A Semimechanistic Pharmacokinetic-Enzyme Turnover Model for Rifampin Autoinduction in Adult Tuberculosis Patients

Wynand Smythe,a Akash Khandelwal,b Corinne Merle,c Roxana Rustomjee,d Martin Gninafon,e Mame Bocar Lo,f Oumou Bah Sow,g Piero L. Olliaro,h Christian Lienhardt,i John Horton,j Peter Smith,a Helen McIlerson,a and Ulrika S. H. Simonssonb

Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africaa; Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Swedenb; Department of Epidemiology and Population Health, Tropical Epidemiological Group, London School of Hygiene and Tropical Medicine, London, United Kingdom; Unit for Clinical and Biomedical TB Research, Medical Research Council, Durban, South Africac; Programme National de Lutte contre la Tuberculose, BP 817, Cotonou, Bénin; Programme National de Lutte contre la Tuberculose, BP 5899, Dakar-Fann, Sénégd; Service Pneumo-phtisiologie, CHU Ignace Deen, BP 634, Conakry, Guineae; UNICEF/UNDP/World Bank/WHO Special Programme on Research and Training in Tropical Diseases (TDR), World Health Organization, Geneva, Switzerlandh; Institut de Recherche pour le Développement, Paris, Franciej; and Tropical Projects, Hitchin, United Kingdomj

The currently recommended doses of rifampin are believed to be at the lower end of the dose-response curve. Rifampin induces its own metabolism, although the effect of dose on the extent of autoinduction is not known. This study aimed to investigate rifampin autoinduction using a semimechanistic pharmacokinetic-enzyme turnover model. Four different structural basic models were explored to assess whether different scaling methods affected the final covariate selection procedure. Covariates were selected by using a linearized approach. The final model included the allometric scaling of oral clearance and apparent volume of distribution. Although HIV infection was associated with a 30% increase in the apparent volume of distribution, simulations demonstrated that the effect of HIV on rifampin exposure was slight. Model-based simulations showed close-to-maximum induction achieved after 450-mg daily dosing, since negligible increases in oral clearance were observed following the 600-mg/day regimen. Thus, dosing above 600 mg/day is unlikely to result in higher magnitudes of autoinduction. In a typical 55-kg male without HIV infection, the oral clearance, which was 7.76 liters · h−1 at the first dose, increased 1.82- and 1.85-fold at steady state after daily dosing with 450 and 600 mg, respectively. Corresponding reductions of 41 and 42%, respectively, in the area under the concentration-versus-time curve from 0 to 24 h were estimated. The turnover of the inducible process was estimated to have a half-life of approximately 8 days in a typical patient. Assuming 5 half-lives to steady state, this corresponds to a duration of approximately 40 days to reach the induced state for rifampin autoinduction.

Rifampin is an indispensable constituent of first-line therapy used to treat drug-susceptible Mycobacterium tuberculosis. During the 2-month intensive phase of standard short-course antituberculosis treatment, patients receive rifampin together with isoniazid, pyrazinamide, and ethambutol. Rifampin and isoniazid are given for a further 4-month continuation phase, completing the 6-month treatment regimen. Isoniazid is responsible for killing the majority of organisms within the first 2 days of treatment. From the third to the seventh day of treatment, rifampin and pyrazinamide continue the bactericidal function (30), while ethambutol protects against the development of rifampin resistance in the event of preexisting isoniazid resistance (8). The ability of rifampin to eradicate persisting organisms has allowed the shortening of treatment from 12 to 6 months (43).

Rifampin is a potent activator of the nuclear pregnane X receptor (PXR), which regulates the transcription of multiple drug-metabolizing enzymes and drug transporters (9, 13). Although the exact mechanism is not known, following chronic intravenous or oral dosing, rifampin induces its own metabolism by increasing its systemic and presystemic clearances (27, 31). This effect might, in part, be attributed to the PXR-mediated induction of P-glycoprotein (P-gp), a trans-membrane efflux transporter expressed in enterocytes and hepatocytes (12, 27), and the class B esterases (38), responsible for the biotransformation of rifampin to its major metabolite, 25-deacetyl rifampin (20).

The steady-state population pharmacokinetics of rifampin have been described for adult African patients (42). The aim of the present work was to develop a semimechanistic pharmacokinetic-enzyme turnover model describing rifampin pharmacokinetics after a single dose and multiple doses in adult patients with tuberculosis (TB). In addition, four different structural basic models were explored in order to assess whether different scaling methods or no scaling affects the final covariate selection procedure.

MATERIALS AND METHODS

Patients. Patients with newly diagnosed pulmonary tuberculosis enrolled in the control arm of the OFLOTUB phase III, parallel-group, multicenter trial (clinical trial identifier NCT00216385) at study clinics in South Africa, Senegal, Guinea, and Benin were invited to participate in a nested pharmacokinetic study. Written informed consent was obtained prior to the study being conducted. A total of 174 patients, 114 males and 60 nonpregnant females, were included in this analysis. Patients were aged 18 to 65 years, weighed between 38 and 80 kg, and were antiretroviral naive. During the 2-month intensive phase of treatment, patients below 50 kg of body weight received 450 mg rifampin together with 225 mg isoniazid, 1,200 mg pyrazinamide, and 825 mg ethambutol, 6 days a week. Patients with a body weight equal to or greater than 50 kg received 600 mg rifampin together with 300 mg isoniazid, 1,600 mg pyrazinamide, and 1,100 mg of each of the other drugs.
ethambutol for 6 days a week. All doses were given orally as fixed-dose combination tablets (provided by Lupin Pharmaceuticals Pvt. Ltd., Mumbai, India) and supervised by directly observed therapy (DOT), performed either by health center staff or by designated representatives, for the duration of the study.

**Blood sampling.** Three venous blood samples per patient were taken after the first dose (preinduced state) and repeated after approximately 28 days (induced state) for the determination of rifampin pharmacokinetics. Samples were drawn 1 to 2 h and 2.5 to 3.5 h postdose from each patient on both occasions. In addition, patients were block randomized to a time for a third sample. After the first dose, the third sample was taken at 4 to 6 h postdose from half the patients, and the remaining patients had a sample taken at 8 to 10 h postdose. At the induced state (after approximately 28 days of treatment), the third sample was taken either predose, at 4 to 6 h postdose, or at 8 to 10 h postdose.

**Drug quantification.** Each 4-ml blood sample, collected into heparinized vacuum plastic tubes, was immediately centrifuged (within 30 min) at 750 × g for 10 min to separate the plasma by using a bench-top centrifuge, and the samples were kept on crushed ice. All plasma specimens were stored in aliquots at −80°C until drug quantification. Plasma concentrations of rifampin were quantified by using high-performance liquid chromatography (HPLC) coupled to tandem mass spectrometry (29).

**Population pharmacokinetic analysis. (i) Software.** Data analysis was performed with a nonlinear mixed-effects approach, as implemented in NONMEM software, version 7.1.2 (Icon Development Solutions) (5), using ADVAN 13 and the first-order conditional estimation method with interaction (FOCE INTER). R (version 2.12.1) was used for graphical analysis and data management (34). Xpose (version 4.0) was used for data exploration and visualization as well as model diagnostics and model comparison (21). PnN 3.3.2 (25, 26) was used for visual predictive checks (VPCs) (18, 19) and prediction-corrected VPCs (pcVPCs) (7) of the models.

(ii) Structural model. A total of 946 rifampin concentration-time observations from 174 patients were included in the analysis. All predose observations (54 out of 1,004) following an unobserved dose at the induced state and all observations falling below the lower level of quantification (LLOQ) (4 of 950 samples; LLOQ = 0.1 mg · liter−1) were excluded. One- and two-compartment distribution models were fit to the data. An enzyme turnover model, as described previously by Hassan et al. (16), was adapted to characterize rifampin’s autoinduction modeled with an enzyme turnover model, where rifampin plasma concentrations (Cp) increase the enzyme production rate (kENZ), which in turn increases the enzyme pool (ENZ) in a nonlinear fashion by means of an Fmax model. ENZ in turn increases rifampin’s clearance (CL).

**FIG 1** Rifampin pharmacokinetic-enzyme model including a one-compartmental disposition model and a transit absorption compartment model. The drug is transferred from the absorption compartment into the central compartment via the rate constant ktr. Rifampin autoinduction was modeled with an enzyme turnover model, where rifampin plasma concentrations (Cp) increase the enzyme production rate (kENZ), which in turn increases the enzyme pool (ENZ) in a nonlinear fashion by means of an Fmax model. ENZ in turn increases rifampin’s clearance (CL).

\[
\frac{dA_{ENZ}}{dt} = k_{ENZ} \cdot (1 + EFF) - (k_{ENZ} \cdot A_{ENZ})
\]

AENZ is the amount of enzyme in the enzyme pool. kENZ is the rate constant for the first-order degradation of the enzyme pool. To normalize the enzyme concentrations to unity at baseline, the zero-order production rate of the enzyme was set to kENZ. EFF is the relationship between the rifampin concentration and the induction of the enzyme through an increased enzyme production rate. Linear and nonlinear relationships for EFF were tested. Induction was modeled as an increase in the enzyme production rate and not as a decrease in the enzyme elimination rate, assuming that rifampin activates nuclear PXR (9). Rifampin plasma concentrations drive the enzyme pool, which in turn affects the oral clearance (CL/F) of the drug:

\[
TV\left(\frac{CL}{F}\right) = \left(\frac{CL}{F}\right)_{BASE} \cdot A_{ENZ}
\]

(2)

(CL/F)BASE is the scaled (or nonscaled for model 1) typical CL/F in the preinduced state and TV(CL/F) is the typical value for oral clearance. In the preinduced state, the amount in the enzyme pool was set to 1. A transit absorption compartment model described previously by Savic et al. (37) and applied as described previously by Wilkins et al. (42) for multiple dosing was used to capture the drug’s highly variable absorption characteristics. The absorption model uses hypothetical transit compartments to mimic a delay in the onset of absorption and produces a gradual increase in the absorption rate in a physiologically plausible manner. Drug transfer from the final transit compartment (in this case, the absorption compartment) to the central compartment occurs via the rate constant ktr:

\[
k_{tr} = \frac{N + 1}{MTT}
\]

(3)

where MTT is the mean transit time and N is the number of transit compartments.

(iii) Stochastic model. Interindividual variability (IIV) was modeled exponentially as in the case for oral clearance (CL/F) (equation 4):

\[
\left(\frac{CL}{F}\right) = TV\left(\frac{CL}{F}\right) \cdot \exp\left(\eta_{CL/F}\right)
\]

(4)

(CL/Fi) is the CL/F value for the ith patient. \(\eta_{CL/F}\) is the IIV, which is assumed to be normally distributed around zero and with a variance of \(\omega^2_{CL/F}\), to distinguish the ith patient’s CL/F from the population-predicted TV(CL/F). Furthermore, the interoccasion variability (IOV) in the pharmacokinetic parameters was explored and modeled as in the case for CL/F (22):

\[
\left(\frac{CL}{F}\right)_j = TV\left(\frac{CL}{F}\right) \cdot \exp\left(\eta_i + \kappa_j\right)_{CL/F}
\]

(5)

(CL/Fij) is the oral clearance for individual i on occasion j. \(\eta_{CL/F}\) is the IIV, normally distributed with a mean of 0 and a variance of \(\omega^2_{CL/F}\). \(\kappa_{CL/F}\)
is the IOV, normally distributed with a mean of 0 and a variance of $\omega^{\text{iov}}_{\text{CL/F}}$. Correlations between variability components were also tested. Different residual error models were investigated, including proportional and slope-interactive models.

(iv) Model evaluation. Model selection was done by use of the objective function value (OFV), which is minus twice the log likelihood of the data; the standard error of parameter estimates; scientific plausibility; and goodness-of-fit plots together with the VPC and, when indicated, the pcVPC.

(v) Covariate analysis. Once the structural model was evaluated, a covariate analysis was performed by using 4 different basic pharmacokinetic–enzyme turnover models: no scaling (model 1), allometric scaling using body weight as the size descriptor applied to CL/F and apparent volume of the central compartment ($V/F$) (3, 17, 40, 41) (model 2), allometric scaling using normal fat mass (NFM) as the size descriptor applied to CL/F and $V/F$ and with ($Ffat_{CL/F}$) (estimated contribution of fat-free mass) and body weight to CL/F or ($Ffat_{V/F}$) (estimated contribution of fat-free mass and body weight to $V/F$) being estimated (4) (model 3), and allometric scaling using FFM as the size descriptor applied to CL/F and $V/F$ (3, 4) (model 4). CL/F and $V/F$ were scaled allometrically standardized to a 70-kg patient using equations 6 and 7, respectively:

$$\begin{align*}
TV\left(\frac{CL}{F}\right)_{\text{BASE}} &= TV\left(\frac{CL}{F}\right)_{\text{STD}} \left(\frac{\text{MASS}}{70}\right)^{\frac{1}{2}} & (6) \\
TV\left(\frac{V}{F}\right)_{\text{BASE}} &= TV\left(\frac{V}{F}\right)_{\text{STD}} \left(\frac{\text{MASS}}{70}\right)^{\frac{1}{2}} & (7)
\end{align*}$$

MASS denotes individual values of the 3 size descriptors body weight (model 2), NFM (model 3), and FFM (model 4) used in the respective basic models. ($CL/F_{\text{STD}}$) is the typical oral clearance at the preinduced state in a patient weighing 70 kg. ($V/F_{\text{STD}}$) is the typical volume of distribution in a patient weighing 70 kg.

The Cockcroft-Gault formula (10) was applied to estimate creatinine clearance ($CL/CR$) from serum creatinine values recorded in units of $\mu$mol · liter$^{-1}$. Constants of 1.23 for men and 1.04 for women were applied.

Individual FFM values ($FFM_i$) were calculated as follows:

$$FFM_i = \frac{\text{WHSmax} \cdot HT^2 \cdot WT}{\text{WHS50} \cdot HT^2 + WT}$$

where $\text{WHSmax}$ and $\text{WHS50}$ denote the estimated maximum contributions of fat mass (i.e., body weight minus FFM) to the CL/F and $V/F$, respectively.

Various parameter-covariate relationships were tested on each of the four different basic models. Sex, age, and HIV status were tested on CL/F, $V/F$, MTT, and 50% effective concentration (EC50), whereas $CL/CB$ was explored only on CL/F (models 2 to 4). The covariate effect of study site, tested as South Africa versus West Africa, was explored on CL/F, $V/F$, and F. Body weight was investigated as a covariate on CL/F and $V/F$ but only in model 1. A fast method to build covariate models in population pharmacokinetic-pharmacodynamic analyses based on the linearization of the first-order conditional estimation (FOCE) (23) was used as an initial step to screen for significant parameter-covariate relationships. The linearization method has many advantages compared to methods based on empirical Bayes estimates (EBEs) or generalized additive models (GAMs), as it does not depend on the accuracy of the EBEs. Briefly, the linearization method consisted of three steps. First, the individual predictions (IPREDs) and first partial derivatives of the IPREDs with respect to etas were extracted from each of the four nonlinear basic pharmacokinetic–enzyme models. Thereafter, each of the four basic models was linearized and further developed by using derivatives and prediction from each respective nonlinear basic model. Finally, covariates were tested using each of the four linearized basic models.

The covariate analysis using the linearized basic models was performed via forward addition and backward elimination using stepwise covariate model (SCM) building as implemented in PaN (15). In the SCM, initially, each covariate relationship was tested in a univariate fashion within NONMEM. The covariate model that resulted in the lowest significant drop in the OFV was carried forward. In the forward step, statistical significance was defined as a decrease in the OFV by more than 3.84 (chi-square distribution; $P < 0.05$; 1 degree of freedom). This step was repeated for the remaining parameter-covariate relationships until no more covariate could be included. Thereafter, a backward deletion was performed to determine the best covariate model for each of the four basic models. In the backward deletion step, each parameter-covariate relationship was then left out one at a time and tested using a statistical significance criterion of 1% (an increase in the OFV of at least 6.635 for 1 degree of freedom). This step was repeated until no more covariates could be excluded.

The continuous covariates were included as linear functions:

$$\begin{align*}
\text{TVP} &= \left(\frac{\theta_1 + \theta_{\text{COV}} \cdot (\text{COV} - \text{COV}_{\text{median}})}{1 + \theta_{\text{COV}} \cdot (\text{COV} - \text{COV}_{\text{median}})}\right) & (11) \\
\text{TVP} &= \left(\frac{\theta_1 + \theta_{\text{COV}} \cdot (\text{COV})}{1 + \theta_{\text{COV}} \cdot (\text{COV})}\right) & (12)
\end{align*}$$

where $\theta_1$ is the typical value of the parameter (TVP) and $\theta_{\text{COV}}$ is the fractional change in the TVP for the COV.

The best covariate model for each of the four basic models identified from the linearization method was subsequently run in nonlinear mixed-effect models using NONMEM in order to generate parameter estimates, standard errors, and VPCs.

(vi) Simulations. Simulations exploring a dose effect (450 and 600 mg) on the magnitude of rifampin autoinduction were performed for typical male patients with and those without HIV infection weighing 55 kg ($\text{FFM}_{\text{median}}$) was predicted for the preinduced and induced states. In addition, CL/F was simulated over time from the preinduced state [$\text{(CL/F)\text{BASE}}$] to the induced state [$\text{(CL/F)\text{AS}}$].

RESULTS

Demographics and covariates of patients included in the rifampin pharmacokinetic–enzyme turnover model are described in Table 1. The final rifampin pharmacokinetic–enzyme model is shown in Fig. 1.

The final model included a nonlinear relationship between the
rifampin concentration and induction of the enzyme through an increased enzyme production rate, such as

$$\text{EFF} = k_{\text{ENZ}} \left(1 + \frac{E_{\text{max}} \cdot C_p}{EC_{50} + C_p}\right)$$

(13)

where $EC_{50}$ is the rifampin concentration that causes half the maximum induction ($E_{\text{max}}$). The parameters of the induction process, $K_{\text{ENZ}}$ and $EC_{50}$, were both well estimated, with relative standard errors of 6% (Table 2). The application of linearization approximation for covariate screening made it possible to explore the effect of covariate screening for different basic models with different approaches with and without allometric scaling. A brief description of the four different basic models and their respective best covariate models is shown in Table 2. The underlying structural model with or without allometric scaling did not influence the final covariates. The best covariate model for model 1 (no scaling) included body weight and sex on CL/F and V/F and HIV on V/F. For model 2 (scaling with body weight), HIV and sex on V/F were selected. For model 3 (scaling with NFM) and model 4 (scaling with FFM), HIV on V/F described the best covariate relationship. The best covariate models for all four basic models were very similar, as all models contained influences of body weight, sex, and HIV infection either as part of the allometric scaling or estimated as a covariate relationship. Among the four investigated basic models, models 1, 2, and 4 contained fewer parameters than model 3. The highest $\Delta$OFV ($\text{OFV}_{\text{best}} - \text{OFV}_{\text{basic}}$) was found for model 1 ($\Delta$OFV = −46.72), followed by model 4 ($\Delta$OFV = −26.03). Both models 1 and 4 could be described as the data, but model 4 was considered to be better, since it contained fewer parameters. Models 4 and 1 cannot be compared based on a likelihood ratio test, since these models are not nested. Model 4 was also not selected as the final model, since the estimate of $k_{\text{ENZ}}$ was not regarded as being plausible. The $\Delta$OFV for model 2 between the basic model and the best covariate model was −21.09 and was higher than that for model 2. Hence, the best covariate model, model 3, was chosen as the final model based on the precision of parameter estimates, scientific plausibility, and $\Delta$OFV. Model 3 included allometric scaling using NFM, i.e., both body weight and FFM. The parameter estimates from the final pharmacokinetic-enzyme turnover model are shown in Table 3, with HIV infection being associated with a 29.6% increase in the typical value of V/F.

The final pharmacokinetic-enzyme turnover model described the rifampin concentration–time data at both the preinduced and induced states, as judged by the pcVPC (Fig. 2). The rate constant for the first-order degradation of the enzyme pool ($k_{\text{ENZ}}$) was estimated to be 0.00369 h⁻¹. As such, the turnover of the inducible process was estimated with a corresponding half-life of approximately 8 days for a typical patient. Assuming 5 half-lives to steady state, this is the equivalent of approximately 40 days to the induced state for rifampin autoinduction. Hence, full induction occurred before the end of the 2-month intensive phase of antituberculosis treatment.

Simulated CL/F and AUC₀−2₄ values for typical 55-kg male patients with and without HIV infection following daily doses of 450 and 600 mg are shown in Table 4. The simulated CL/F from the

### TABLE 2 Comparison of the four different basic models and their subsequent best covariate models

<table>
<thead>
<tr>
<th>Model</th>
<th>Basic model (no. of fixed-effect parameters)</th>
<th>Best covariate model (no. of fixed-effect parameters)</th>
<th>OFV</th>
<th>Basic model</th>
<th>Best covariate model</th>
<th>$\Delta$OFV</th>
<th>% IIV decrease(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No scaling (10)</td>
<td>WT and sex-CL/F, WT and sex-V/F, HIV-CL/F (15)</td>
<td>2,169.17</td>
<td>2,122.45</td>
<td>−46.72</td>
<td>2.65</td>
<td>48.03</td>
</tr>
<tr>
<td>2</td>
<td>Allometric scaling with WT (10)</td>
<td>HIV-V/F, sex-V/F (12)</td>
<td>2,154.90</td>
<td>2,133.56</td>
<td>−21.34</td>
<td>16.30</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Allometric scaling with NFM (12)</td>
<td>HIV-V/F (13)</td>
<td>2,145.89</td>
<td>2,128.40</td>
<td>−21.09</td>
<td>2.90</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Allometric scaling with FFM (10)</td>
<td>HIV-V/F (11)</td>
<td>2,157.44</td>
<td>2,131.41</td>
<td>−26.03</td>
<td>5.86</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ % IIV_decrease = $\frac{\sigma_{\text{final}}^2 - \sigma_{\text{base}}^2}{\sigma_{\text{base}}^2} \times 100.$

$^b$ % IIV_decrease = $\frac{\sigma_{\text{final}}^2 - \sigma_{\text{base}}^2}{\sigma_{\text{base}}^2} \times 100.$

$^c$ Allometric scaling was done on oral clearance (CL/F) and the apparent volume of the central compartment (V/F) using body weight (WT), fat-free mass (FFM), or normal fat mass (NFM).

$^d$ $\Delta$OFV is the difference in the objective function value (OFV) between the basic model and the best covariate model ($\text{OFV}_{\text{base}} - \text{OFV}_{\text{best}}$).
TABLE 3 Parameter estimates based on the final rifampin pharmacokinetic-enzyme turnover model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimated value</th>
<th>% RSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TV(CL/F)STD (liters · h⁻¹)</td>
<td>10.0</td>
<td>3.7</td>
</tr>
<tr>
<td>TV(V/F)STD (liters)</td>
<td>86.7</td>
<td>2.3</td>
</tr>
<tr>
<td>MTI (h)</td>
<td>0.713</td>
<td>1.6</td>
</tr>
<tr>
<td>No. of transit compartments</td>
<td>1 FIX</td>
<td>1 FIX</td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>0.00369</td>
<td>5.6</td>
</tr>
<tr>
<td>$EC_{\text{50}}$ (mg · liter⁻¹)</td>
<td>0.0705</td>
<td>6.3</td>
</tr>
<tr>
<td>$k_{\text{ENZ}}$ (h⁻¹)</td>
<td>1.04</td>
<td>2.6</td>
</tr>
<tr>
<td>CL-V correlation (%)</td>
<td>91.6</td>
<td>20.7</td>
</tr>
<tr>
<td>(Ffat)CL/F</td>
<td>0.311</td>
<td>40.2</td>
</tr>
<tr>
<td>(Ffat)TV/F</td>
<td>0.188</td>
<td>49.1</td>
</tr>
<tr>
<td>IIVCL/F (%)</td>
<td>30.0</td>
<td>12.3</td>
</tr>
<tr>
<td>IIVTV/F (%)</td>
<td>19.2</td>
<td>14.8</td>
</tr>
<tr>
<td>IIVEC50 (%)</td>
<td>493.0</td>
<td>19</td>
</tr>
<tr>
<td>IOV,MTT (%)</td>
<td>68.0</td>
<td>7</td>
</tr>
<tr>
<td>IOV,F (%)</td>
<td>16.2</td>
<td>11.2</td>
</tr>
<tr>
<td>V/F-HIV (%)</td>
<td>29.6</td>
<td>17.2</td>
</tr>
<tr>
<td>Additive error (mg · liter⁻¹)</td>
<td>0.965</td>
<td>2.8</td>
</tr>
<tr>
<td>Proportional error (%)</td>
<td>9.9</td>
<td>4.7</td>
</tr>
</tbody>
</table>

$^a$ IIV, interindividual variability expressed as a coefficient of variation; IOV, interoccasion variability expressed as a coefficient of variation; RSE, relative standard error reported on the approximate standard deviation scale; TV(CL/F)STD, the typical oral clearance at the preinduced state in a patient weighing 70 kg; TV(V/F)STD, the typical apparent volume of distribution in a patient weighing 70 kg; MTI, mean transit time; $E_{\text{max}}$, maximal increase in the enzyme production rate; $EC_{\text{50}}$, estimated contribution of fat-free mass and body weight to TV/F; (Ffat)CL/F, estimated contribution of fat-free mass and body weight to TV/F; (Ffat)TV/F, estimated contribution of fat-free mass and body weight to V/F; V/F-HIV, increase in apparent volume of distribution in HIV-infected patients; 1 FIX, number of transit compartments fixed to 1.

first dose to the steady state of autoinduction in a typical patient is illustrated in Fig. 3. Model-based simulations of oral clearance in a typical patient without HIV infection increased from 7.76 liters · h⁻¹ at the preinduced state to similar induced-state clearance values of 14.16 and 14.37 liters · h⁻¹ following 450- and 600-mg doses, respectively. Hence, autoinduction resulted in 1.82- and 1.85-fold increases in the CL/F from the preinduced to the induced state, corresponding to 41 and 42% reductions in the AUC₀⁻二十四 following multiple 450- and 600-mg doses, respectively.

Table 4 shows the simulated AUC₀⁻二十四 and C_max values for patients with or without HIV infection receiving 450- or 600-mg daily doses of rifampin according to body weight. Patients weighing less than 50 kg and receiving the 450-mg dose had a median AUC₀⁻二十四 that was approximately 10% lower than that of patients weighing 50 kg or more who received the 600-mg dose. These differences in AUC₀⁻二十四 Values can be accounted for by differences in body weight. Figure 4 illustrates the simulated C_max for different subgroups using the final pharmacokinetic-enzyme turnover model. The median C_max was lower for HIV-infected patients than for patients without HIV, irrespective of the dose and duration of dosing. Strikingly, fewer than one-third of all patients, irrespective

FIG 2 Prediction-corrected visual predictive check (pcVPC) of the final rifampin pharmacokinetic-enzyme turnover model stratified by occasion (occasion 1, preinduced state [a]; occasion 2, after at least 28 days of rifampin administration [b]). The solid and dashed lines are the medians and 5th and 95th percentiles of the observed rifampin plasma concentrations, respectively. Shaded areas are the 90% prediction intervals for the medians and 5th and 95th percentiles of simulated data. The open circles are observed patient concentration-time data.

TABLE 4 Predicted CL/F and AUC₀⁻二十四 values for typical 55-kg male patients with and without HIV infection at the preinduced and induced states following daily rifampin doses of 450 and 600 mg

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value for treatment and patient group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>450 mg, 450 mg, 600 mg, 600 mg</td>
</tr>
<tr>
<td></td>
<td>TB, TB + HIV, TB, TB + HIV</td>
</tr>
<tr>
<td>(CL/F)BASE (liters · h⁻¹)</td>
<td>7.76, 7.76, 7.76, 7.76</td>
</tr>
<tr>
<td>(CL/F)IND (liters · h⁻¹)</td>
<td>14.16, 14.62, 14.37, 14.82</td>
</tr>
<tr>
<td>Fold increase in CL/F</td>
<td>1.82, 1.88, 1.85, 1.91</td>
</tr>
<tr>
<td>AUC₀⁻二十四, BASE (mg · h · liter⁻¹)</td>
<td>53.86, 51.01, 71.80, 68.01</td>
</tr>
<tr>
<td>AUC₀⁻二十四, IND (mg · h · liter⁻¹)</td>
<td>31.70, 30.80, 41.80, 40.50</td>
</tr>
<tr>
<td>AUC₀⁻二十四 reduction (%)</td>
<td>41.14, 39.62, 41.78, 40.45</td>
</tr>
</tbody>
</table>

$^a$ BASE, after a single dose; IND, induced state; TB, patients infected with tuberculosis; TB + HIV, patients infected with tuberculosis and HIV; CL/F, oral clearance; fold increase in CL/F, (CL/F)IND/(CL/F)BASE; AUC₀⁻二十四 area under the concentration-time curve from 0 to 24 h; AUC₀⁻二十四 reduction, reduction in AUC₀⁻二十四 from the preinduced to the induced state.
of dose and HIV status, achieved a $C_{\text{max}}$ above the target of 8 mg·liter$^{-1}$ (32) at the induced state.

### DISCUSSION

Our model shows that rifampin autoinduction yields similar increases in rifampin oral clearance with doses of 450 and 600 mg daily. Corresponding decreases in $\text{AUC}_{0-24}$ values at the induced state of 41 and 42% were observed following multiple daily 450- and 600-mg doses, respectively. Although HIV infection was associated with a 30% increase in the apparent volume of distribution, simulations demonstrated that the effect of HIV on rifampin exposure was not of clinical significance, as similar induced-state $\text{AUC}_{0-24}$ values were observed between the two patient populations. The turnover half-life for the induction process was estimated to be approximately 8 days. This corresponds to an attainment of an induced state of induction in a typical patient after 40 days of treatment, assuming 5 half-lives to steady state.

There have been several reports of the autoinduction of rifampin pharmacokinetics (1, 2, 6, 33). Loos and colleagues previously demonstrated that rifampin systemic clearance was increased 1.6-fold (from 5.69 to 9.03 liters·h$^{-1}$) following 3 weeks of multiple oral or intravenous 600-mg daily doses (27, 28). That finding is similar to our estimates of 1.82- and 1.85-fold increases in the $\text{CL/F}$ following daily doses of 450 and 600 mg, respectively, in a typical patient. Loos et al. (28) observed that rifampin bioavailability decreased from 93% to 68% during 3 weeks of drug administration. This could not be attributed solely to an increase in the rate of hepatic clearance and suggests that an inducible presystemic pathway exists. As P-gp is expressed on the apical surface of enterocytes (24), these cells are able to eliminate rifampin into the luminal space, whereby the drug may be excreted along with feces in an inducible fashion. In our pharmacokinetic–enzyme turnover model, the induction process was expressed as a change in the $\text{CL/F}$ over time. The inclusion of a change in bioavailability by time or by dose (mg/kg of body weight) was not supported by the data. The $\text{CL/F}$ over time predicted by our model is therefore a description of both hepatic and presystemic processes, although their relative contributions are not known. Of 174 patients, 162 were sampled on two occasions: on the first day of treatment (occasion 1) and again approximately 1 month following treatment initiation (occasion 2). The median sampling day on occasion 2 was day 29, with a range spanning from 26 to 50 days. The study therefore included information prior to rifampin-mediated induction to beyond 5 induction half-lives (40 days). The study therefore contained adequate information about the induction

### TABLE 5

Median and 90% prediction interval values of simulated $\text{AUC}_{0-24}$, $C_{\text{max}}$, and normal fat mass in patients with ($n = 1,000$) or without ($n = 1,000$) HIV infection at the preinduced and induced states following daily rifampin doses of 450 mg (body weight of $<50$ kg) or 600 mg (body weight of $\geq 50$ kg)$^a$

<table>
<thead>
<tr>
<th>Parameter</th>
<th>450 mg, TB</th>
<th>450 mg, TB + HIV</th>
<th>600 mg, TB</th>
<th>600 mg, TB + HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFM (Kg)</td>
<td>43</td>
<td>37</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>$\text{AUC}_{0-24}$, BASE (mg·h·liter$^{-1}$)</td>
<td>65.84 (38.38–116.60)</td>
<td>63.46 (39.08–113.39)</td>
<td>71.24 (41.50–123.81)</td>
<td>72.39 (42.56–121.04)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-24}$, IND (mg·h·liter$^{-1}$)</td>
<td>42.00 (20.98–87.39)</td>
<td>43.30 (23.27–91.80)</td>
<td>47.40 (24.66–92.10)</td>
<td>48.40 (25.52–95.36)</td>
</tr>
<tr>
<td>$C_{\text{max}}$, BASE (mg·liter$^{-1}$)</td>
<td>7.45 (4.34–12.55)</td>
<td>6.24 (3.95–10.41)</td>
<td>7.89 (4.80–12.66)</td>
<td>6.89 (4.37–11.01)</td>
</tr>
<tr>
<td>$C_{\text{max}}$, IND (mg·liter$^{-1}$)</td>
<td>6.65 (3.77–11.24)</td>
<td>6.10 (3.33–10.54)</td>
<td>7.24 (4.12–21.21)</td>
<td>6.45 (3.64–10.61)</td>
</tr>
</tbody>
</table>

$^a$The 90% prediction interval was obtained from the 5th and 95th percentiles of simulated data. The original data set was replicated, generating 1,000 new individuals retaining the original covariate distribution. NFM, normal fat mass; BASE, after a single dose; IND, induced state; TB, patients infected with tuberculosis; TB + HIV, patients infected with tuberculosis and HIV; $\text{AUC}_{0-24}$, area under the concentration–time curve from 0 to 24 h; $C_{\text{max}}$, maximum plasma concentration.
process, which is reflected by the good precision of the parameters characterizing induction, i.e., the enzyme production rate \( k_{\text{ENG}} \) and \( EC_{50} \) (the rifampin concentration that causes half the maximum induction \( [E_{\text{max}}] \)), which both had relative standard errors of 6%.

No significant covariate relationship was found between \( CL/F \) and HIV infection. Therefore, the \( (CL/F)_{\text{IND}} \) for the two patient populations was predicted to be the same (Table 4). Despite the absence of an association between HIV infection and \( CL/F \), a clinically nonrelevant higher \( (CL/F)_{\text{IND}} \) was seen for HIV-infected patients. HIV infection was associated with a 29.6% increase in the \( V/F \) compared to that of patients without HIV infection, resulting in lower \( C_{\text{max}} \) values for HIV-infected patients. Sahai and colleagues (36) similarly found that HIV-infected patients had lower rifampin plasma concentrations than patients without HIV infection. The basis for an increased volume of distribution in HIV patients is not known, although it has been shown that HIV causes morphological and physiological changes that may alter the pharmacokinetics of drugs. In our study, the increased \( V/F \) values for HIV-infected patients led to smaller oscillations in the concentration-versus-time profile. In the pharmacokinetic-enzyme turnover model, this pharmacokinetic profile results in an increased enzyme production rate compared to that in patients without HIV infection, which is observed as a higher \( (CL/F)_{\text{IND}} \), seen for HIV-infected patients. HIV infection was, however, not shown to be of clinical significance; similar induced-state \( \text{AUC}_{0-24} \) values were simulated for typical patients with and without HIV infection (Table 4). In the simulations using the same covariate distribution as that observed in the study (Table 5), the induced-state \( \text{AUC}_{0-24} \) values for HIV-infected patients were slightly higher than those for patients without HIV infection, which was probably due to a relatively higher dose: HIV-infected patients had a median dose of 11.7 mg/kg (median body weight of 51 kg), while patients without HIV infection had a median dose of 10.7 mg/kg (median body weight of 56 kg).

The three different models used for allometric scaling with size were selected based on a previous report by Anderson and Hoflford (4), where three different scaling approaches were described. \( CL/F \) and \( V/F \) were scaled using various size descriptors (body weight in model 2, NFM in model 3, and FFM in model 4). Model 3 scaled using NFM was selected as the final model. This was based on the parameter estimates and the drop in the OFV. NFM (expressed for \( CL/F \) and \( V/F \)) includes estimated fractions of fat mass \((F_{\text{fat}})\) and hence their contributions to the predictions of \( CL/F [(F_{\text{fat}})_{\text{CL}/F}] \) and \( V/F [(F_{\text{fat}})_{\text{V}/F}] \). Fat mass contributes to overall body size and may have an indirect influence on both metabolic and renal clearances, although it has minimal metabolic activity. Moreover, a drug may have distribution properties that are more directly linked to fat mass.

Rifampin pharmacokinetics have been shown to be nonlinear apart from autoinduction (1, 11, 35). In this analysis, nonlinear pharmacokinetics apart from the autoinduction process were not supported by the data, most probably due to the limited dose range included. As the pharmacokinetic model did not include observations of doses higher than 600 mg, higher doses could not be reliably simulated. The currently recommended daily doses of rifampin (8 to 12 mg/kg) are believed to be at the lower end of the dose-response curve (33, 39). In light of several ongoing studies exploring the activity of increased doses of rifampin and other rifamycins, pharmacokinetic studies aimed at exploring the magnitude of autoinduction for higher doses are required. However, our simulations found that close-to-maximum induction was achieved after a dose of 450 mg daily; a negligible increase in the \( CL/F \) was observed following the 600-mg/day regimen. Therefore, should the assumptions of our model apply to higher doses, an increase of the dose beyond 600 mg would not result in autoinduction of a higher magnitude than that observed with daily doses of 450 to 600 mg.

The pharmacokinetic-pharmacodynamic relationships for rifampin are not well described. Hence, the true target exposure is yet to be identified. Simulations showed that fewer than one-third of all patients achieved the minimum recommended peak concentration of 8 mg · liter\(^{-1}\) (32) at the induced state following multiple 450- or 600-mg daily doses of rifampin. The \( C_{\text{max}}\)-to-MIC ratio was suggested previously to be important for the activity of rifampin against Mycobacterium tuberculosis (14). Notably, in the patient group with a body weight of <50 kg receiving the 450-mg dose, a lower median \( C_{\text{max}} \) was seen than for the patient group with a body weight of ≥50 kg receiving the 600-mg dose, suggesting that inappropriate dosing by body weight could play a role in selection for rifampin resistance.

The application of the linearization method made it possible to explore the effect of covariate screening for different basic models with different scaling approaches. This was exemplified by the time required to fit the final model with one parameter-covariate relationship, which was 26 s using the FOCE linearization covariate search (25), compared to 37 h with the FOCE INTER estimation. The underlying structural model did not influence the covariate selection procedure, as the same covariates were selected regardless of the basic structural model. In the final model, HIV infection was associated with a \( V/F \) that was 30% higher than that for HIV-negative patients. The \( V/F\)-HIV covariate relationship resulted in only slightly higher \( CL/F_{\text{IND}} \) values for the HIV-infected population than for the HIV-negative population. Similarly, lower \( C_{\text{max}} \), \( \text{BASE} \) and \( C_{\text{max}} \), \( \text{IND} \) values were predicted for the HIV-infected population due to the covariate relationship with \( V/F \). However, all these differences were judged not to be of clinical importance. As the HIV-infected patients in our study were antiretroviral naive, the \( V/F\)-HIV covariate relationship is most likely disease related.

In conclusion, a semimechanistic pharmacokinetic-enzyme turnover model for rifampin autoinduction in adult tuberculosis patients was successfully developed. Different allometric scaling approaches as well as no scaling did not influence covariate selection. HIV infection was associated with a 30% increase in the \( V/F \) for a typical patient. This was shown not to be of clinical significance, as simulations for typical patients demonstrated similar induced-state exposures (\( \text{AUC}_{0-24} \)) for patients with and those without HIV infection. Maximum induction is likely achieved after 450-mg daily dosing, as negligible increases in \( CL/F \) values were observed following the 600-mg/day regimen, suggesting that dose increases beyond 600 mg/day would likely not result in an autoinduction of a higher magnitude than that observed in this study. The turnover of the inducible process was estimated to a corresponding half-life of approximately 8 days for a typical patient. Assuming 5 half-lives to the steady state, this is the equivalent of approximately 40 days to the induced state for rifampin autoinduction.
REFERENCES