Population pharmacokinetics of nevirapine in an unselected cohort of HIV-1-infected individuals

Monique M. R. de Maat,¹ Alwin D. R. Huitema,¹ Jan W. Mulder,² Pieter L. Meenhorst,²
Eric C. M. van Gorp² & Jos H. Beijnen^{1,3}

¹Slotervaart Hospital, Department of Pharmacy & Pharmacology, ²Department of Internal Medicine, Amsterdam and ³University of Utrecht, Faculty of Pharmacy, Utrecht, The Netherlands

Aims To study the population pharmacokinetics of nevirapine and to identify relationships between patient characteristics and pharmacokinetics in an unselected population of patients attending our outpatient clinic.

Methods Ambulatory HIV-1-infected patients from the outpatient clinic of the Slotervaart Hospital who were being treated with a nevirapine-containing regimen were included. During each visit, blood samples were collected for the determination of nevirapine plasma concentrations and clinical chemistry parameters. Variables that were collected at baseline were serology for hepatitis B (HBV) and C (HCV) viruses, liver enzymes, and total bilirubin (TBR). In addition, information about concomitant use of St John's wort and patient demographics were included. The pharmacokinetics of nevirapine were described by first-order absorption and elimination using nonlinear mixed effect modelling (NONMEM V1.1). Population pharmacokinetic parameters (apparent clearance (CL/F), volume of distribution (V/F), absorption rate constant (k_a)) were estimated, as were interindividual, interoccasion, and residual variability in the pharmacokinetics. The influence of patient characteristics on the pharmacokinetics of nevirapine was determined.

Results From 173 outpatients a total number of 757 nevirapine plasma concentrations at a single random time point and full pharmacokinetic curves for 13 patients were available resulting in a database of 1329 nevirapine plasma concentrations. Mean CL/F , V/F , and k_a were 3.27 l h^{-1} , 106 l , and 0.166 h^{-1} , respectively. CL/F of nevirapine was correlated with weight, chronic HCV infection, and baseline aspartate aminotransferase (ASAT). Chronic HCV and baseline ASAT $>1.5 \times$ upper limit of normal (ULN) decreased CL/F by 27.4% and 13.2%, respectively, whereas an increase in body weight of 10 kg increased CL/F by 0.14 l h^{-1} . A trend towards a lower CL/F in patients of the Negroid race was observed. No significant covariates were found for V/F .

Conclusions The pharmacokinetics of nevirapine were adequately described by our population pharmacokinetic model. Weight, chronic HCV infection, and baseline ASAT were found to be significant covariates for CL/F of nevirapine. The model incorporating these significant covariates may be an important aid in further optimizing nevirapine-containing therapy.

Keywords: nevirapine, patient characteristics, population pharmacokinetics

Introduction

Nevirapine (Viramune[®]) is a non-nucleoside reverse transcriptase inhibitor (NNRTI), which is indicated for use

in the treatment of human immunodeficiency virus type 1 (HIV-1) infection. The drug binds directly to the viral reverse transcriptase to block polymerase activity by causing a disruption of the catalytic site [1]. The licensed dosage of nevirapine in HIV-1-infected adults is 200 mg once daily during the first 2 weeks, followed by 200 mg twice daily thereafter [2]. However, it is also used in a once daily dosing regimen of 400 mg [3].

The pharmacokinetics of nevirapine are characterized

Correspondence: M. M. R. de Maat, PharmD, Slotervaart Hospital, Department of Pharmacy & Pharmacology, Louwesweg 6, 1066 ec Amsterdam, The Netherlands. Tel.: (+31)20-5124481; Fax: (+31)20 5124753; E-mail: apmod@slz.nl

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by rapid and nearly complete oral absorption, rapid distribution, and prolonged elimination [4]. *In vitro* studies using human liver microsomes demonstrated that CYP3A is primarily responsible for the oxidative metabolism of nevirapine to its major (inactive) metabolites, although other CYP enzymes may have a secondary role [5]. Nevirapine metabolism is subject to autoinduction, resulting in a decrease in the terminal half-life from 45 h following a single dose to approximately 25–30 h after multiple dosing [1]. The urinary excretion of nevirapine is minor, since only a small fraction (< 3%) is eliminated as parent compound in urine [1].

Although nevirapine, when used in combination therapy, has proven to be safe and effective [6, 7], highly drug-resistant virus rapidly emerges when administered in suboptimal regimens [8]. Havlir *et al.* reported a correlation between plasma trough concentrations of nevirapine and the virological response in HIV-1-infected patients [9]. Furthermore, an analysis of plasma concentrations obtained in the INCAS Study showed that a high exposure is associated with improved virological response in the short as well as in the long term [10]. In contrast, a relationship between plasma concentration of nevirapine and toxicity has not been established conclusively.

Interpatient variability may be influenced by many factors such as comedication, comorbidity, etc. Knowledge of such factors could be very useful in dose individualization when a target plasma concentration of nevirapine has been defined. Zhou *et al.* demonstrated that the apparent clearance (CL/F) of nevirapine was correlated with gender, with a typical value of 3.97 l h⁻¹ for men compared with 3.02 l h⁻¹ for women [11]. In addition, severe hepatic dysfunction has been shown to increase exposure to nevirapine substantially [12]. Thus far, no other patient characteristics have been identified that could explain the interpatient variability in the pharmacokinetics of nevirapine.

The objective of this study was to develop a population pharmacokinetic model for nevirapine and to identify the relationships between patient characteristics and pharmacokinetics in a representative patient population attending a routine outpatient HIV clinic.

Methods

Patients

Ambulatory HIV-1-infected patients from the outpatient clinic of the Slotervaart Hospital, Amsterdam, The Netherlands, were recruited. Data were collected retrospectively from January 1997 to April 2000. All patients were using nevirapine as part of their antiretroviral regimen and had at least one nevirapine plasma sample available

for analysis. No other restrictions were made for inclusion into this study.

Approval was obtained from the institutional review board of Slotervaart Hospital and all patients gave written informed consent.

Sampling and bioanalysis

At each visit to the clinic, a single blood sample was obtained for the determination of nevirapine concentration. In our hospital, a strict protocol is utilized in which plasma concentrations of antiretroviral drugs are routinely and frequently measured within a therapeutic drug monitoring (TDM)-program. Therefore, patients are familiar with the need to remember the time of ingestion of the last dose. Additionally, sampling times are recorded electronically in the Department of Clinical Chemistry. Time after ingestion is extracted from this information. Cases where plasma concentration was determined to check compliance were not included in this analysis. In addition to the sparse randomly timed samples, full pharmacokinetic curves from 13 patients were available, obtained as part of another study [3]. All nevirapine plasma concentrations were determined at steady-state. Concentrations of nevirapine were measured by a validated high-performance liquid chromatographic method (h.p.l.c.) [13] which was validated over the range of 0.05–10 µg ml⁻¹ using 250 µl of plasma. Recovery of nevirapine from human plasma was 94.5%. Within- and between-day coefficients of variation were less than 4.5% for all quality control samples covering the complete calibration curve. The corresponding accuracies ranged from 97.3 to 105.2%.

Pharmacokinetic analyses

All analyses were performed with the nonlinear mixed-effect modelling program (NONMEM) version V (double precision, level 1.1) [14]. The first-order conditional estimation (FOCE) method was used throughout. The performance of the tested models was assessed by both statistical and graphical methods. The minimal value of the objective function (equal to minus twice the log likelihood) as calculated by NONMEM was one of the parameters used to assess goodness-of-fit. Discrimination between hierarchical models was based on this value using the log likelihood ratio test [14]. Standard errors for all parameters were calculated using the COVARIANCE option of NONMEM and individual Bayesian pharmacokinetic parameters were obtained with the POSTHOC option [14]. For graphical model diagnostics, the S-plus (MathSoft Inc, Seattle, USA) based model building aid Xpose 3.0 was used [15].

Basic pharmacokinetic model

An open one-compartment model with first-order elimination was used to describe the data. Both zero-order and first-order absorption models with and without absorption lag-time were tested. Furthermore, different time-dependent absorption models as described by Higaki *et al.* were tested [16]. Also, a two-compartment model and Michaelis-Menten-elimination were tested.

Interindividual variability in the different pharmacokinetic parameters was estimated with a proportional error model. Interoccasion (intraindividual) variability was also estimated with a proportional model as suggested by Karlsson & Sheiner [17]. For instance, variability in CL/F was estimated using $CL/F_{ij} = \theta^*(1 + \eta_i + \kappa_j)$, in which CL/F_{ij} represents the apparent clearance of the i^{th} individual at the j^{th} occasion, θ is the typical value of CL/F in the population, η_i is the interindividual random effect with mean 0 and variance ω^2 and κ_j is the interoccasion random effect with mean 0 and variance π^2 . Covariance between different (interindividual variability) was tested. Also covariance between different kappas (interoccasion variability) was tested. This latter covariance was modelled as $P_j = \theta_1^*(\kappa_{1j} + \theta_2^*\kappa_{2j})$, in which P_j is the value of parameter P at occasion j , κ_{1j} is the interoccasion random effect of parameter 1, κ_{2j} is the interoccasion random effect of parameter 2 and θ_2 is the correlation factor between these interoccasion effects.

Residual variability was estimated with an additive error model. Since larger residual variability was likely to be associated with samples collected closer to the time of intake, for instance because of irregular absorption, a mixture additive error model was used to describe residual variability. This model is represented by:

$$C_{ij} = \hat{C}_{ij} + \theta_{ip} \times \varepsilon_{ij}$$

in which C_{ij} and $\hat{C}_{ij}$ are, respectively, the i^{th} measured and model predicted drug concentration of the j^{th} individual, ε_{ij} is the residual random error with mean 0 and variance σ^2 and θ_{ip} is an increment proportion (ip), whose value is to be estimated but fixed to 1 for time points exceeding 2 h after intake. The value of σ^2 may vary between individuals. Therefore the assumption of a constant σ^2 for all individuals may result in bias. In order to reduce this bias, two populations with different values for σ^2 were assumed to exist. Therefore residual error parameters estimated were the fraction of patients in population 1, residual variability of population 1 and 2 and the increment proportion.

Covariate model building

In order to establish possible relationships between the pharmacokinetics of nevirapine and patient characteristics, the following covariates were collected at baseline: gender (SEX), race (RACE), chronic hepatitis C (HCV)

and/or chronic hepatitis B (HBV) status, and liver enzymes (LE) including alanine aminotransferase (ALAT, U l⁻¹), aspartate aminotransferase (ASAT, U l⁻¹), alkaline phosphatase (AP, U l⁻¹), gamma-glutamyltransferase (GGT, U l⁻¹), and serum total bilirubin (TBR, $\mu\text{mol l}^{-1}$). In addition, covariates determined during treatment with nevirapine were collected and included age (AGE, years), body weight (WT, kg), concomitant use of St John's wort, serum glucose (GLU, mmol l⁻¹), serum creatinine (KR, mmol l⁻¹), serum albumin (ALB, g l⁻¹), serum total protein (TP, g l⁻¹), amylase (AM, U l⁻¹), and creatine kinase (CK, U l⁻¹). The constituents, quality, and dose of St John's wort were not taken into account because of too few patients using this agent concomitantly. Patients were taking few other drugs with their antiretroviral therapy. In addition, little or no effect on the pharmacokinetics of nevirapine by coadministered drugs has been reported. The number of patients who were taking specific additional drugs was too small to include in this analysis. Therefore, no other concomitantly used drugs were included as a covariate. AGE, GLU, KR, ALB, TP, AM, CK, and WT were examined as continuous variables. Sex, Race, St John's Wort, HCV, and HBV were examined as dichotomous variables. The absolute baseline LEs (ALAT, ASAT, AP, GGT) and TBR were also transformed to dichotomous variables (below or exceeding 1.5 times the upper limit of normal (ULN)). In the light of the recommendations of the European Medicines Evaluation Agency (EMA), the choice of a breakpoint of $1.5 \times \text{ULN}$ was made. It is unlikely that patients with high LEs will start nevirapine-containing regimens in the future. From a small fraction of patients, baseline LEs and TBR were not available. In order to avoid bias, a covariate was included in the model indicating missing data. For instance, the influence of a dichotomous covariate X on CL/F with missing data of X for some individuals was modelled as $\text{TVCL} = \theta_1 \times \theta_2^{X \times (1-\text{MISS})} \times \theta_3^{\text{MISS}}$, in which TVCL is the typical value of CL/F in the population, MISS is 1 for records with missing data and 0 for all other records, θ_1 is the typical value of an individual with $X = 0$ (no missing data), θ_2 is the relative difference in CL/F for individuals with $X = 1$ (no missing data) and θ_3 is the relative difference in CL/F for individuals with missing data.

A covariate was included in an intermediate model when inclusion of this covariate was both statistically significant and relevant. A covariate was considered statistically significant when inclusion of the covariate was associated with a decrease in minimal value of the objective function associated with a P value of ≤ 0.05 (log-likelihood ratio test). Relevance was reached when the typical value of the pharmacokinetic parameter of interest changed at least 10% within the observed range of that covariate in the population.

All significant and relevant covariates were included in an intermediate model. Finally, a stepwise backward elimination procedure was carried out. Again, a parameter was only retained in the model when the influence of this parameter was statistically significant (log-likelihood ratio test: $P \leq 0.05$) and relevant (as defined earlier).

The actual significance level of the covariates included into the model was assessed with a randomization test, where a large number of datasets are created that could have arisen under the null hypothesis (i.e. the covariate is not related to the pharmacokinetic parameter). These datasets are created by random permutation of the empirical distribution of the covariate in the original dataset. The final model is applied to these datasets. The distribution of the difference in objective function between the models with and without the (randomly permuted) covariate is obtained and the actual significance level (one-sided test) can be calculated. In this validation, at least 1000 datasets were created for all covariates. Wings

for NONMEM (version 300) was used to perform these tests [18].

Results

Patients

Data from 173 HIV-1-infected patients were available and clinical details are presented in Table 1. The median age was 41.5 years (interquartile range (IQR) 36.1–48.2), and median body weight was 72 kg (IQR 65–79). The patient population was predominantly male (89.6%) and Caucasian (89%). Five patients were concomitantly using St John's wort. Baseline LEs were not available in 3 to 13% of patients (depending on the specific enzyme). A total number of 757 nevirapine plasma concentrations at a single random time point and full pharmacokinetic profiles from 13 patients (two curves per patient consisting of 17 and 27 time points) were available, resulting in a database of 1329 nevirapine plasma concentrations. Excluding the data from the full pharmacokinetic curves,

Table 1 Characteristics of 173 HIV type 1 infected individuals enrolled in this study of the population pharmacokinetic analysis of nevirapine.

Parameter		Median [IQR]	>1.5 x ULN (number of patients)
Age (years)		41.5 [36.1–48.2]	
Gender M/F (%)	155/18 (89.6/10.4)		
Weight (kg)		72 [65–79]	
Race			
Caucasian (%)	154 (89.0)		
Negroid (%)	15 (8.7)		
Asian (%)	4 (2.3)		
Clinical chemistry			
Baseline ASAT (U l ⁻¹)**		14 [11–18]	14
Baseline ALAT (U l ⁻¹)**		17 [11–23]	21
Baseline GGT (U l ⁻¹)**		18 [11–35]	36
Baseline AP (U l ⁻¹)**		72 [60–88]	3
Baseline TBR (μmol l ⁻¹)**		13 [10–17]	9
Glucose (mmol l ⁻¹)		5.8 [5.3–6.3]	
Creatinine (μmol l ⁻¹)		78 [72–87]	
Albumin (g l ⁻¹)		44 [42–46]	
Total protein (g l ⁻¹)		75 [71–78]	
Amylase (U l ⁻¹)		73 [53–99]	
Creatine kinase (U l ⁻¹)		57 [38–93]	
Clinical immunology at baseline			
CD4/CD8 ratio		0.3 [0.19–0.49]	
CD4 cell count (10 ⁶ l ⁻¹)		325 [200–473]	
CD8 cell count (10 ⁶ l ⁻¹)		1020 [718–1385]	
Molecular biology at baseline			
Plasma log ₁₀ HIV-1 RNA (copies ml ⁻¹)		<2.30 [<2.30–4.14]	
HCV/no HCV (%)	10/163 (5.8/94.2)		
HBV/no HBV (%)	11/162 (6.4/93.6)		

ALAT = alanine aminotransferase, AP = alkaline phosphatase, ARV = antiretroviral, ASAT = aspartate aminotransferase, F = female, GGT = gamma-glutamyltransferase, HBV = hepatitis B infection, HCV = hepatitis C infection, IQR = interquartile range, M = male, PI = protease inhibitor, TBR = Total bilirubin, ULN = Upper limit of normal.

**ASAT $n = 167$, ALAT $n = 167$, GGT $n = 150$, AP $n = 166$, TBR $n = 164$.

Table 2 Final parameter estimates of basic and final pharmacokinetic model.

	Basic model Est	RSE (%)	Final model Est	RSE (%)	P value
CL/F (l h ⁻¹)	3.27	2.3	3.35	2.4	
θ_{weight} (kg ⁻¹) [*]			0.0136	47.1	0.03
$\theta_{\text{hepatitis C}}$ [*]			0.726	10.7	<0.005
$\theta_{\text{ASAT} > 1.5 \text{ ULN}}$ [*]			0.868	8.2	0.049
$\theta_{\text{ASAT missing}}$ [*]			0.812	16	
V/F (l)	106	8.2	106	8.2	
k_a (h ⁻¹)	1.66	11.7	1.68	11.4	
Interindividual variability CL/F (%)	27.4	13.4	24.9	15.5	
Interoccasion variability CL/F (%)	20.4	12.6	20.4	12.6	
Interoccasion variability V/F (%)	37.9	32.2	38.3	32.2	
Interindividual variability k_a (%)	38.2	40.1	37.8	39.7	
Correlation factor interoccasion variability CL/F and V/F	0.710	44.4	0.692	45.4	
Fraction in population 1 (%)	89.4	4.6	89.0	4.8	
Additive error population 1 (mg × l ⁻¹)	0.326	7.0	0.326	7.0	
Additive error population 2 (mg × l ⁻¹)	0.993	22.3	0.996	22.5	
Increment proportion ($t < 2$ h)	2.68	7.8	2.68	7.8	

ASAT = aspartate aminotransferase, CL/F = apparent clearance, Est = parameter estimate, k_a = absorption rate constant, RSE = relative standard error (as calculated with COVARIANCE option of NONMEM), V/F = volume of distribution; P value estimated with randomization test.

^{*}CL/F = $\theta_{\text{CL/F}} \times (1 + \theta_{\text{weight}} [\text{WT}-70]) \times (\theta_{\text{hepatitis C}})^{\text{HCV}} \times (\theta_{\text{ASAT} > 1.5 \times \text{ULN}})^{(1-\text{MISS})} \times \text{ASAT} \times (\theta_{\text{ASAT missing}})^{\text{MISS}}$, in which WT is weight, HCV is 1 for individuals with chronic hepatitis C infection and 0 for all others, ASAT is 1 for patients with baseline ASAT >1.5 × ULN and 0 for all others, and MISS is 1 for patients with no baseline ASAT value and 0 for all others.

Figure 1 Concentration–time data for nevirapine in a randomly selected population of HIV-1 infected patients.

a mean of 4–5 samples per patient (range 1–10) was used. Figure 1 shows the nevirapine concentration–time data.

Pharmacokinetics

The population pharmacokinetics of nevirapine were best described by a one-compartment model with first-order absorption and elimination. The results of parameters generated from this model are summarized in Table 2. The use of absorption lag-time or time-dependent absorption models did not increase the goodness-of-fit, neither did that of a two-compartment-model or one with Michaelis–Menten-elimination. Estimates of CL/F, V/F and k_a were 3.27 l h⁻¹, 106 l and 1.66 h⁻¹, respectively. Interindividual variability in V/F and interoccasion variability in k_a could not be estimated.

Furthermore, the inclusion of the correlation factor between interoccasion variability of CL/F and V/F resulted in an increased goodness-of-fit. Figure 2 shows the predicted concentrations from the basic model *vs* observed concentrations of nevirapine (Panel a). The inclusion of two populations with different residual errors and the introduction of an increment proportion (θ_{ip}) both resulted in a dramatic increase in goodness-of-fit (Δ Objective function –300 and –200, respectively). A large fraction of the population (89.4%) was associated with a relatively small additive error of 0.326 mg l⁻¹, whereas the other fraction was associated with a larger additive error of 0.996 mg l⁻¹. The residual variability in the samples collected until 2 h after ingestion was estimated to be 2.7-fold higher than samples collected after this period (Table 2).

The different covariates were introduced separately into the basic model for CL/F and V/F. SEX, WT, HCV, ALAT, ASAT, TBR, and RACE had a relevant relationship with CL/F, which was associated with a significant and relevant increase in goodness-of-fit. For V/F, none of the covariates was significantly correlated. A step-wise backward elimination was then performed to eliminate nonsignificant and nonrelevant covariates from the intermediate model to develop the final model. Only WT, HCV, and ASAT had a significant and relevant relationship with CL/F, although RACE was of borderline significance (*P* value log-likelihood ratio test = 0.055). Subsequently, a randomization test was performed, which yielded a *P* value of 0.058 and, conse-

Figure 2 Model predicted *vs* observed concentrations of nevirapine using the basic model (Panel a) and the final model (Panel b).

quently, RACE was removed from the final model. The results of the final pharmacokinetic model are presented in Table 2. Figure 2 (Panel b) shows the model predicted concentration *vs* the observed concentration of nevirapine using the final model.

The results of the randomization test applied to the final model showed that WT, HCV, and ASAT were significantly related to the CL/F of nevirapine (Table 2). As shown in Figure 2, the final model (Panel b) describes the data better than the basic model (Panel a). The magnitudes of reduction in CL/F were 27.4% and 13.2% for HCV and ASAT $>1.5 \times \text{ULN}$, respectively, whereas an increase of 10 kg in WT increases the CL/F by 0.141 h^{-1} . The following equation describes the final model for CL/F:

$$\text{CL/F} = (3.35 + 0.0136 \times [\text{WT}-70]) \times 0.726^{\text{HCV}} \times 0.868^{\text{ASAT} \times (1-\text{MISS})} \times 0.812^{\text{MISS}}$$

in which HCV is 1 for individuals with chronic hepatitis C infection and 0 for all others, ASAT is 1 for patients with baseline ASAT $>1.5 \times \text{ULN}$ and 0 for all others, and MISS is 1 for patients with no baseline ASAT value and 0 for all others.

Discussion

The population pharmacokinetics of nevirapine were best described by a one-compartment model with first-order absorption and elimination. Application of the basic pharmacokinetic model to the complete data set resulted in typical values of CL/F and V/F of 3.27 l h^{-1} and 106 l , respectively. That for k_a was high (1.66 h^{-1}), indicating rapid absorption after oral administration. In the study performed by Zhou *et al.* the interindividual variability in CL/F was modest (20%) [11], but interoccasion variability was not taken into account. In our study, we were able to estimate both interoccasion and interindividual variability in CL/F. The interindividual variability in CL/F was somewhat higher (27.4%) than

found by Zhou *et al.*, which may be explained by our use of an unselected cohort.

A small proportion of the population (10.6%) was observed to be associated with a larger additive error than the rest, which could not be explained by any of the patient characteristics or other identifiable factors.

WT, HCV, and ASAT had a significant relationship with CL/F. Nevirapine is extensively metabolized in the liver by CYP450 enzymes. A value of ASAT $>1.5 \times \text{ULN}$ at baseline and coinfection with HCV may reflect hepatic dysfunction, thus resulting in a smaller capacity of the liver to metabolize nevirapine to its inactive metabolites. No effect of renal function on CL/F was found, which was expected based on the minor role of the kidney in the elimination of nevirapine. Gender was also found to be a significant covariate for CL/F when introduced in a univariate manner in the basic model, but not when it was tested in the multivariate analysis. However, the median weight of women and men in this study population differed considerably (58 and 72 kg, respectively). Thus, the lack of significance of gender as a covariate may be explained by a correlation with WT.

Although not significant, patients from the Negroid race appeared to have lower CL/F than those from other races (data not shown). CYP3A is primarily responsible for metabolism of nevirapine to its metabolites. Ethnic differences in pharmacokinetics have been reported for several drugs [19–24]. Wandel *et al.* [20] found a significantly lower systemic clearance of midazolam, metabolized by CYP3A, in African Americans when compared with European Americans. The reduction in hepatic CYP3A activity was associated with the possession of a variant CYP3A4*1B allele, which is more frequent in African Americans. Besides genetic factors, environmental factors (e.g. diet) could also contribute to ethnic differences in the pharmacokinetics of nevirapine.

St John's wort has been shown to increase CL/F of nevirapine by 35%, probably by inducing CYP3A [25].

Although the effect of St John's wort did not meet our criteria for significance, this earlier finding was compatible with the 21% increase in CL/F found in this study.

We and others have described a correlation between the plasma concentration of nevirapine and its efficacy [9, 10]. In addition, there are indications that a relationship between plasma concentration and toxicity exists. For example, Barreiro *et al.* demonstrated that the incidence of rash could be diminished by using a slowly escalating dose of nevirapine, (namely 100 mg for the first week, and increasing by 100 mg daily per week until achieving the maximum dose by the fourth week) [26]. Relationships between plasma concentration and efficacy and/or toxicity suggest that therapeutic drug monitoring of nevirapine might be useful combined with our model for the Bayesian estimation of individual pharmacokinetic parameters.

In conclusion, a model to describe the pharmacokinetics of nevirapine was developed. For this purpose, we used a patient population attending a routine HIV outpatient clinic. Patient characteristics causing interindividual variability in nevirapine pharmacokinetics were identified, and may lead to a further optimization of nevirapine-containing therapy.

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