Integration of population pharmacokinetics and pharmacogenetics: an aid to optimal nevirapine dose selection in HIV-infected individuals

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Background: Nevirapine is metabolized by CYP2B6 and polymorphisms within the CYP2B6 gene partly explain inter-patient variability in pharmacokinetics. The aim of this study was to model the complex relationship between nevirapine exposure, weight and genetics (based on combined analysis of CYP2B6 516G>T and 983T>C single nucleotide polymorphisms).

Methods: Non-linear mixed-effects modelling was used to estimate pharmacokinetic parameters from 275 patients. Simulations of the nevirapine concentration profile were performed with dosing regimens of 200 mg twice daily and 400 mg once daily for individuals with body weights of 50, 70 and 90 kg in combination with CYP2B6 genetic variation.

Results: A one-compartment model with first-order absorption best described the data. Population clearance was 3.5 L/h with inter-patient variability of 24.6%. 516T homozygosity and 983C heterozygosity were associated with 37% and 40% lower clearance, respectively. Body weight was the only significant demographic factor influencing clearance, which increased by 5% for every 10 kg increase. For individuals with higher body weight, once-daily nevirapine was associated with a greater risk of sub-therapeutic drug exposure than a twice-daily regimen. This risk was offset in individuals who were 516T homozygous or 983C heterozygous in which drug exposure was optimal for 95% of patients with body weight of ≤70 kg.

Conclusions: The data suggest that a 400 mg once-daily dose could be implemented in accordance with CYP2B6 polymorphism and body weight. However, the use of nevirapine once daily (immediate release; off-label) in the absence of therapeutic drug monitoring is not recommended due to the risk of inadequate exposure to nevirapine in a high proportion of patients. There are different considerations for the extended-release formulation (nevirapine XR) that demonstrate minimal peak-to-trough fluctuations in plasma nevirapine levels.

Keywords: CYP2B6, body weight, antiretroviral agents, dose selection, NONMEM

Introduction
Nevirapine-based antiretroviral combinations are first-line regimens for HIV-1 infection in most resource-poor settings, due to relatively low cost, manageable pill burden and excellent efficacy. However, the use of nevirapine is limited by two main factors: an immune-mediated hypersensitivity reaction that manifests as hepatotoxicity, fever and/or rash; and a fragile genetic barrier to the development of drug resistance. Nevirapine is metabolized primarily by the cytochrome P450 3A4 and 2B6 enzymes into its major metabolites 2-hydroxynevirapine and 3-hydroxynevirapine, respectively. There is also a minor contribution from CYP3A5. These isoenzymes are characterized by wide inter-individual variability in expression and activity in human liver microsomes.
The 516G>T single nucleotide polymorphism (SNP) in CYP2B6 has been reported to have a major impact on the pharmacokinetics and pharmacodynamics of efavirenz. Some studies have shown that 516G>T is associated with nevirapine plasma concentration. Recent studies have also shown that the 983T>C SNP was associated with significantly higher nevirapine plasma levels in black patients.

Previous studies have found body weight, ethnicity, gender and underlying liver disease to be important in explaining nevirapine pharmacokinetics. Several studies have examined the relationship between exposure to nevirapine and virological response. The risk of virological failure in patients who receive nevirapine-based antiretroviral therapy increases 5-fold when nevirapine plasma concentrations are <3.0 mg/L compared with patients with higher concentrations. As a result, a trough concentration (C_{trough}) target of 3.0 mg/L has been proposed as a minimum effective concentration (MEC).

The recommended dose of nevirapine is 200 mg once daily for the first 2 weeks, followed by 200 mg twice daily. However, the pharmacokinetic profile of nevirapine, in particular its long half-life, may allow once-daily dosing at 400 mg daily (following the 200 mg daily lead-in period). Several studies have shown that 400 mg once-daily dosing gives a similar virological and immunological response to a 200 mg twice-daily regimen. However, van Heeswijk et al. reported that nevirapine C_{trough} were lower for the once-daily regimen, which might result in an increased risk of developing drug resistance in vulnerable patients.

Identifying sources of variability in nevirapine pharmacokinetics could therefore be of importance in the clinical management of HIV infection and may aid in optimal dosage selection. The purpose of this study was to develop and validate a population pharmacokinetic model for nevirapine and identify covariates that affect pharmacokinetic variability. In particular, the influence of the CYP2B6 516G>T and 983T>C SNPs and their effect on nevirapine trough plasma concentrations for twice- and once-daily nevirapine regimens were evaluated.

### Methods

#### Patients

A total of 113 HIV-positive patients on nevirapine-based regimens (38 patients receiving 400 mg once daily) were recruited from the Department of HIV Medicine, Royal Free NHS Trust, London and 162 HIV-positive patients were recruited from the German Competence Network for HIV/AIDS (KompNet Cohort) (200 mg twice daily). The first cohort included 11 patients with six blood samples collected in the dosing interval, 9 patients who had blood collection on two different occasions and 102 patients who had one random blood drawn. In the second cohort, all patients had one random blood drawn. Plasma was obtained and stored at −80°C before analysis. All the patients had an HIV viral load of <50 copies/mL at the time of sampling. Associations of CYP2B6 polymorphisms with nevirapine plasma concentrations in these cohorts have previously been published.

Patients were only recruited if they had achieved steady-state on a nevirapine-based regimen, in combination with two nucleoside reverse transcriptase inhibitors (NNRTIs) or one NRTI plus one nucleotide reverse transcriptase inhibitor and were known to be fully compliant. Patients on a concomitant ritonavir-boosted protease inhibitor and other known major interacting drugs were excluded. All blood sampling was performed after written informed consent had been obtained in accordance with local ethics committee indications. The following covariates were available: age; gender; body weight; and pharmacogenetics (CYP2B6 516G>T and 983T>C).

#### Genotyping

Total genomic DNA was isolated using the QIAamp DNA mini kit according to the manufacturer’s instructions. Following extraction, purity was assessed by comparing the A_{260} and A_{280} ratio. DNA was quantified using PicoGreen® dsDNA Quantitation Reagent (Molecular Probes, CA, USA) and normalized to 20 ng/mL. Pre-amplification for exon 4, exon 9 and exons 7 and 8 (combined) was then conducted to discriminate from the CYP2B6 pseudogene (CYP2B7) by modification of previously reported methods. Genotyping for 516G>T and 983T>C was then performed on the resultant amplicons by real-time PCR allele discrimination using standard methodology (95°C for 15 min followed by 40 cycles of 95°C for 15 s and 60°C for 1 min) in a DNA Engine Opticon® 2 system (MJ Research Inc., USA). Full PCR conditions as well as primer and probe sequences are available on request.

#### Quantification of drug levels

Plasma obtained from blood samples was heat inactivated and nevirapine concentrations were determined using HPLC with UV detection using validated assays as previously described. The lower limit of quantification of nevirapine was taken as the lowest point on the standard curve (100 ng/mL). Intra-assay and inter-assay coefficients of variation at 100 ng/mL were 6.7% and 8.2%, respectively. The Liverpool laboratory participates in an external quality assurance scheme (KKT, The Hague, The Netherlands).

#### Population pharmacokinetic analysis

The pharmacokinetic model was developed using NONMEM® (ICON, version VI 2.0) installed under nmmp (Metrum institute). Data processing and graphical analyses were done using Microsoft Office Excel 2007 for Windows (Microsoft Corporation, Redmond, WA, USA).

The model building strategy was as follows: one- and two-compartment models with first- or zero-order absorption without and with lag time were fitted to the data using the first-order conditional method of estimation. Proportional, additional and combined proportional and additional error models were evaluated to describe residual variability. Inter-occasion variability was also tested. The minimal objective function value (OFV; equal to −2 log likelihood) was used as a goodness-of-fit metric with a decrease of 3.84 corresponding to a statistically significant difference between models (P=0.05, χ² distribution, one degree of freedom). Residual plots were also examined. Once the appropriate structural model was established, the following covariates were explored: body weight; age; gender; ethnicity; and CYP2B6 516G>T and 983T>C polymorphisms. Dichotomous and continuous variables, here defined as X, were introduced into the model using the following parameterizations, respectively:

\[
TVCL = \theta_0 + \theta_1 \times X + \theta_2 \times (X - \text{median value}) \quad (1)
\]

where TVCL is the typical value of nevirapine apparent clearance (CL/F) of the population; in equation 1, \(\theta_0\) is the value of CL/F for the individual's X=0, and \(\theta_1\) is the relative difference in CL/F for the individual's X=1. In equation 2, \(\theta_0\) is the typical CL/F at the median body weight, \(\theta_1\) is the change in CL/F per kg, and X is the continuous variable.
individual’s body weight or age). Graphical methods were used to explore the relationship of covariates versus individual predicted pharmacokinetic parameters. Each covariate was introduced separately into the model and only retained if inclusion in the model produced a statistically significant decrease in OFV of 3.84 (P < 0.05). A backwards elimination step was then carried out once all relevant covariates were incorporated and covariates were retained if their removal from the model produced a significant increase in OFV (>6.63 points; P ≤ 0.01, χ² distribution, one degree of freedom).

To perform a visual predictive check, 1000 datasets were simulated using the parameter estimates defined by the final model with the SIMULATION SUBPROBLEMS option of NONMEM®. Datasets were simulated for nevirapine 200 mg twice daily and 400 mg once daily. From the simulated data, 90% prediction intervals (PIs) (P5–P95) for each regimen were constructed. Observed data from the original dataset were superimposed for both regimens. At least 90% of data points within the PI (5% above and below) was indicative of an adequate model.

In addition, in order to confirm the stability and robustness of the model, bootstrap re-sampling was used. Bootstrapping was performed with the software package Perl-speaks-NONMEM 5.1.23 The median values and 90% confidence intervals for the parameter estimates were obtained from 200 bootstrap replicates of the original dataset and compared with the original population parameters.

Table 1. Summary of patient demographics and baseline clinical characteristics of patients included in the pharmacokinetic modelling

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study participants, n (M/F)</td>
<td>275 (161/114)</td>
</tr>
<tr>
<td>200 mg twice daily, n</td>
<td>237</td>
</tr>
<tr>
<td>400 mg once daily, n</td>
<td>38</td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>42 (18–82)</td>
</tr>
<tr>
<td>Weight (kg), median (range)</td>
<td>72.5 (47–132)</td>
</tr>
<tr>
<td>Caucasian ethnicity, n (%)</td>
<td>183 (66.5)</td>
</tr>
<tr>
<td>Black ethnicity, n (%)</td>
<td>92 (33.5)</td>
</tr>
<tr>
<td>516GT, n (%)</td>
<td>126 (46)</td>
</tr>
<tr>
<td>516TT, n (%)</td>
<td>19 (7)</td>
</tr>
<tr>
<td>983TC, n (%)</td>
<td>9 (3)</td>
</tr>
</tbody>
</table>

n, number of patients; M, male; F, female; 516GT, heterozygous patients; 516TT, homozygous patients; 983TC, heterozygous patients.

Table 2. Nevirapine (NVP) final parameter estimates and standard errors obtained from the final population pharmacokinetic model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basic model (RSE %)</th>
<th>Final model (RSE %)</th>
<th>Bootstrapped median (90% PI) in the final model</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (L/h)</td>
<td>3.14 (2.4)</td>
<td>3.51 (3.0)</td>
<td>3.5 (3.3, 3.7)</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>153 (8.7)</td>
<td>150 (8.7)</td>
<td>148.5 (127.3, 172.6)</td>
</tr>
<tr>
<td>k₀ (h⁻¹)</td>
<td>1.25 (22.5)</td>
<td>1.20 (22)</td>
<td>1.22 (0.7, 1.67)</td>
</tr>
<tr>
<td>IIV CL/F (%)</td>
<td>36 (10.6)</td>
<td>31 (10.8)</td>
<td>32 (29, 34)</td>
</tr>
<tr>
<td>Residual error proportional (%)</td>
<td>9.2 (11.0)</td>
<td>9.2 (10.8)</td>
<td>10.8 (7.9, 13)</td>
</tr>
<tr>
<td># associated with BW on NVP CL/F</td>
<td>0.018 (32.8)</td>
<td>0.0183 (0.008, 0.027)</td>
<td></td>
</tr>
<tr>
<td># associated with 516GT on NVP CL/F</td>
<td>−0.5 (27.3)</td>
<td>−0.5235 (−0.7, −0.3)</td>
<td></td>
</tr>
<tr>
<td># associated with 516TT on NVP CL/F</td>
<td>−1.3 (16.7)</td>
<td>−1.3 (−1.7, −0.9)</td>
<td></td>
</tr>
<tr>
<td># associated with 983TC on NVP CL/F</td>
<td>−1.4 (13.2)</td>
<td>−1.38 (−1.7, −0.3)</td>
<td></td>
</tr>
</tbody>
</table>

RSE, relative standard error; IIV, inter-individual variability; BW, body weight; 516GT, heterozygosity; 516TT, homozygosity; 983TC, heterozygosity. RSE defined as (SEestimate/estimate)×100.

Final pharmacokinetics model TVCL = θ₀ + θ₁×(BW–median weight) + θ₂×X516GT + θ₃×X516TT + θ₄×X983TC.

Results

Population analysis was performed with 406 drug concentrations from 275 patients receiving nevirapine-containing regimens for ≥4 weeks. Three patients with peak concentrations <1 mg/L were excluded due to suspected non-adherence to therapy. Their exclusion improved the model fit, thus they were not included in the final model. The demographic characteristics of the patients are shown in Table 1.

Nevirapine pharmacokinetics of 272 HIV-positive patients with 403 drug concentrations were best described by a one-compartment model with first-order absorption and first-order elimination. A one-compartment model with zero-order absorption or a two-compartment model did not improve the fit. In the model, residual variability was best described by a proportional structure; the inclusion of an additive structure did not improve the model. Inter-individual random effects were described by an exponential model that was supported only for CL/F. The introduction of an absorption lag time did not improve the model fit. In the basic model the mean population estimates for CL/F, apparent volume of distribution (V/F) and absorption constant (k₀) were 3.14 L/h, 153 L and 1.25 h⁻¹, respectively; the inter-individual variability in CL/F expressed by the coefficient of variation (CV) was 0.13. The residual variability was 0.0085.

A total of six covariates (weight, age, gender, ethnicity, CYP2B6 516G>T and 983T>C) were analysed using a stepwise backward elimination. CL/F significantly (P < 0.001) correlated with three covariates: weight; CYP2B6 516G>T; and 983T>C. The mean population estimate for CL/F was 3.5 L/h; the final covariate model is detailed in Table 2. Inclusion of body weight resulted in an improvement of the goodness of the fit (ΔOFV = 9.7), a slight decrease in inter-individual variability of 2% and CL/F increased.
by 0.18 L/h with body weight increases of 10 kg. No other demographic covariates proved to be statistically significant.

The impact on CL/F for each variant genotype of 516G>T and 983T>C was expressed as $CL = CL_0 + \theta_1 \times HET + \theta_2 \times HOM$, where HET and HOM indicate genotypic status being equal to 1 for heterozygous and homozygous individuals, respectively, and 0 for the wild-type patients. $CL_0$ is the typical value of CL/F for individuals carrying wild-type alleles. The current dataset had only wild-type and heterozygous individuals for CYP2B6 983T>C. To date, no homozygotes for this polymorphism have been described. In subjects who were heterozygous for 516GT CL/F decreased by 0.5 L/h, and in homozygotes the model showed a more consistent decrease in CL/F of 1.3 L/h. Patients with the 983TC genotype also showed a significant decrease in CL/F of 1.4 L/h. A summary of the final population estimates is presented in Table 2; the inclusion of the genotypes decreased CL/F inter-individual variability by 4%.

The final model was carried out using the following equation: $TVCL = \theta_0 + \theta_1 \times (BW - 72.5) + \theta_2 \times 516GT + \theta_3 \times 516TT + \theta_4 \times 983TC$. The diagnostic plots for the final model suggested that predicted and observed data were in agreement (Figure 1). The individual weighted residuals did not reflect any particular systematic trends.

A 90% PI was generated from 1000 simulations for nevirapine 200 mg twice daily and 400 mg once daily, with the covariate values of those individuals used in the building process (Figure 2). Observed data from patients used in the model building process were superimposed onto the PI. The proportion of nevirapine concentrations >P95 was 5.3% and <P5 was 2.6% in patients receiving 400 mg of nevirapine once daily ($n=38$), and 2% were >P95 and 2.5% were <P5 in patients receiving 200 mg of nevirapine twice daily ($n=362$). These findings suggested that overall the final model performed adequately.

In addition, from the original dataset, 200 bootstrap replicate datasets were generated and used to evaluate the stability of the final model. The median values of the parameter estimates from the bootstrapping were very similar to the mean population estimates for the final model (Table 2). The 90% PI for the parameter estimates obtained from the bootstrap procedure revealed adequate estimation of the pharmacokinetic parameters.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Goodness of fit plots for the final pharmacokinetic model illustrating (a) population predictions of nevirapine versus observed concentrations, (b) individual predictions of nevirapine versus observed concentrations (where the continuous lines show the lines of unity and the broken lines show the lines of regression) and (c) weighted residuals versus time post-dose (where the continuous line shows the line at an ordinate value of zero).

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Ninety percent PIs determined from simulated data of nevirapine (a) 200 mg twice daily and (b) 400 mg once daily. The mean population prediction is shown as a continuous line and the 90% PI is shown as a broken line. NVP, nevirapine.
Figure 3. Steady-state 90% PI (P5–P95) determined from simulated data of nevirapine (NVP) administered at different doses. The mean population prediction (continuous thick line) and the 90% PI (grey area) are represented for each category. The broken horizontal line is at an ordinate value of 3 mg/L (proposed MEC). (a) Steady-state NVP concentrations predicted at a 200 mg twice-daily dose. Proportion below the MEC: 516GG, 50 kg 12%, 70 kg 19% and 90 kg 28%; 516TT, 50 kg 0.3%, 70 kg 1% and 90 kg 3%; and 983TC, 50 kg 0.2%, 70 kg 1% and 90 kg 2%. (b) Steady-state NVP concentrations predicted at a 400 mg once-daily dose. Proportion below the MEC: 516GG, 50 kg 20%, 70 kg 31% and 90 kg 43%; 516TT, 50 kg 1%, 70 kg 3% and 90 kg 7%; and 983TC, 50 kg 0.6%, 70 kg 2% and 90 kg 6%.
parameters for both fixed and random effects and robustness of the final model.

In order to evaluate the combined clinical impact of the pharmacogenetic factors and body weight, simulated concentration–time courses of a single dose of nevirapine (200 mg twice daily and 400 mg once daily at steady-state to typical individuals with body weights of 50 kg, 70 kg and 90 kg were performed. The simulations were carried out firstly with a population of individuals homozygous for the common alleles (516GG and 983TT) and secondly with the variant alleles 516TT and 983TC (Figure 3). For 400 mg once-daily simulations, the proportions of individuals with potentially sub-therapeutic (i.e. <MEE) C\text{\textit{\textsubscript{\textit{Trough}}}} were 516TT versus 516GG: 50 kg (1% versus 20%); 70 kg (3% versus 31%); and 90 kg (7% versus 43%). For 200 mg twice-daily simulations these proportions were: 50 kg (0.3% versus 12%); 70 kg (1% versus 19%); and 90 kg (3% versus 28%). Similarly, proportions for potentially sub-therapeutic C\text{\textit{\textsubscript{\textit{Trough}}} for 983TT} individuals were: 50 kg (0.6% versus 20%); 70 kg (2% versus 31%); and 90 kg (6% versus 43%). For 200 mg twice-daily simulations these proportions were: 50 kg (0.2% versus 12%); 70 kg (1% versus 19%); and 90 kg (2% versus 28%).

**Discussion**

The non-NRTIs, efavirenz and nevirapine, are extensively used as part of a first-line regimen or for simplification of highly active antiretroviral therapy due to their simplicity, tolerability and efficacy. Both drugs are metabolized by CYP2B6, a highly polymorphic enzyme with numerous SNPs and associated haplotypes. The possible significance of CYP2B6 pharmacogenetics for clinical drug treatment is emerging, with consistent pharmacokinetic effects demonstrated for efavirenz. It has recently been shown that CYP2B6 can also play an important role in the biotransformation of nevirapine. The non-NRTIs, efavirenz and nevirapine, are extensively used as part of a first-line regimen or for simplification of highly active antiretroviral therapy due to their simplicity, tolerability and efficacy. Both drugs are metabolized by CYP2B6, a highly polymorphic enzyme with numerous SN Ps and associated haplotypes. The possible significance of CYP2B6 pharmacogenetics for clinical drug treatment is emerging, with consistent pharmacokinetic effects demonstrated for efavirenz. It has recently been shown that CYP2B6 can also play an important role in the biotransformation of nevirapine.

This study examined the impact of the CYP2B6 516G>T and 983T>C SNPs on nevirapine clearance and simulated C\text{\textit{\textsubscript{\textit{Trough}}} obtained from once-daily and twice-daily nevirapine regimens. The model that best described nevirapine pharmacokinetics was a one-compartment model with first-order absorption and elimination, and the model estimate parameters are consistent with values previously published. The volume of distribution was slightly greater compared with a previous study, although still in range. This may be due to the relatively high body weight of the patients (average body weight 75 kg) and nevirapine being lipophilic and weakly basic. The drug might be taken up by adipose tissues, thus resulting in a large apparent volume of distribution.

Inter-individual variability was identified only for CL/F. The population PK and pharmacogenetics of nevirapine twice and once daily may have contributed to the inter-individual variability for V/F. Body weight was the only demographic covariate significantly related to CL/F, which increased by 5% with body weight increase of 10 kg. The inclusion of CYP2B6 genetics also improved the model fit. The impact of 516G>T was tested including heterozygous and homozygous subjects, showing that both genotypes influenced CL/F to a significant extent (\text{\textit{\textsubscript{\textit{AOFV}}} = −27.8}). Particularly significant was the effect of the 516TT genotype, which decreased CL/F by 37%. Importantly, there was a gene–dose effect with 516GT decreasing CL/F by 15% compared with the 516GG genotype. CYP2B6 516G>T is one of the most commonly occurring variants, leading to a Gln172His change in amino acid. Although, it is not directly in the protein active site, residue 172 along with additional nearby SNP residues (in linkage disequilibrium), could affect ligand binding altering the size and flexibility of the active site. A recent study by Chou et al. also evaluated the impact of the CYP2B6 516G>T polymorphism in a Cambodian population. The study showed a decrease in clearance from 516GG to the 516GT and 516TT genotypes of 11% and 37%, respectively. The results of this study and the current analysis indicate a consistent effect of CYP2B6 516G>T polymorphism in different populations.

The impact of 983T>C was also statistically significant (\text{\textit{\textsubscript{\textit{AOFV}}} = −9.4}), with heterozygotes for this allele having a 40% lower CL/F. This SNP usually occurs as part of the *18 haplotype. Recombinant expression of the variant, in which the highly conserved hydrophobic Ile at position 328 within the J helix has been changed into Thr, showed undetectable expression and activity in COS-1 cells. This suggests that the resulting effect of this variant could be a loss of protein function resulting from a hydrophobicity change from Ile to the polar Thr. These alterations might explain the high impact of 983TC on CL/F.

The total decrease in OFV after the inclusion of the SNPs was 32.2, thus 516G>T and 983T>C were included in the final model. Overall, these results are in agreement with other studies previously published. In contrast, in a recent study, Haas et al. did not find any association between CYP2B6 516G/T and nevirapine plasma concentrations. However, this lack of association was observed in a single-dose study of nevirapine pharmacokinetics, prior to auto-induction of the enzymes and achievement of steady-state.

Nevirapine pharmacokinetics permits a once-daily regimen, and several clinical trials have evaluated once-daily administration. The 2NN study showed that total drug exposure (AUC_{\text{\textit{T}}}) was comparable in once-daily and twice-daily administrations. However, van Heeswijk et al. showed a significant difference in C\text{\textit{\textsubscript{\textit{Trough}}} levels, which were lower for the once-daily regimen. Similar findings were reported by Molto et al. who estimated nevirapine C\text{\textit{\textsubscript{\textit{Trough}}} for the two regimens using a population pharmacokinetic approach accounting for body weight. However, the impact of body weight on CL/F was more than double compared with this study (change in CL/F with a body weight increase of 10 kg, 0.4 versus 0.18 L/h). Also, in the study of Molto et al. the CL/F is relatively low (2.95 L/h), which resulted in a smaller proportion of simulated subjects with sub-therapeutic plasma concentrations compared with the present study. Cooper and van Heeswijk indicated that the interquartile range of CL/F was 2.80–4.21 L/h and de Maat et al. indicated a change in CL/F of 0.14 L/h with a body weight increase of 10 kg, which are similar to the values presented in this report. A limitation of the present study is that the majority of the samples are from patients recruited for therapeutical drug monitoring (TDM) and with limited information on diseases status. TDM patients are often selected (e.g. non-adherence, investigational dosing regimens, unfavourable drug interaction, suspected toxicity) and this could have impacted on the percentage (9.8%) of patients on 200 mg twice daily being below the MEC. These factors and a relatively limited number of patients on 400 mg once daily may have contributed...
to affect the model predictions. However, the predicted parameters were in the range of a previous study.14 Malto et al.10 and van Heeswijk et al.19 both suggested that the once-daily regimen might place patients at risk of subtherapeutic concentrations at the end of the dose interval ($C_{\text{Group}} < 3 \text{ mg/L}$), increasing the risk of the development of drug resistance. More recently, data have been presented on a new extended-release formulation of nevirapine dosed once daily (nevirapine XR). In the VERXV trial there was non-inferior efficacy of nevirapine XR compared with the immediate-release twice-daily formulation.36 Nevirapine XR gave a ‘flatter’ plasma concentration–time curve than twice-daily dosing.

In the present study a population pharmacokinetic model was used to assess the complex relationship between drug exposure, weight and genetics (based on combined analysis of CYP2B6 516G>T and 983T>C SNPs). Simulation of drug exposure was performed for different groups across a range of body weights and genetics, for twice- and once-daily nevirapine regimens. Using a mixed-effects modelling approach with data from two distinct cohorts the potential utility of pharmacogenetic testing in optimizing dose based on body weight was explored.

For individuals with higher body weight, once-daily nevirapine was associated with a greater risk of subtherapeutic drug exposure than a twice-daily regimen. This risk was offset in individuals who were 516T homozygous or 983C heterozygous in which drug exposure was optimal for >95% of patients with a body weight of ≥70 kg. This individualized approach, integrating population pharmacokinetic analysis, weight-based dosing and pharmacogenetics, could also be applied to dosing strategy in populations. For example, twice-daily dosing is likely to be more robust in individuals weighing ≥90 kg for a population with a low frequency of these CYP2B6 variants (e.g. Caucasian). In contrast, black Africans even those weighing ≥90 kg are more likely to achieve an adequate drug level with once-daily nevirapine dosing, although there will still be some individuals who remain sub-therapeutic. This is important since the nucleoside backbone of WHO first-line regimens is moving away from stavudine towards once-daily dosing that could be co-formulated with nevirapine.

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Population PK and pharmacogenetics of nevirapine twice and once daily


