)	Parameter	Estimate	RSE (%)
$k_a$ ( $h^{-1}$ )	0.53*	-	$k_{1e}$ ( $h^{-1}$ )	0.341	28
$CL/F$ ( $l \cdot h^{-1}$ )	14.8	4	$k_e$ ( $h^{-1}$ )	0.113	27
$V_c/F$ (l)	51.6	11	$\eta$ $CL/F$	0.255	12
$Q/F$ ( $l \cdot h^{-1}$ )	8.19	26	$\eta$ $k_{1e}$	0.533	10
$V_p/F$ (l)	106	44	$\sigma_{BP}$	0.339	6
$\beta_{CLCR}$ on $CL/F$	0.178	35	$\sigma_{SP}$	0.357	7

Abbreviations are as follows: RSE, relative standard error;  $k_a$ , absorption rate constant; \* fixed value,  $CL/F$ , apparent elimination clearance;  $V_c/F$ , apparent central volume of distribution;  $Q/F$ , apparent intercompartmental clearance;  $V_p/F$ , apparent peripheral volume of distribution;  $\beta_{CLCR}$  on  $CL/F$ , influential factor of creatinine clearance on  $CL/F$ ;  $\theta_{LPV/r}$  on  $CL/F$ , influential factor of lopinavir/ritonavir co-administration on  $CL/F$ ;  $F$ , unknown bioavailability;  $k_{1e}$ , blood plasma to seminal plasma transfer rate constant;  $k_e$ , seminal plasma elimination rate constant;  $\eta$ , inter-individual variability;  $\sigma_{BP}$ , residual variability estimate for blood plasma concentrations;  $\sigma_{SP}$ , residual variability estimate for seminal plasma concentrations.



Visual Predictive Check for FTC BP concentrations (left) and SP concentrations (right)

	BP $AUC_{0-24}$	SP $AUC_{0-24}$	SP-to-BP $AUC_{0-24}$ ratio
Sample size	236	209	209
Median ( $mg \cdot l^{-1} \cdot h$ )	12.95	38.04	2.91
Range ( $mg \cdot l^{-1} \cdot h$ )	8.36 - 25.13	13.40 - 148.18	0.84 - 10.08

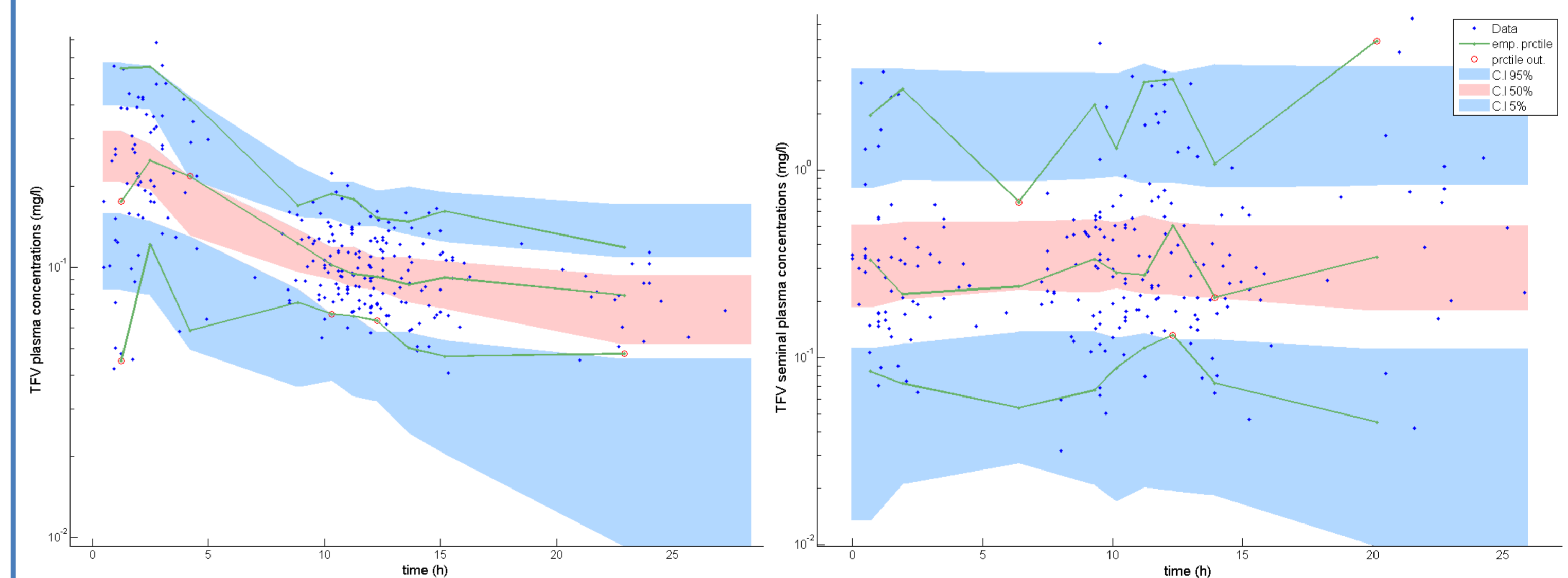
Median SP  $AUC_{0-24}$  and SP-to-BP  $AUC_{0-24}$  ratio were slightly lower for patients with detectable spVL compared to patients with undetectable spVL (36.83 vs 38.57  $mg \cdot l^{-1} \cdot h$  for SP  $AUC_{0-24}$ ; 2.60 vs 2.91 for SP-to-BP exposures ratio) but did not reach significance ( $p=0.96$  and  $p=0.51$  respectively, Wilcoxon signed-rank test).

The impact of FTC seminal plasma  $AUC_{0-24}$  and SP-to-BP  $AUC_{0-24}$  ratio on spVL detectability was not significant ( $p=0.943$  and  $0.893$  respectively, mixed effects logistic regressions).

Despite FTC penetration in the male genital tract was variable (CV SP-to-BP  $AUC_{0-24}$  ratio = 54.7 %), SP  $AUC_{0-24}$  were higher than BP  $AUC_{0-24}$  for more than 99 % of the men.

### TFV Results

Parameter	Estimate	RSE (%)	Parameter	Estimate	RSE (%)
$k_a$ ( $h^{-1}$ )	1.35	41	$k_{1e}$ ( $h^{-1}$ )	0.0963	28
$CL/F$ ( $l \cdot h^{-1}$ )	45.8	3	$k_e$ ( $h^{-1}$ )	0.0339	29
$V_c/F$ (l)	268	16	$\eta$ $CL/F$	0.146	48
$Q/F$ ( $l \cdot h^{-1}$ )	197	39	$\eta$ $Q/F$	1.94	45
$V_p/F$ (l)	1630	43	$\eta$ $k_e$	0.889	7
$\beta_{LPV/r}$ on $CL/F$	0.591	13	$\sigma_{BP}$	0.263	8
$\beta_{CLCR}$ on $CL/F$	0.269	34	$\sigma_{SP}$	0.374	7



Visual Predictive Check for TFV BP concentrations (left) and SP concentrations (right) in log-scale

	BP $AUC_{0-24}$	SP $AUC_{0-24}$	SP-to-BP $AUC_{0-24}$ ratio
Sample size	248	217	217
Median ( $mg \cdot l^{-1} \cdot h$ )	2.97	7.01	2.24
Range ( $mg \cdot l^{-1} \cdot h$ )	2.08 - 7.06	1.25 - 107.29	0.53 - 34.13

TFV penetration in the male genital tract was highly variable (CV SP-to-BP  $AUC_{0-24}$  ratio = 125 %). SP  $AUC_{0-24}$  were higher than BP  $AUC_{0-24}$  for 87 % of the men.

Median SP  $AUC_{0-24}$  and SP-to-BP  $AUC_{0-24}$  ratios were lower for patients with detectable spVL compared to patients with undetectable spVL (4.78 vs 7.02  $mg \cdot l^{-1} \cdot h$  for SP  $AUC_{0-24}$ ; 1.58 vs 2.28 for SP-to-BP  $AUC_{0-24}$  ratio) but did not reach significance ( $p=0.32$  and  $p=0.25$  respectively, Wilcoxon signed-rank test).

No association between TFV penetration in the male genital tract and spVL detectability was shown ( $p=0.808$  for SP  $AUC_{0-24}$  and  $p=0.768$  for SP-to-BP  $AUC_{0-24}$  ratios, mixed effects logistic regressions). The impact of combined TFV+FTC SP  $AUC_{0-24}$  or SP-to-BP  $AUC_{0-24}$  ratios on spVL detectability was not significant ( $p=0.984$  and  $0.735$ , respectively).

## Conclusion

These are the first population models describing FTC and TFV pharmacokinetics in blood plasma and seminal plasma. FTC and TFV seminal plasma concentrations were higher than blood plasma concentrations. FTC and TFV accumulate in seminal plasma and the median SP-to-BP  $AUC_{0-24}$  ratios were estimated at 2.91 and 2.24 respectively. TFV penetration in the male genital tract seems to be more variable than FTC penetration (CV SP-to-BP  $AUC_{0-24}$  ratios 125 % vs 54.7 %). For FTC, SP  $AUC_{0-24}$  were higher than BP  $AUC_{0-24}$  for more than 99 % of the men compared to 87 % for TFV.