

Modified renal function in pregnancy: impact on emtricitabine pharmacokinetics

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INTRODUCTION

Emtricitabine (FTC) is a once-daily potent nucleoside reverse transcriptase inhibitor approved for the treatment of human immunodeficiency virus (HIV) infection in adult patients.

According to current 2013 World Health Organization guidelines, FTC can also be used during gestational period:

- to continue an antiretroviral treatment initiated while women were non-pregnant
- to begin a treatment for the own health of pregnant women, as well as for the prevention of mother-to-child transmission of HIV.

Pregnancy and labor are associated with physiological changes which could lead to variations in pharmacokinetics.

FTC pharmacokinetics has been previously described in healthy volunteers and in HIV-infected patients. However, very few studies have explored the effects of pregnancy on FTC pharmacokinetics.

As knowledge about FTC pharmacokinetic changes during pregnancy is limited and as only data about late pregnancy are available in the litterature, the aims were:

- to describe FTC pharmacokinetics in a large population of pregnant women during the different trimesters of pregnancy and at delivery
- to assess and explain the pharmacokinetic variability during pregnancy

METHODS

Patients, Treatments and Sampling

The population included non-pregnant women NPW (n=103), pregnant women PW (n=46) and women at labor WAL (n=48) receiving FTC for the treatment of HIV infection or for the prevention of mother-to-child transmission. Our population combines NPW+PW+WAL from therapeutic drug monitoring (TDM) study [200 mg/day] and WAL from the TEmAA clinical study previously published [400 mg at the start of labor]¹. A total of 457 FTC plasma concentrations were available for the analysis.

Pharmacokinetic Model

MONOLIX 4.1.3. and SAEM algorithm were used to develop a population pharmacokinetic model.

Continuous covariates (CO) such as age, weight, serum creatinine and creatinine clearance (CL_{CR}) were tested according to the following equation:

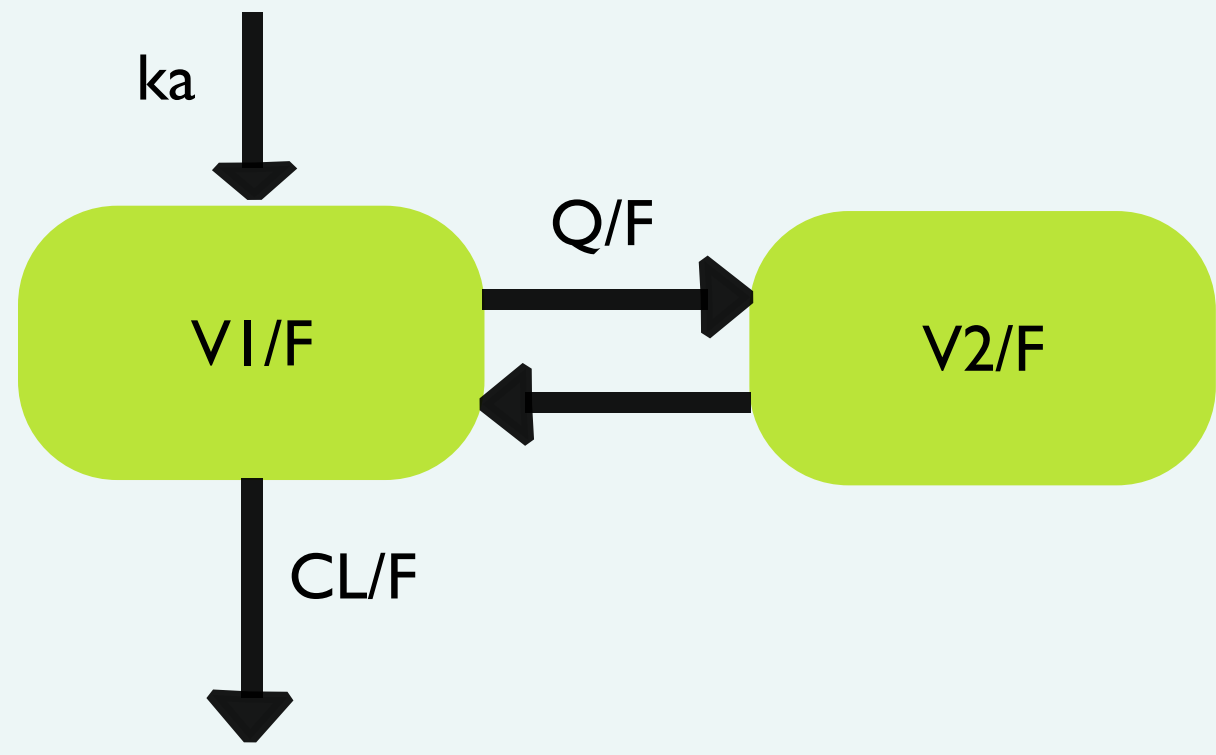
$$CL = \theta_{CL} \cdot \left(\frac{CO}{\text{median}(CO)} \right)^{\beta_{CO}}$$

Categorical CO such as pregnancy status, delivery, trimesters of pregnancy and associated antiretroviral drugs were tested using:

$$CL = \theta_{CL} \cdot \beta_{CO}^{CO}$$

Gestational age (GA) was tested according to the following equations:

$$CL = \theta_{CL} \cdot \left[1 + \left(\frac{GA^{\gamma}}{GA_{50}^{\gamma} + GA^{\gamma}} \right) \right] \text{ and } CL = \theta_{CL} \cdot \left[\left(\frac{GA}{\text{median}(GA)} \right)^{\beta_{GA}} \right]^{\text{PREG}}$$



With ka, absorption rate constant; CL/F, apparent elimination clearance; V1/F, apparent central volume of distribution; Q/F, apparent intercompartmental clearance; V2/F, apparent peripheral volume of distribution.

¹ Hirt et al. 2009, Antimicrob Agents Chemother.

RESULTS

Characteristics of the population

Median [Min-Max]						
	No.of samples	Age (yr)	BW (kg)	SCR (μmol.l ⁻¹)	CL _{CR} (ml.min ⁻¹)	GA (wk)
Pregnant women* (n=83)	307	31 [19-43]	70 [47-106]	49 [27-119]	160 [70-335]	37 [5-41]
Non-pregnant women (n=103)	150	40 [16-72]	69 [37-130]	66 [35-183]	106 [35-247]	-

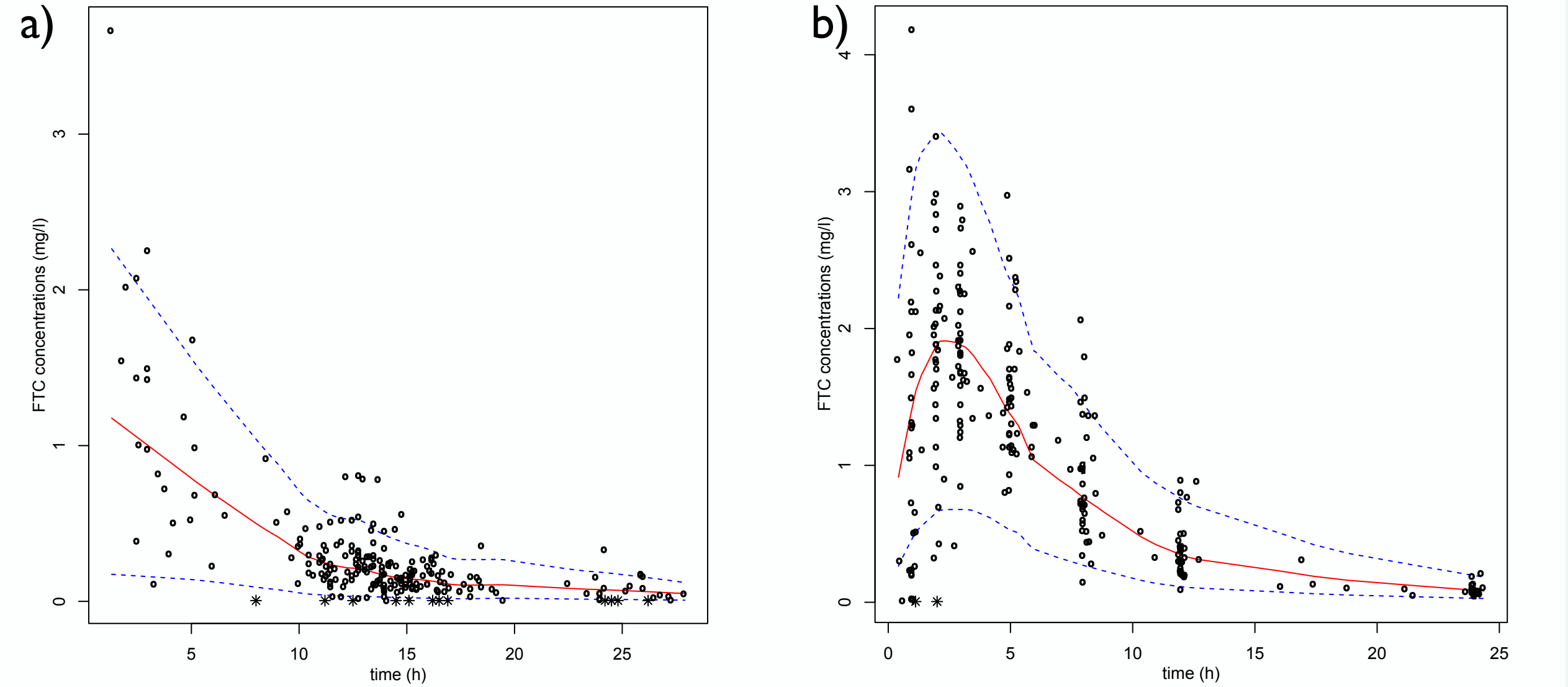
* including women at labor, BW for body weight, SCR for serum creatinine, CL_{CR} for creatinine clearance calculated by the Cockcroft and Gault formula and GA for gestational age.

Model Parameters

Structural model			Statistical model		
Parameter	Estimate	RSE %	Parameter	Estimate	RSE %
ka (h ⁻¹)	0.616	32	η ka	0.503	36
CL/F (l.h ⁻¹)	22.3	3	η CL/F	0.151	14
V1/F (l)	100	16	σ _{TDM}	0.505	6
Q/F (l.h ⁻¹)	5.89	22	σ _{TEmAA}	0.373	6
V2/F (l)	76.1	28			
β _{CL_{CR}} CL/F	0.33	16			

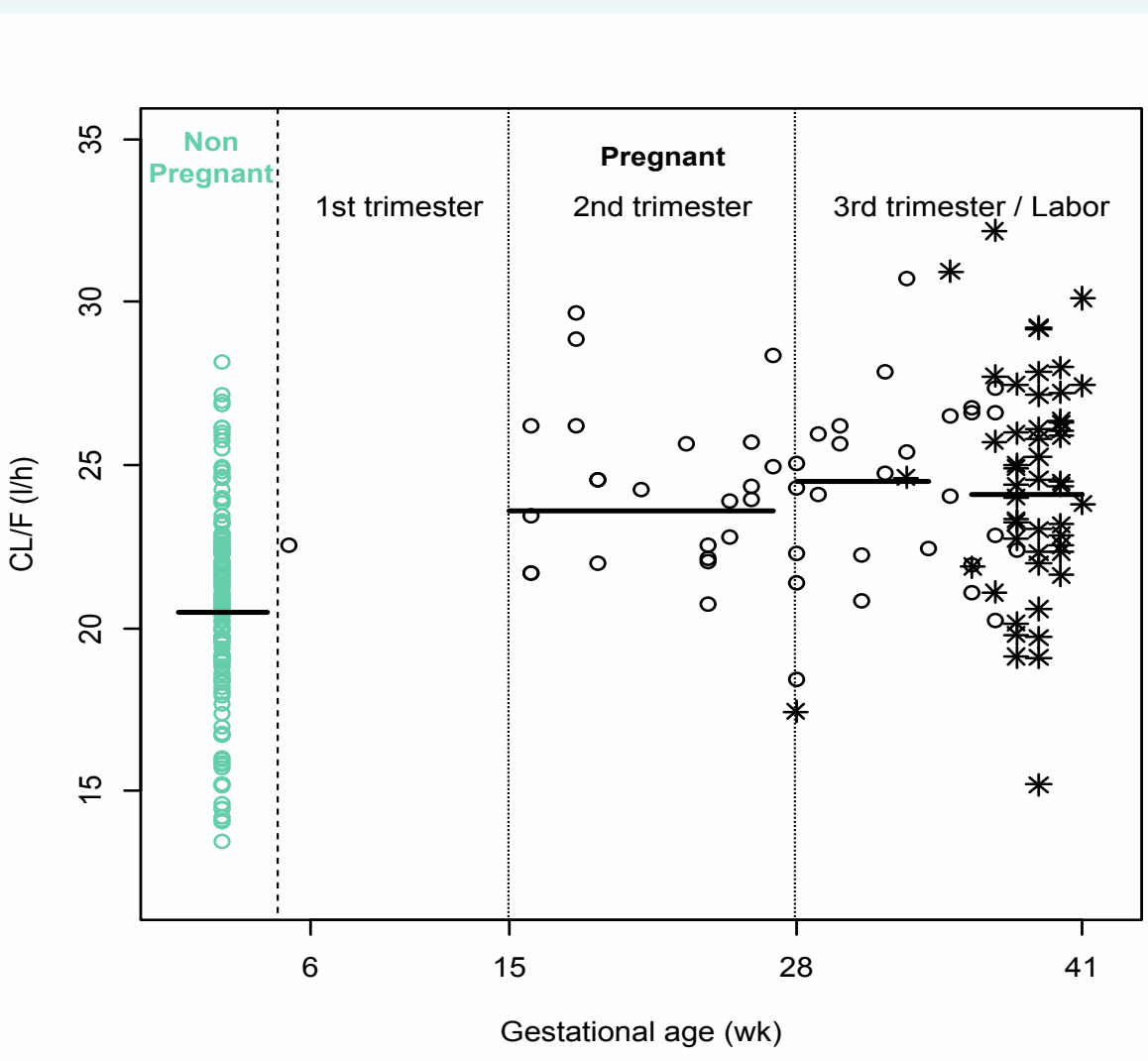
With RSE, the relative standard error; β_{CL_{CR}} CL/F, the influential factor of CL_{CR} on CL/F; η the interindividual variability; σ_{TDM} the residual variability estimate for therapeutic drug monitoring study; σ_{TEmAA} the residual variability estimate for TEmAA clinical study previously published.

Validation: VPC



Visual Predictive Check stratified by dose: comparison between the 5th (dashed line), 50th (solid line) and 95th (dashed line) percentiles obtained from 1000 simulations and the observed data (circles) for FTC concentrations in (a) TDM study [200 mg dose] and (b) TEmAA clinical study previously published [400 mg dose].

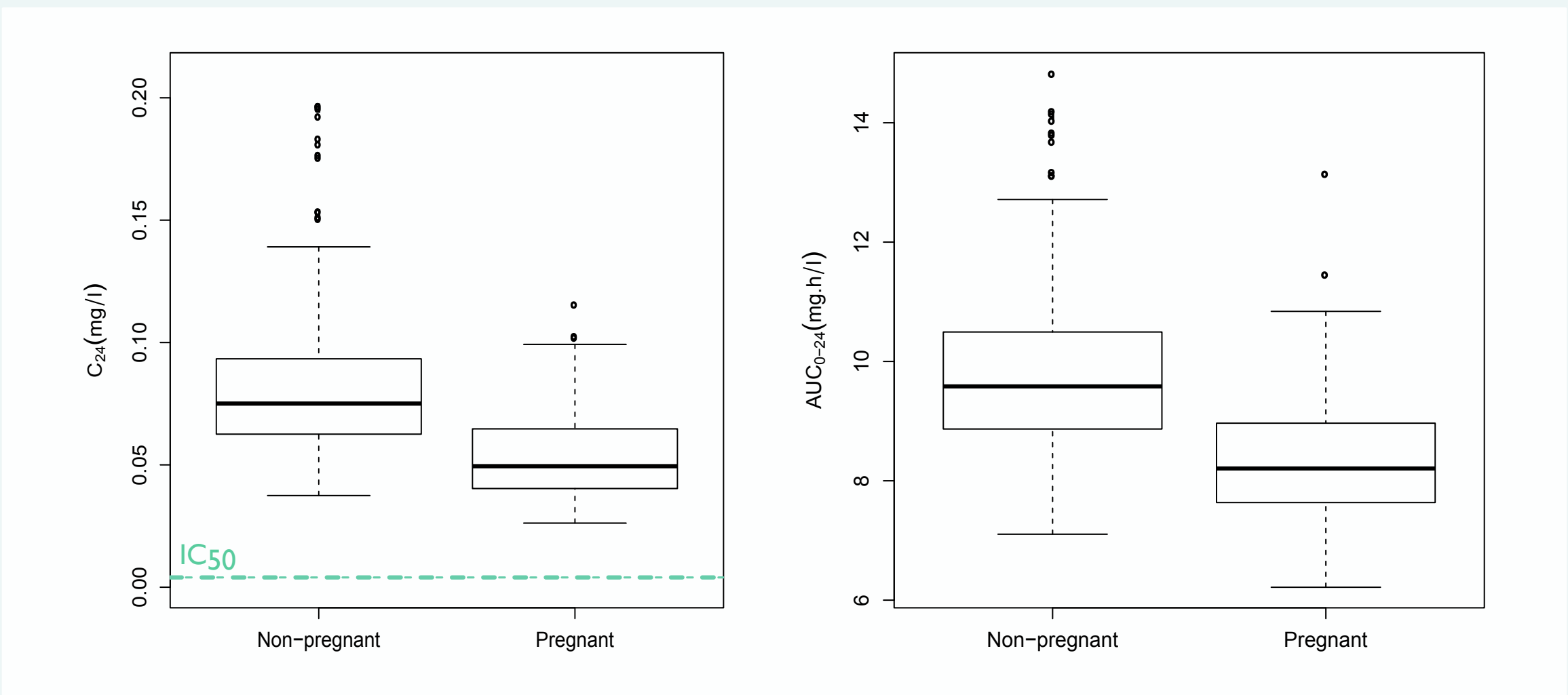
Comparison of CL/F between non-pregnant women and pregnant women



FTC apparent elimination clearance geometric mean was 20.5 l.h⁻¹ [range: 13.5-28.1 l.h⁻¹] in non-pregnant women and was 24.1 l.h⁻¹ [range: 15.2-32.2 l.h⁻¹] in pregnant women. The increase of CL/F in pregnant women was significant compared to non-pregnant women (t-test, p<0.001) and reflected a modified renal function.

CL/F geometric means were close during the different trimesters of pregnancy: 23.9 l.h⁻¹ in the 2nd trimester of pregnancy, 24.5 l.h⁻¹ in the 3rd trimester of pregnancy and 24.1 l.h⁻¹ on the day of delivery.

Comparison of AUC₀₋₂₄ and C₂₄ between non-pregnant women and pregnant women



Emtricitabine C₂₄ geometric mean was lower in pregnant women compared to non-pregnant women (0.054 vs 0.079 mg.l⁻¹) (t-test, p<0.001), but still well over the inhibitory concentration 50 % (IC₅₀ = 0.004 mg.l⁻¹).

Emtricitabine daily exposures (AUC₀₋₂₄) geometric mean was lower in pregnant women compared to non-pregnant women (8.30 vs 9.77 mg.h.l⁻¹) (t-test, p<0.001). The magnitude of decrease was similar whatever the trimester of pregnancy (14 % decrease in the 2nd trimester of pregnancy; 16.5 % decrease in the 3rd trimester of pregnancy and 15 % decrease on the day of delivery).

Even if 93 % of pregnant women had an AUC₀₋₂₄ lower than the typical efficient exposure of 10 mg.h.l⁻¹, 92 % of these exposures were higher than 7 mg.h.l⁻¹ (30 % reduction of typical FTC exposure considered of clinical relevance)².

² Stek et al. 2011, HIV Med.

CONCLUSIONS

The FTC pharmacokinetics in pregnant and non-pregnant women was satisfactorily described by a two-compartment model, including a significant effect of CL_{CR} on CL/F. FTC apparent elimination clearance was increased by 18 % during pregnancy and reflected a modified renal function with a 50 % increase in glomerular filtration rate. FTC exposures in pregnant women were slightly lower (15 %) than the ones in non-pregnant women. The magnitude of change in FTC exposures during pregnancy was not considered as clinically relevant, both during the 2nd and 3rd trimester of pregnancy. Thus, no FTC dosing adjustments were suggested for pregnant women.