Population pharmacokinetics of tenofovir in HIV-1 uninfected members of sero-discordant couples and effect of dose reporting methods

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Abstract

Antiretroviral pre-exposure prophylaxis (PrEP) was shown to be effective for preventing HIV-1 infection in individuals who had HIV-1 seropositive partners (the Partners PrEP Study) with once daily dosing of tenofovir and tenofovir/emtricitabine. We developed a population pharmacokinetic model for tenofovir and investigated the impact of different dose reporting methods. Dosing information was collected by patient-reported dosing information (PRDI) from 404 subjects (corresponding to 1280 drug concentration records) from the main trial and electronic monitoring based adherence collected from 211 subjects (corresponding to 327 drug concentration records) in an ancillary adherence study. Model development was conducted with NONMEM (7.2) using PRDI with a steady-state assumption or using PRDI substituted with electronic monitoring records where available. A two-compartment model with first-order absorption was the best model from both modeling approaches with a need of absorption lag time when including electronic monitoring based dosing records in the analysis. Age, body weight and creatinine clearance were significant covariates on clearance, but only creatinine clearance was retained in the final models per stepwise selection. Sex was not a significant covariate on clearance. Tenofovir population pharmacokinetic parameter estimates and precision of the parameters from the two final models were comparable with the point estimates of the parameters differing from 0% to 35% and bootstrap confidence intervals widely overlapping. These findings indicate that the PRDI was sufficient for population pharmacokinetic model development in this study, with high level of adherence per multiple measures.
Introduction

The nucleotide reverse transcriptase inhibitor (NRTI) tenofovir disoproxil fumarate (TDF) has been used in combination with other antiretroviral agents for the treatment of HIV-1 infection. TDF, the oral prodrug formulation of tenofovir, was approved by the US FDA for pre-exposure prophylaxis (PrEP) in 2012 in a fixed-dose combination with emtricitabine (FTC) to reduce the risk of sexually acquired HIV-1 among people who are at high risk of HIV infection. The Partners PrEP Study, a phase 3 trial that contributed to the approval, demonstrated the efficacy of TDF alone and in combination with FTC in reducing the risk of HIV-1 acquisition in HIV-1 seronegative members of serodiscordant heterosexual couples (1).

Successful HIV-1 prevention depends on individuals’ sustained adherence to the medication during periods of risk. Poor drug adherence has been an important challenge in some PrEP trials (2). Tenofovir-containing regimens failed to show efficacy of reducing the risk of acquiring HIV-1 in studies where drug adherence was low as evidenced by undetectable plasma tenofovir concentrations in a high percentage of participants (3, 4). In the Partners PrEP Study, blood samples were drawn during clinic visits to determine drug concentrations in plasma after completion of the study as a measure of drug adherence. In addition, an ancillary study was conducted to determine drug adherence using multiple methods which included counting pills during home visit (announced in the main trial and unannounced in the ancillary study), using electronic monitoring in which the time of pill container openings was recorded by a micro-electronic circuit in the cap, and drawing blood samples for measurement of plasma tenofovir concentrations in all subjects in the main trial and a randomly selected subset in the ancillary study (5). Results from the Partners PrEP Study showed that both TDF monotherapy and the combination of TDF and FTC were effective for reducing the risk of HIV-1 acquisition in HIV-1
seronegative partners and the drug adherence was high – estimated to be 97% by the pill counts in the main trial, and 99.1% and 97.2% by unannounced pill counts and MEMS, respectively, in the ancillary study.

In addition to providing a measure of adherence, plasma concentrations could provide important information on sources of variability in drug exposure. The study of population pharmacokinetics using nonlinear mixed effects modeling methodology is suitable for large scale, sparse sample collection, such as was done in the Partners PrEP Study. However, reliable dosing records and informative pharmacokinetic sampling are important for unbiased pharmacokinetic parameter estimation. Several population pharmacokinetic models for tenofovir have been reported (6-16). However, all of them include data from HIV-1 infected subjects or a mix of healthy and HIV infected population (7) except our recent reports using a population of healthy women (15,16). In the current study, patient-reported dosing information (PRDI) was collected in the main trial, and electronic adherence measurements were available in the adherence sub-study. Our objectives were to develop population pharmacokinetic model for tenofovir and investigate the impact of different types of dosing records on population pharmacokinetic parameters.

Materials and Methods

Study design

The Partners PrEP Study was a multi-site, randomized, double-blind, placebo-controlled clinical trial conducted in Kenya and Uganda. Detailed description of the study was published previously (1). Briefly, a total of 4,758 heterosexual HIV-1 couples in which one member was HIV-1 seronegative and the other HIV-1 seropositive were enrolled in the study. The HIV-1 uninfected
participants were randomly assigned in a 1:1:1 ratio to receive once-daily oral TDF (300 mg), combination of FTC (200 mg)/TDF (300 mg), or matching placebo. The subjects were followed with monthly clinic visits for provision of study medication, HIV-1 testing and symptom evaluation, for up to 36 months. At each monthly visit, adherence was assessed by self-report questionnaire and pill count. Plasma samples were collected on the visits at first month and every 3 months thereafter. A total of 1,147 HIV-uninfected participants in Uganda with at least 6 months of follow-up remaining in the main trial were enrolled in an ancillary adherence study, full details of which are described elsewhere (5). In the ancillary study which involved a convenience sample from three study sites with approximately equal distribution among study arms, additional adherence assessment was performed using two validated objective measures: 1) pill counts at the unannounced visits (UPC) to the participant’s home on a random day monthly for the first 6 months and quarterly thereafter; and 2) electronic adherence measurements using MEMS (WestRock, Richmond, VA) recording the date and time of pill container openings. The MEMS data were downloaded during the monthly clinic visits. Participants found to have UPC adherence < 80% were enrolled in a counseling-based adherence intervention (5). Blood samples were collected during the unannounced home visits at months 6, 12, and 24 to measure systemic levels of study medication. Age, body weight, creatinine clearance, and gender information for the subjects were recorded. Tenofovir concentrations in the plasma samples were determined by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) as previously reported (17). The lower limit of quantitation (LLOQ) was 0.31 ng/mL.

Modeling strategy and population pharmacokinetic model
Population pharmacokinetic analysis was conducted within software NONMEM (version 7.2) with intel/gfortran compilers interfaced with wings for NONMEM (WFN) or Perl-speaks-NONMEM (PsN) (18, 19). Models were developed using datasets generated under the following three scenarios: 1) tenofovir plasma concentrations with patient reported dosing information (PRDI) for times of the dose prior to the blood collections where the steady-state assumption was made for the administered doses (PRDI dataset); 2) tenofovir plasma concentrations with time information collected by MEMS without assumption of steady-state for the MEMS-recorded doses (EMS dataset); and 3) the combined dataset of 1) and 2) with patient self-reported times of the dose prior to the blood collections substituted with MEMS records where available (COMBINED dataset). One- and two-compartment models with first-order absorption with and without incorporating a lag time were tested using the first-order conditional estimation method with interaction. Inclusion and exclusion of concentrations below the LLOQ (BQL) were tested. When the BQL values were included, M3 method was applied with LAPACIAN option as previously reported (20). Pharmacokinetic parameters were assumed to follow a log normal distribution as defined in equation 1 where \( \eta \) denotes the difference between \( \theta_i \), the parameter of the \( i \)th individual, and \( \theta_{pop} \), the population mean for the parameter and \( \eta_s \) are normally distributed with mean zero and variance \( \omega^2 \).

\[ \theta_i = \theta_{pop} \times \exp(\eta) \]  

(1)

Residual error models including additive error, constant coefficient of variation error, and a combination of additive and constant coefficient of variation error were tested for description of residual variability. An inter-individual variability for the additive error was also tested as previously reported (21).
Covariate selections

Sex, age, body weight, and creatinine clearance (estimated by the Cockcroft-Gault equation) were evaluated for their influence on the pharmacokinetic parameters of tenofovir. The covariate model was built using a stepwise forward addition procedure followed by backward elimination (22). For continuous variables such as age, creatinine clearance, and body weight, the covariates were centered to the median values of the variable for age and creatinine clearance, and to a standard value of 70 kg for body weight, respectively. Models with linear, power, and exponential functions were tested.

Model selection

R scripts and XPOSE4 were used to generate diagnostic plots (23, 24). Goodness-of-fit was determined by visualization of scatter plots of predicted vs. observed tenofovir plasma concentrations, conditional weighted residuals vs. time of post-dose, and distribution of normalized prediction distribution errors (25). The objective function value (OFV) approximately equal to -2 × log (likelihood) (-2LL), the difference of which between two hierarchical models follows a $\chi^2$ distribution. A decrease in OFV for more than 3.84 was considered as statistically significant ($p < 0.05$ with df = 1) for inclusion of one extra parameter in the model. During the backward elimination step for the covariate model development, a more stringent criterion with an increase in OFV for more than 10.83 ($p < 0.001$ with df = 1) was utilized to retain a covariate in the model. Selection of the structural PK model and residual error model was based on a global judgment of the model adequacy based on goodness-of-fit plots, successful convergence, biological plausibility, precision of the model parameter estimates, and objective function values.

Model evaluation
To check the stability of the selected models, nonparametric bootstraps of 1000 iterations were conducted to estimate 95% confidence intervals of the population parameters. Visual predictive checks with proportions of BQLs predicted by the model were performed as previously described (26) to characterize the model’s predictability. Briefly, final models were used to simulate 1000 data sets with the same study design as the original data set. The observed tenofovir plasma concentrations as well as the 5th, 50th, and 95th percentiles (90% prediction intervals) were plotted against the corresponding percentiles of the simulated values. The observed fractions of BQLs were plotted along with 95% prediction interval for the predicted fraction of BQLs from the simulated datasets. The agreement of distributions between the observations and simulations was inspected visually.

Results

Availability of data and demographics of patients

For the PRDI dataset, a total of 1280 tenofovir plasma concentrations were available from 404 participants in the Partners PrEP Study main trial (3.2 concentrations per participant); 214 of the concentrations (17%) were BQL. For the EMS dataset, a total of 327 tenofovir plasma concentrations were available from 211 patients who participated in the ancillary adherence study (1.5 concentrations per participant); and 8% of the concentrations in this dataset were BQL. In the COMBINED dataset, MEMS records replaced the patient-reported dosing records when available. The median follow up time for the participants in the ancillary adherence study was 11.3 months. There were no statistically significant differences between the demographics (Table 1) of EMS dataset participants and the participants without EMS data in terms of age, sex and body weight except that creatinine clearance was significantly different (p< 0.05).
Population PK model for tenofovir

A two-compartment model with first-order absorption was the best pharmacokinetic model to describe the disposition of tenofovir for the PRDI and COMBINED datasets (Figure 1). The major difference was that inclusion of a lag time (ALAG1) and fixing absorption rate constant (Ka) was needed in the model for the COMBINED dataset, but not in the PRDI dataset. The analysis with EMS dataset did not result in a robust and credible model. Rather, majority of the models were sensitive to initial estimates or results in parameters that were not consistent with the known pharmacokinetics of tenofovir. Accordingly, the EMS dataset was not used in further analyses.

The final model parameters of tenofovir from the PRDI and COMBINED models are shown in Table 2. Except for peripheral volume of distribution (Vp/F) and Ka, the values of the parameters identified in both models were similar. A combination of proportional and additive error model was the best to describe the residual variability of tenofovir plasma concentrations in both models. Inclusion of inter-individual variability (IIV) on the additive error significantly decreased the objective function value. The inter-individual variability (%CV) of clearance (CL/F) was similar with 19% and 16%, respectively, between the two models. In addition to the inter-individual variability on CL/F and the additive error, which was estimated in both models, replacing patient-reported dosing records by MEMS in the combined dataset supported the estimation of additional inter-individual variability for Vc/F and Ka. Age, body weight and creatinine clearance were significant covariates on clearance for both analyses, but only creatinine clearance was retained in the final model because body weight and age are correlated...
with creatinine clearance. Inclusion of creatinine clearance decreased the objective function value by 53 and 63 points in the models with PRDI and COMBINED datasets, respectively. The diagnostic plots are shown in Figures 2 and 3, respectively, for the models based on PRDI and COMBINED datasets. No major bias was observed in the diagnostic plots.

**Stability and predictability of the models**

Population pharmacokinetic parameter estimates of the final models from the PRDI and COMBINED datasets were similar in the median of the parameters estimated during the bootstrap process and fall within the range of 2.5th-97.5th percentiles of the bootstrap replicates (Table 3). The median values of the models derived from the PRDI and the COMBINED datasets were close and the 95% confidence intervals largely overlapped for the pharmacokinetic parameters for both models. Visual predictive checks showed that the line of 50th percentiles of simulated tenofovir plasma concentrations using the two final models almost overlapped with that of the observed tenofovir concentrations (Figure 4). Despite under-estimation of the concentrations above the value of C\text{max} that were commonly observed in previously reported studies, approximately 90% of the observed plasma concentrations fell within the range of the 5th-95th percentiles of the simulated concentrations. The observed BQL fraction was higher than the simulation-based confidence intervals for the 15 hours after dosing.

**Discussion**

We developed a population pharmacokinetic model of tenofovir in a large PrEP trial incorporating both objective and subjective measures of dosing times. Population pharmacokinetics of tenofovir have been described in HIV-infected patients previously by several authors (6-16) but none of them used electronic monitoring for adherence. We have
previously reported population pharmacokinetic models for tenofovir in plasma (15) and
tenofovir in plasma and intracellular tenofovir diphosphate in healthy women (16) with different
methods of adherence correction utilizing superposition principles within the model framework.
The current study includes both men and women and provided an opportunity to test sex as a
covariate. No sex effect was observed on total body clearance (CL/F) for tenofovir in this
analysis. This is in agreement with a recent pharmacokinetic study of oral TDF in healthy
Chinese research participants where no significant differences in pharmacokinetic parameters
were found between men and women and pharmacokinetic profiles were comparable to Western
populations (27). The current US FDA label also states that tenofovir pharmacokinetics are
similar in male and female subjects. Creatinine clearance was a significant covariate of clearance
and is biologically meaningful as tenofovir is a renally cleared drug. Population
pharmacokinetic parameters are in general agreement with previous reports (6-16).

In the current work, no significant improvement was found in the model using electronic
adherence measurements as dosing records compared to using patient reported dosing
information alone. However, a clear advantage of electronic adherence measures in population
pharmacokinetic model development was shown by Savic, et al., where within-individual
variability (inter-occasion variability) of atazanavir was almost completely explained when
dosing was defined by electronic adherence measures (28) compared with patient-recollected
dosing information in the ANRS 134 - COPHAR 3 trial. We believe that a few important
methodological and study design aspects could have led to such different conclusions drawn
from the present work versus the previous work. First, the plasma sampling schedule was rich
and informative to capture the full temporal pharmacokinetic profile of atazanavir from 35
subjects in the ANRS 134-COPHAR 3 trial. A total of nine plasma concentrations per subject
were collected over 6 months, which include pre-dose, 1, 2, 3, 4, and 8 hours post-clinic-observed dose at Week 4, and trough concentrations at Week 8, 16, and 24. In contrast, only one plasma sample per clinic visit was collected in the Partners PrEP Study. More PK sample collections in this large randomized controlled clinical trial were deemed logistically unfeasible. Second, the contribution of pharmacokinetic data with respect to clinic visits was evenly distributed across various clinic visits in the present study whereas approximately 66% of the total data was captured in one clinic visit (at Week 4) in the ANRS 134- COPHAR 3 trial. Third, the Partner’s PrEP Study had high adherence rates (>90%, by pill counts), thus, the additional information provided by MEMS beyond self-reported dosing might have been small. However, Savic *et al* reported almost 100% adherence in the ANRS 134 - COPHAR 3 trial indicating that, with sufficient sample times, the increased precision of MEMS data improves the explanatory value of the model. In the current analysis, only a subset (26%) of plasma concentrations were associated with MEMS records. Thus, a direct comparison of MEMS only versus PRDI could not be tested. We did not utilize the “gold standard” approach described by Savic, *et al* where concentrations were selected and/or excluded based on ‘reliable dosing history’ defined as concordance (within 3 hours) between electronic measurement of dose intake and self-reported dose intake. Such treatment resulted in only <5% of the data to be excluded in their case. In contrast, approximately 20% of the data met that exclusion criterion in our EMS dataset. We believe that exclusion of data with external criteria could potentially exclude important information in the data and proceeded with a philosophy of data driven exploration. We did not model inter-occasion variability in pharmacokinetic parameters because of inherent unidentifiability by study design (i.e., only a single concentration was measured at every quarterly visit). The absorption rate constant was fixed by local search due to numerical instabilities posed
during modeling of the COMBINED dataset. The random effect parameter estimates were comparable between the models using electronic and patient recollected adherence information. However, between subject variability on central volume and absorption rate constant provided better model fits in terms of NONMEM objective function values and diagnostic plots in case of the COMBINED dataset. This finding could be due to the potential loss of information due to resetting of pharmacokinetics when the steady-state option (SS=1) in NONMEM is executed with the PDRI dataset. An inter-individual variability parameter on additive residual error component was retained in both scenarios of analysis, indicating that a similar degree of dosing errors may be present in both cases. Some of the shortcomings of electronic adherence monitoring include, participants taking out multiple doses with one opening or opening the device without removing pills or taking at another time than cap opening time and device non-use due to stigma or unanticipated travel.

Several BQL values were observed in this study. More than 90% of all the BQL values were observed within 24 hours after the participant reported dose administration and approximately 27% occurred within 12 hours after the dose administration. The M3 method was applied for appropriate handling of these observations (20). The current model was not able to describe the BQL values that were occurring within 12 hours post dose (Figure 3, bottom panel). Several BQL values did not make pharmacokinetic sense when compared within an individual’s data by comparing to their dosing history. For instance, a participant had a plasma concentration as BQL at 3.5 hours after a dose recorded at a clinic visit but the same subject had plasma concentration as 233 and 242 ng/ml at 3.6 and 2.9 hours, respectively, in other visits. Another subject had BQL values between 2-14 hours after a dose administration in five out of six clinic visits, but had a plasma concentration of 178 ng/ml at 2.7 hours after dosing at the sixth clinic visit. A recent
clinical study (HPTN 066) with directly observed dosing of oral tenofovir showed that 24 hour post-dose plasma concentrations of tenofovir were well above the limit of quantitation with a median of ~ 52 ng/ml (29). Thus, many of the BQL values may represent several potential sources of errors such as in the dosing history either by PRDI or MEMS, sample mix up, analytical errors and administrative errors. A sensitivity analysis was conducted by fitting the final model to the dataset excluding BQLs. Population pharmacokinetic parameters were comparable to the dataset with BQL values except for a notable difference in the residual variability. With exclusion of the BQL values, proportional error (%CV) was reduced to 8-9% from 20-21% and additive error (standard deviation) was reduced to ~10 ng/ml from 28-30 ng/ml.

In conclusion, our analysis described population pharmacokinetics of tenofovir in a healthy human population using both objective and subjective measures of dosing information. Parameter estimates were comparable between both methods of dose description. Creatinine clearance was a significant covariate of tenofovir clearance. We did not identify a clear advantage of EMS data in our model building. However, the adherence level was very high in the Partners PrEP Study and plasma concentration sampling was very sparse, thus, leaving little room for improvement that more dose timing accuracy could add to our model results. In several previous reports with more informative pharmacokinetic sampling, the advantage of adding EMS was significant in population pharmacokinetic analysis even with smaller sample size.

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References


Figure 1. The model structures of tenofovir population pharmacokinetics. (A) Model from analysis using patient reported dosing data (PRDI dataset). (B) Model from analysis using combined data set in which patient reported dosing data were replaced with MEMS data when available (COMBINED dataset).

Figure 2. Basic goodness-of-fit plots for PRDI Model

Figure 3. Basic goodness-of-fit plots for COMBINED Model

Figure 4. Visual predictive check for PDRI model (left panel) and COMBINED model (right panel). Solid red and black lines represent median of observed and simulated concentrations, respectively. Broken red and black lines represent upper and lower 90% observed and prediction intervals, respectively. Bottom LLOQ panel represents the proportion of BQLs observed (solid blue line) with 95% prediction variability in blue shaded area.
Table 1. Summary of datasets and participant demographics

<table>
<thead>
<tr>
<th>Covariate</th>
<th>PRDI Dataset</th>
<th>COMBINED Dataset</th>
<th>EMS only Dataset</th>
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<tbody>
<tr>
<td>Participants</td>
<td>404</td>
<td>404</td>
<td>211</td>
</tr>
<tr>
<td>TFV Concentrations</td>
<td>1280</td>
<td>1278</td>
<td>327</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35 ± 8</td>
<td>35 ± 8</td>
<td>36 ± 7</td>
</tr>
<tr>
<td>(Mean± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kgs)</td>
<td>61 ± 11</td>
<td>61 ± 11</td>
<td>60 ± 10</td>
</tr>
<tr>
<td>(Mean± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRCL (ml/min)</td>
<td>106 ± 31</td>
<td>106 ± 31</td>
<td>100 ± 33</td>
</tr>
<tr>
<td>(Mean± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (% Male)</td>
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<td>55</td>
<td>50</td>
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Table 2. Population pharmacokinetic parameters of tenofovir using different dosing reporting methods in the analysis.

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<thead>
<tr>
<th>Parameters</th>
<th>PRDI Combined Data</th>
<th>Base Model</th>
<th>Final Model</th>
<th>Base Model</th>
<th>Final Model</th>
<th>Combined Data</th>
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<td></td>
<td>Mean*</td>
<td>Mean (RSE)</td>
<td>Bootstrap Median (95% CI)</td>
<td>Mean (S.E)</td>
<td>Mean (RSE)</td>
<td>Bootstrap Median (95% CI)</td>
</tr>
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<td>NONMEM OFV</td>
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<td>9912.708</td>
<td>9914.648 (9263.063-10607.98)</td>
<td>9915.521</td>
<td>9852.249</td>
<td>9843.429 (9177.683-10457.48)</td>
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<td>θCL (L/h)</td>
<td>55</td>
<td>57 (2)</td>
<td>58 (52 - 61)</td>
<td>58 (2)</td>
<td>61.5 (2)</td>
<td>62 (57 – 65)</td>
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<tr>
<td>θVc (L)</td>
<td>478</td>
<td>393 (14)</td>
<td>393 (109 - 653)</td>
<td>518 (14)</td>
<td>345 (10)</td>
<td>345 (211 – 692)</td>
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<tr>
<td>θV (L/h)</td>
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<td>4.7 (77)</td>
<td>4.7 (1.46–128.15)</td>
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<td>1.5 FIXED</td>
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<td>θKa (L/h)</td>
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<td>178 (19)</td>
<td>178 (90–227)</td>
<td>187 (17)</td>
<td>231 (9)</td>
<td>231 (125–335)</td>
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<td>θVp (L)</td>
<td>667</td>
<td>614 (10)</td>
<td>614 (523–869)</td>
<td>735 (18)</td>
<td>830 (10)</td>
<td>830 (612–1101)</td>
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<td>θALAG1 (hr)</td>
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<td>0.41 (18)</td>
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<td>16 (9)</td>
<td>16 (14 – 17)</td>
<td>19 (3)</td>
<td>16 (14)</td>
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<td>IIV on Vc</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>43 (51)</td>
<td>25 (119)</td>
<td>25 (22 – 62)</td>
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<tr>
<td>IIV on Ka</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>69 (71)</td>
<td>61 (29)</td>
<td>61 (44 – 82)</td>
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**RESIDUAL VARIABILITY**

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<tr>
<th></th>
<th>ADDITIVE (ng/ml)</th>
<th>30</th>
<th>28 (9)</th>
<th>28 (22.03 – 39.57)</th>
<th>41 (7.29)</th>
<th>30.2 (8.48)</th>
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<td>132</td>
<td>143 (12)</td>
<td>143 (109 – 164)</td>
<td>93 (14)</td>
<td>136 (11)</td>
<td>136 (103 – 155)</td>
<td></td>
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</table>

* Covariance step for base model with PDRI dataset was not successful and thus RSE was not estimated

b CL = θCL*(CRCL/120)

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