Pharmacokinetic-Pharmacodynamic model of Rilpivirine in treatment-naïve HIV-1-infected patients treated with the single-tablet regimen rilpivirine/emtricitabine/tenofovir disoproxil fumarate

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INTRODUCTION

- Rilpivirine (RPV) presents a wide inter-individual pharmacokinetic (PK) variability
- Trough plasma concentration (Ctrough) of RPV is correlated with virologic response but no clear threshold value has been established [1] [2]
- Consequently, we first developed a population PK (PopPK) model to describe the RPV PK and its variability in routine HIV-infected patients [3]
- A shorter half-life (25h) than reported in the Summary of Product Characteristics was found, in line with the result of Aouri *et al.* [4]

OBJECTIVE

- The aim of the present study was to develop a pharmacodynamic (PD) model to establish concentration-response relationships for future treatment optimization

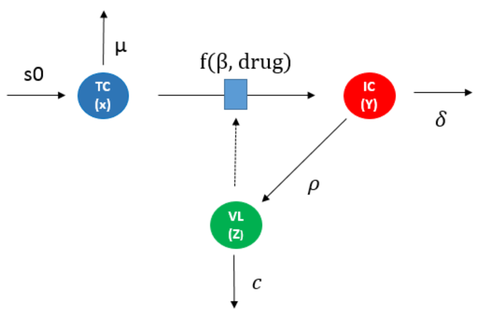
METHODS

Population and samples collection

- A multicenter, retrospective and observational study was conducted in patients treated with the once-daily (QD) regimen RPV (25 mg) / TDF (245 mg) / FTC (200mg) for whom sparse RPV plasma concentrations were determined within the context of routine therapeutic drug monitoring
- Plasma HIV-RNA load (VL), CD4 cells (CD4) and drug-resistance associated mutations were collected at baseline and during the monitoring
- The individual RPV Ctrough were predicted at each occasion based on the PopPK model using Bayesian approach

Model development

- PD analysis was performed with Monolix2016R1 software
- A HIV dynamics model was developed based on the model proposed by Perelson *et al.* [5] to estimate the effect of RPV concentrations both on the rate of CD4 infection by the virus and on VL as follows :



- $\frac{dX}{dt} = s0 - \mu X - f(\beta,drug) \times Z \times X$
- $\frac{dY}{dt} = f(\beta,drug) \times Z \times X - \delta \times Y$
- $\frac{dZ}{dt} = \rho \times Y - c \times Z$

$$\mathbf{f(\beta, drug)} = \boldsymbol{\beta} \times \frac{\boldsymbol{C50RPV}}{\boldsymbol{C50RPV} + \text{Ctrough}}$$

C50RPV: RPV concentration producing 50% of the maximum effect
s0, ρ : production rate constant of uninfected target cell (TC) (X) and (VL) (Z)
μ, c, δ : elimination rate constant of (X), (Z) and infected cells (IC) (Y)
β : infection rate constant of (X)

Model evaluation

→ The performance of the final model was evaluated using standard goodness-of-fit (GOF) plots
→ A visual predictive check (VPC) was performed, by simulating replicates from the PD model to examine the agreement between the observed data (CD4 and VL) and prediction intervals

PD simulations

The PD model was used to simulate the rate of virological success (VL < 40 copies/ml) at 96 weeks as a function of Ctrough. 1000 simulations were performed for each Ctrough (range: 50-300 ng/ml, step 5 ng/ml). The mean predicted response rate and the corresponding 95% confidence interval (CI) were calculated

RESULTS

- A total of 63 treatment-naïve patients were included in the study with a follow-up duration ranging from 2 to 30 months

Table 1 Baseline patients characteristics

Characteristic	Median (range) or n (%)
Male gender	52 (82.5%)
Age, years	37 (19-70)
Body Mass Index (BMI), kg/m²	23.2 (17.5-45.4)
CD4 cells, /mm³	441 (24-1 609)
Plasma HIV RNA, copies/ml	15,800 (40-3,141,000)
< 40 copies/ml	1 (0.016%)
Co-infection	
HBV	3 (4.6 %)
HCV	3 (4.6 %)
Genotypic data	59 (94%)
Non-Nucleoside reverse transcriptase resistance mutations	10 (15.9%)
RPV specific resistance mutations	2 (3.2%)

- VL was < 40 copies/ml in 50/55 (91%) patients at M6, 48/53 (91%) at one year and 41/43 (95%) at two years
- 17 patients stopped treatment at 6 months (M6) (n=2), M12 (n=3), M24 (n=8), M30 (n=4)
- Reasons of discontinuations were : pharmacological adjustment (n=4), pregnancy (n=3), virologic failure (n=4), side effects (n=5), not available (n=1)
- **Virologic failure was observed in 4 patients**: two of them developed RPV specific resistance mutations at M11 (**E138K**) and M20 (**Y181C+M230L**), respectively

PD model

Base model

- The parameters of the PD model were s0, δ, c, ρ, VL at baseline (VL_0), CD4 cell count at baseline ($CD4_0$)
- The model was over-parameterized: δ and c needed to be fixed to the previously reported value of 15 and 92 per month respectively [5]
- The interindividual variability (IIV) of δ, s0, ρ and c could not be accurately estimated, and were fixed to zero
- C50RPV could not be accurately estimated, probably due to the high level of response in the population (only 4 virologic failures)

Final model

- Consequently, the percentage of virus growth inhibition by RPV (I_{RPV}) was estimated instead, using the following equation: $\boldsymbol{f(drug) = (1 - I_{RPV})}$
- The relationship between individual RPV Ctrough and I_{RPV} was modelled using power function with Ctrough centered at the median value
- The inclusion of this relation improved the model, as shown by the significant decrease of the objective function and by both GOF and VPC plots

- All parameters were estimated with a good precision (Relative Standard Error < 30%)
- I_{RPV} typical value was estimated at 38 %

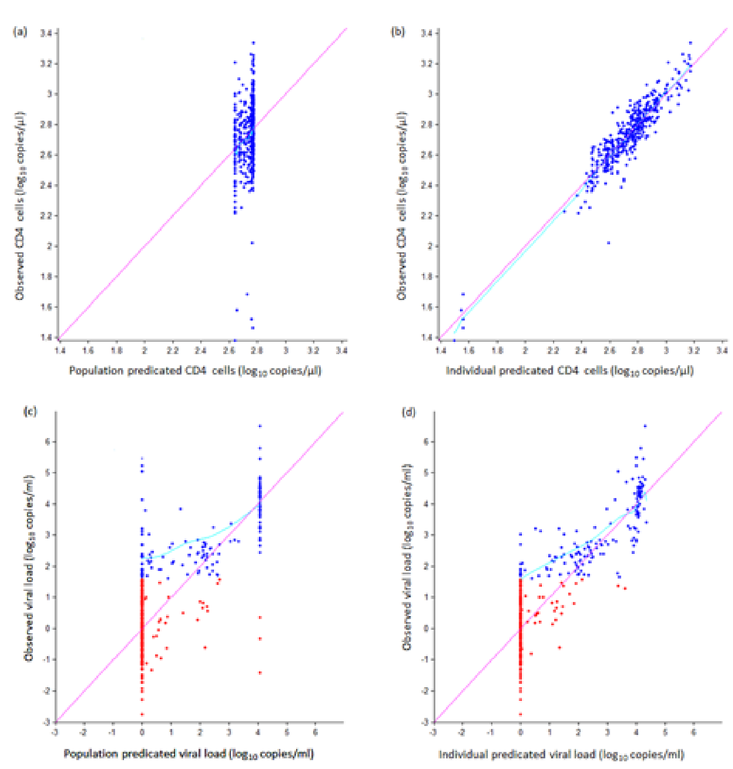
Table 2: Final Model RPV PD parameters estimates

Parameters	Estimate	RSE (%)
s0 (month^{-1}/μl)	237	3%
δ (month^{-1})	15 (fixed)	-
c (month^{-1})	92 (fixed)	-
ρ (10^5) (month^{-1})	2.61	2%
VL_0 (copies/ml)	11 600	9%
$CD4_0$ (cells/μl)	440	7%
I_{RPV}	**0.38**	8%
pCRPV	**0.132**	1%
ωI_{RPV}	0.59	18%
ωVL_0	5460	14%
$\omega CD4_0$	0.501	9%
σVL_0, additive	0.846	4%
$\sigma CD4_0$, additive	0.0889	5%

Parameters were assumed to follow a log-normal distribution, except pCRPV, VL_0 (normal distribution) and I_{RPV} (logit-normal distribution)

- Satisfactory GOF plots: PRED and IPRED *versus* observations trends (blue line) close to identity line (pink line) for CD4. Bias for VL.

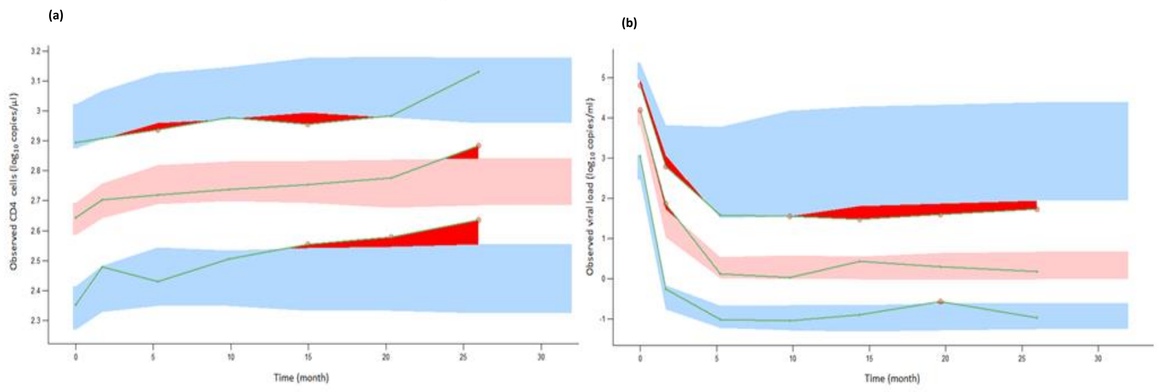
Figure 2 : Goodness-of-fit plots for the final model



(a): observed CD4 cells *versus* population predicted (PRED) CD4 cells. **(b)**: observed CD4 cells *versus* individual predicted (IPRED) CD4 cells. **(c)**: observed viral load *versus* PRED viral load. **(d)**: observed viral load *versus* IPRED viral load. The pink lines indicate the expected trends, the blue lines display the trend of the data, the blue circles represent the observed data and the red circles represent the below the limit of quantification (BLQ) data

- A bias associated with an over-estimation of the highest VL values was observed on the VPC

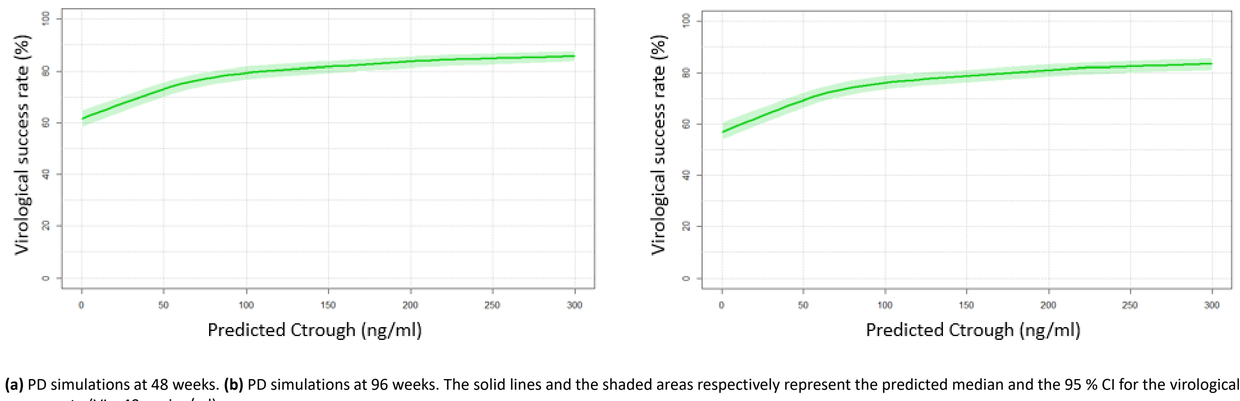
Figure 3 : VPC for the final model



(a) VPC for CD4. **(b)** VPC for VL.
Green solid lines represent 10th, 50th, and 90th percentiles of observed data. Red and blue shaded areas represent 90% Cis of the respectively simulated 50th, 10th and 90th percentiles. Outliers are highlighted with red dots and areas.

- The currently suggested target of 50 ng/ml for RPV Ctrough [6] is associated with virological success (VL< 40 copies/ml) in 72 % and 70 % of patients at 48 and 96 weeks, respectively.

Figure 4 : PD simulations



(a) PD simulations at 48 weeks. **(b)** PD simulations at 96 weeks. The solid lines and the shaded areas respectively represent the predicted median and the 95 % CI for the virological success rate (VL< 40 copies/ml)

CONCLUSION

- The PD model suggested that the currently used 50 ng/mL RPV Ctrough efficacy target might be under-evaluated.
- However, our PD model showed some limitations (lack of stability, bias on VL estimation).
- A full PK/PD model will be developed incorporating the PK parameters to improve model stability and performance, in order to better define the target Ctrough.
- Moreover, an other PK-PD model will be develop including pre-treated patients.

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