Population pharmacokinetics of rifampin in pulmonary tuberculosis patients

including a semi-mechanistic model to describe variable absorption

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ABSTRACT

This article describes the population pharmacokinetics of rifampin in South African pulmonary tuberculosis patients. Three datasets containing 2913 rifampin plasma concentration-time data points, collected from 261 South African pulmonary tuberculosis patients aged 18-72 years and weighing 28.5-85.5 kg, and receiving regular daily treatment including rifampin (450-600 mg) for at least 10 days, were pooled. A compartmental pharmacokinetic model was developed using nonlinear mixed-effects modeling. Variability in the shape of the absorption curve was described using a flexible transit compartment model, in which a delay in the onset of absorption and a gradually changing absorption rate were modeled as the passage of drug through a chain of hypothetical compartments, ultimately reaching the absorption compartment. A previously-described implementation was extended to allow its application to multiple-dosing data. The typical population estimate of oral clearance was 19.2 L·h\(^{-1}\), while volume of distribution was estimated to be 53.2 L. Interindividual variability was estimated to be 52.8% for clearance and 43.4% for volume of distribution. Interoccasional variability was estimated on oral clearance (22.5%) and mean transit time during absorption (67.9%). The use of single-drug formulations was found to increase both the mean transit time (by 104%) and clearance (by 23.6%) relative to fixed-dose combinations. A strong correlation between clearance and volume of distribution suggested substantial variability in bioavailability, which could have clinical implications, given the dependence of treatment effectiveness on exposure. The final model successfully described rifampin pharmacokinetics in the population studied, and is suitable for simulation in this context.
INTRODUCTION

Rifampin (rifampicin, RIF) is an essential component of first-line tuberculosis (TB) pharmacotherapy. Its antimycobacterial utility against *Mycobacterium tuberculosis* infections is characterized by a high sterilizing activity (the ability to eliminate semi-dormant or persisting organisms in TB lesions). In addition, it prevents the emergence of resistance to its companion drugs (38).

The treatment success rate in South Africa was 68% in 2002, compared to 65% in 2001 and 66% in 2000 (69). These rates are still unsatisfactory when compared with the World Health Organization (WHO) target of 85% (70). The adoption of Directly-Observed Treatment, Short-course (DOTS) in most treatment centres in South Africa and the country’s relatively strong healthcare infrastructure are the major pillars upon which South Africa’s National TB treatment programme depends. In addition to poor patient adherence, sub-optimal dosing in combination with highly variable bioavailability have been suggested as factors that might be worthy of investigation to increase TB treatment success rates (9, 37, 65). Increased interindividual (IIV) or interoccasional variability (IOV) may affect the efficacy of the drug by increasing the likelihood of subtherapeutic concentrations. This, potentially complicated by rifampin’s well-reported autoinduction of its own metabolism (3, 31, 32, 74), could lead to delayed or incomplete responses to treatment and an increase in the risk of the emergence of drug resistance. In this article, we develop a nonlinear mixed-effects model to characterize the variability in the population pharmacokinetic parameters of rifampin, and to identify any contributing covariate factors, with a view to better understanding this risk.
METHODS

Patients

Data from three clinical studies in pulmonary tuberculosis patients were pooled to form the dataset used in the analysis (Table I). Patients were recruited from DP Marais SANTA Centre, a short distance outside urban Cape Town, and Brewelskloof Hospital, in the Breede Valley. Both centres are located in South Africa’s Western Cape province. The study participants were males and non-pregnant females over the age of 18. All subjects were fasted from 10 pm on the evenings prior to blood sampling, and provided full written informed consent prior to inclusion in the studies. Ethical approval for all the studies was granted by the research ethics committees of the University of Cape Town, South Africa and the participating study centers. All formulations used during the study were those usually administered at the centers concerned and were approved for use in the country by the national medicines regulatory authority, with a single exception, which is discussed further on.

South African tuberculosis treatment guidelines at the time of the study (2002-2003) were based on the World Health Organization’s Directly Observed Treatment (Short Course) (DOTS) tuberculosis control strategy (33, 40) and recommended a rifampin-containing regimen administered daily 5 times per week (Monday to Friday) with a weekend drug holiday. Rifampin was administered in combination with isoniazid for a total of 6 months of treatment. In the first 2 months, known as the intensive phase, pyrazinamide, ethambutol (and in some cases, streptomycin) were added to the regimen. All sites followed international published guidelines on rifampin dosing, using crude weight criteria: subjects weighing less than 50 kg received either 450 mg or 480 mg daily, depending
upon the formulations available, whereas those weighing greater than 50 kg received 600 mg daily (5). The mean dose given across all 261 subjects was $10.6 \pm 1.43$ mg·kg$^{-1}$.

The first subset, which we shall refer to as DPM1, comprised 91 pulmonary tuberculosis patients treated with a rifampin-containing drug regimen for a minimum of 10 days. Twelve patients received 450 mg/day of rifampin orally, 28 patients received 480 mg/day of rifampin orally, and 51 patients received 600 mg/day of rifampin orally Monday to Friday. The mean dose in this group was $10.4 \pm 1.22$ mg·kg$^{-1}$. Three blood samples for rifampin pharmacokinetics were taken twice weekly, on Tuesdays and Fridays, at random times between 0 and 12 h post-dose, producing a total of 12 samples taken over 4 occasions. In addition to rifampin, patients received their concomitant prescribed medications as usual. Details of these were carefully noted for possible inclusion in the analysis to identify covariates affecting the pharmacokinetics of rifampin.

The second data subset (DPM2) included 31 pulmonary tuberculosis patients treated with first-line tuberculosis treatment for at least 14 days prior to the study. Subjects in this group were excluded if they had previous hepatic, renal, or gastrointestinal disorder, and if they had a recent history of concomitant illness, blood donation, or substance abuse. All patients weighed 50 kg or more, and received 600 mg/day of rifampin orally from Monday to Friday. The mean dose in this group was $10.1 \pm 1.18$ mg·kg$^{-1}$. Blood samples for rifampin pharmacokinetics were taken pre-dose, and subsequently at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0 and 24.0 hours post-dose on Tuesdays on up to 4 occasions over a 6-week period. Patients in DPM2 received their other prescribed medications as usual except for the days of pharmacokinetic blood sampling, upon which only rifampin and other components of antimycobacterial therapy were administered. A subset of patients in this group ($n=$22) received a formulation not approved by the national regulatory agency.
on a single occasion. However, it was shown to be bioequivalent to the reference formulation, and data from this treatment group were included in the DPM2 subset on that basis.

The third and final subset (BKH) included 139 pulmonary tuberculosis patients, admitted at the end of the two-month intensive phase of treatment which included rifampin (36). Ninety-eight patients received 450 mg/day of rifampin orally, and 41 patients received 600 mg/day of rifampin orally, on a daily basis, without a weekend drug holiday. The mean dose in this subset was $10.9 \pm 1.55 \text{ mg\cdot kg}^{-1}$.

Blood samples for the determination of rifampin pharmacokinetics were taken on the study day (Thursday) pre-dose and subsequently at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0 and 8.0 hours post-dose. In addition to rifampin, patients received their other prescribed medications as usual. Subjects in this category were sampled on one day only.

Covariate information and full medical histories were recorded for each patient during the initial interview and by examination of their clinical case records. Information gathered included age, weight, height, body mass index (BMI), gender, phase of treatment (intensive or continuation), details of previous tuberculosis episodes, and the date that rifampin treatment was started, and use of concomitant medication, alcohol, tobacco, and drugs of abuse. Adherence to treatment on the pharmacokinetic study days was confirmed by direct observation of drug ingestion.

**Specimen collection and storage**

Venous blood samples for determination of rifampin pharmacokinetics were collected into lithium heparin vacuum tubes (Vacuette®, Greiner Bio-One International AG, Kremsmuenster, Austria) through an intravenous cannula (Introcan® 1.1 x 32 mm, B. Braun AG, Melsungen, Germany)
inserted into an arm vein. The samples were stored for up to 20 minutes in darkness on ice, before being centrifuged (using a Sigma 3E-1 benchtop centrifuge – Osterode am Harz, Germany), at 1 500 \( \times \) g for 10 minutes at ambient temperature. The plasma was subsequently harvested into labelled 1.5 mL microcentrifuge tubes (Greiner Bio-One International, Kremsmuenster, Austria) and stored at -80°C until analysis.

Patients were requested to undergo voluntary testing for the presence of HIV (10 subjects declined) using an automated ELISA method (AxSYM HIV Ag/Ab Combo, Abbott Diagnostics, Germany). Counseling was provided pre- and post-test, for all subjects. Confirmatory testing was carried out in subjects whose initial screening result was positive using the Enzygnost Anti-HIV 1/2 Plus (Dade Behring, Liederbach, Germany), a second ELISA test.

**Bioanalytics**

Plasma concentrations of rifampin were determined by high-performance liquid chromatography (HPLC) using ultraviolet (UV) detection (60). The HPLC system consisted of a Discovery C8 analytical column of dimensions 15 cm x 4.6 mm and particle diameter 5 \( \mu \)m (Supelco, Bellefonte, Pennsylvania, USA) in conjunction with a reverse-phase guard column (2.5 cm x 0.46 cm, packed with Pelliguard LC-8: Upchurch Scientific, Oak Harbor, Washington, USA). The mobile phase consisted of acetonitrile (BDH, Poole, United Kingdom) and 0.1 % trifluoroacetic acid (Riedel-de Haën, Seelze, Germany) in the ratio 60:40. The UV detection wavelength was 270 nm and the flow rate was 2.0 mL min\(^{-1}\). Fifty \( \mu \)L of sample was injected directly onto the column and the retention time was approximately 3.45 minutes.
Frozen plasma samples were allowed to thaw in a water bath at ambient temperature. The C18 solid-phase extraction column (Bond Elut 3.0 cm - Varian, Palo Alto, California, USA) was primed with 1 mL 0.5 mM potassium phosphate buffer (pH 4.5) and 0.5 mL of plasma was applied to the column. The sample was drawn onto the column and allowed to stand for 10 minutes. The column was washed with 1 mL of the phosphate buffer. Bound rifampin was eluted into a tinted analytical vial using 0.5 mL acetonitrile (BDH, Poole, United Kingdom) and 0.5 mL methanol (BDH). All solvents were of HPLC grade.

Standard curves were linear and provided a detection range of 0.3-25 mg·L⁻¹. Quality control (QC) samples of 0.75 mg·L⁻¹, 10 mg·L⁻¹ and 20 mg·L⁻¹ were interspersed between the samples. The coefficient of variation for intraday precision was 8.57%, and for interday precision, 9.21%. Mean (± standard deviation) recovery was assessed by measuring the rifampin concentration obtained from spiked plasma samples corresponding to points on standard curves in mobile phase, and was 89.3 ± 6.78%. Apart from the assessment of recovery, plasma was used as the matrix for standard curves and QC samples.

**Pharmacokinetic data analysis**

A total of 2 913 concentration-time observations in 261 subjects were available for modelling. Model-building was conducted using NONMEM (version VI, level 1.0 beta) (6), implemented on a computing cluster running Red Hat Linux 7.0 (Mandrakesoft, Paris, France) with GNU Fortran (g77) 2.96, a component of GCC 2.96 (Free Software Foundation, Boston, USA). Model-building steps and associated analysis data were managed using the software utilities Census (68) and Xpose v4.0 (23). The first-order conditional estimation (FOCE) method, with ε-η interaction, was used for the
estimation of typical population pharmacokinetic parameters, random variability (interindividual and interoccausal, IIV and IOV) in these parameters, and residual variability between observed and predicted plasma concentrations. Correlations between variability components were also tested.

Model selection was achieved by use of the objective function value (OFV), a goodness-of-fit estimate which is minus twice the log likelihood of the data, as well as by examination of relative standard error (RSE) values and goodness-of-fit plots. Differences between the objective function of a full and a reduced model are approximately chi-square distributed, with \( n \) degrees of freedom, where \( n \) is the number of parameters fixed in the reduced model. A drop of > 3.84 in the objective function after addition of a single model parameter was regarded as significant, corresponding to a 5% significance level with a single degree of freedom.

One- and two-compartment models with linear absorption and elimination, models incorporating lag times, and models incorporating sequential zero- and first-order absorption (20) were fitted to the data during the initial stage of model building. Elimination was assumed to take place from the central plasma compartment in all models tested. The absorption model was subsequently modified as described later. IIV for all parameters was modelled as exponential variance parameters. IOV was modeled following the method of Karlsson et al (24). Residual variability, arising from unspecified within-subject variability, model misspecification and experimental error, was described using a slope-intercept model comprising additive and constant coefficient of variation components.

Two approaches were tested to develop the model for rifampin pharmacokinetics. In the first, an enzyme turnover model was adapted to try to characterize autoinduction in rifampin metabolism
Using this framework, the dependence of enzyme formation on the concentration of drug in the central compartment was tested, along with the effect of enzyme levels on clearance.

Absorption, which a graphical inspection of the data revealed to be highly variable, was modeled using a method proposed by Savić et al, which envisages absorption as a multiple step process occurring as the drug travelled through a number of hypothetical ‘transit’ compartments (42, 56, 59). Transit compartments were used to mimic a delay in absorption onset and a gradual increase in absorption rate in a more physiologically plausible manner than the use of lag times. Drug transfer from the final transit compartment to the central compartment occurred through an absorption compartment, from which drug was absorbed according to the first-order rate constant $k_a$. The optimal (non-integer) number of transit compartments ($n$) was estimated using Equation 1, in which $dA_1/dt$ is the rate of drug change in the absorption compartment, $Dose$ is amount of drug administered (mg), $F$ is bioavailability, $k_{tr}$ is a transit rate constant describing movement of drug between transit compartments $n-1$ and $n$ (h$^{-1}$), $t$ is time (h), $k_a$ is the first-order absorption rate constant, and $\Gamma(n)$ is the gamma function, which extends the factorial expression $n!$ to non-integer, complex and real numbers.

\[
\frac{dA_1}{dt} = Dose \cdot F \cdot k_{tr} \cdot \frac{(k_{tr} \cdot t)^n \cdot e^{-k_{tr} \cdot t}}{\Gamma(n)} - k_a \cdot A_1
\]

(1)

\[
\Gamma(n) = \sqrt{2\pi} \cdot n^{n+0.5} \cdot e^{-n}
\]

(2)

The Stirling approximation was used to compute $\Gamma(n)$ numerically (Equation 2).

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

(3)
The rate constant $k_{tr}$ was calculated from an estimate of the mean transit time ($MTT$, h), the average amount of time spent by a drug molecule travelling from the first transit compartment to the absorption compartment, as in Equation 3.

The transit-compartment approach as originally proposed allowed application of the model for single-dose data only, since the nature of the differential equations used in implementing the model allowed the initial conditions of the system (the dose administered) to be set at time 0 only, and did not allow for the introduction of new drug boluses into the system at later time points. In order to apply this model to a repeated-dose design, modifications were required. Time ($t$) in Equation 1, the actual time at which a given sample was drawn, was changed to time after dose ($t_{ad}$) by subtracting the time of the last dose ($t_{Dose}$) from $t$ (Equation 4). In this way, each dosing event happened at time 0, meeting the requirements of the original model and thus allowing the transit model to accommodate multiple-dosing schemes.

$$\frac{dA_t}{dt} = \frac{Dose \cdot F \cdot k_{tr} \cdot \left((k_{tr} \cdot t_{ad})^n \cdot e^{-k_{ad} \cdot t_{ad}}\right)}{\Gamma(n)} - k_a \cdot A_t$$

An enzyme turnover model (18) was adapted in an attempt to characterize autoinduction in rifampin metabolism (31). Using this framework, the dependence of enzyme formation on the concentration of drug in the plasma compartment was tested, along with the effect of enzyme levels on clearance.

A number of potential covariate relationships on the pharmacokinetic parameters were tested, including the demographic variables age, weight, and sex, HIV status, study site, and the choice of formulation type. Formulation type was either fixed-dose combination (FDC), in which rifampin and other drugs were administered together the same formulation to promote compliance, or single-drug, in which rifampin and other drugs were administered as separate tablets. Potential covariates were
initially identified by using stepwise generalized additive modeling (GAM), as implemented in Xpose. The covariates selected in the GAM analysis were tested in the model by stepwise addition using an OFV change of > 3.84 (corresponding to a significance level of 5%) as the cut-off for inclusion, followed by stepwise deletion using an OFV change of > 10.84 (corresponding to a significance level of 0.1%) as a prerequisite for retaining a covariate in the model (34). The effects on rifampin pharmacokinetics of significant covariate relations were explored using simulations. New individuals were simulated to represent the spectrum of possible covariate configurations \((n = 1000\) of each permutation), and the resulting concentration-time data plotted in combination with locally-weighted least-squares regression lines (loess smooths) in order to detect differences (10).

The tool Perl-speaks-NONMEM was used to run a nonparametric bootstrap of 800 iterations to provide unbiased estimates of the standard errors and the 95% confidence intervals of the estimated parameters (28, 29). The resampled datasets were stratified by location to ensure that they were suitably representative of the structure of the original pooled dataset.

Model-based estimates of individual values of area under the concentration-time curve to 24 hours \((AUC_{0-24})\) were calculated from the empirical Bayes estimates (EBEs) of parameters as in equation 5, where \(CL/F\) is oral clearance at steady-state in \(L\cdot h^{-1}\) and \(Dose\) is rifampin dose in mg.

\[
AUC_{0-24} = \frac{Dose}{(CL/F)}
\]  

A visual predictive check was employed to characterize the model’s simulation properties. The final model was used to simulate 400 new datasets based upon the design of the original dataset. For each of the original data points, a 95% prediction interval was obtained by extracting the 2.5% and 97.5%
quantiles of their simulated distributions. These were then plotted against the observations.
RESULTS

The pooled patient rifampin plasma concentration-time data were best described by the transit-compartment absorption model, which was sufficiently flexible to allow for the acceptable fitting of almost all subjects. Two-compartment models provided no advantage in terms of improvement in diagnostic plots or change in OFV (ΔOFV = 0.169), and were discarded early in the model-building process. Models incorporating lag times and sequential zero- and first-order absorption processes produced substantially poorer fits than those provided by the transit model, based on a graphical assessment of their ability to describe the data and the degree to which estimates of IIV on the key structural parameters were reduced, and were similarly rejected (Table II).

The model was parameterized in terms of oral clearance (CL/F, where F is unknown bioavailability), apparent volume of distribution of the central compartment (V/F), absorption rate constant (ka), mean transit time (MTT) and number of transit compartments (n). While the fit provided by the enzyme-turnover model was better than simple first-order input and combined zero- and first-order absorption models, it failed to describe a number of individuals with particularly slow or atypical absorption. The data did not support the inclusion of both the complex model for absorption and an enzyme turnover model to account for autoinduction. Consequently, the disposition model was simplified to a one-compartment model parameterised in terms of CL/F and V/F.

The final model itself is illustrated as Figure 1. The rate of change of drug in the absorption compartment was described by Equation 1, as described earlier; in addition, the first term was log-transformed to reduce potential numerical instability during computation.
\[
\frac{dA_2}{dt} = k_a \cdot A_1 - \frac{CL}{V} \cdot A_2
\]  

(6)

The rate of change of drug in the central compartment was defined by Equation 6, in which \(A_2\) is the amount of drug in the compartment (mg), \(CL\) is clearance (L·h\(^{-1}\)), and \(V\) is volume of distribution (L).

Variability in \(CL/F\) was separated into IIV (\(\eta_{CL/F}, CV = 52.8\%\)) and IOV (\(\kappa_{CL/F}, CV = 22.5\%\)). Parameters related to absorption exhibited the most variability. IIV in \(k_a\) was estimated to be 66.3\%, in \(MTT\) to be 60.1\%, and in \(n\) to be 156\%, while IOV in \(MTT\) was estimated at 67.9\%. A strong correlation between \(CL/F\) and \(V/F\) was estimated (0.947).

Of the tested covariate relations, only the inclusion of the formulation type (single-drug formulation or FDC) as a covariate on \(CL/F\) and \(MTT\) remained in the model after the conclusion of the stepwise deletion process (\(\Delta OFV \geq 10.83, p \leq 0.001\)). There was a significant difference in oral clearance when subjects administered FDCs were compared with subjects administered single-drug formulations; the estimated typical value of \(CL/F\) for subjects receiving single-drug formulations was 23.6\% greater than that estimated for subjects receiving FDCs, translating into slightly increased exposure for the FDC group. In patients who received their rifampin as a single-drug formulation, \(MTT\) was 104\% greater than in those who took fixed-dose combination (FDC) formulations, resulting in peak concentrations approximately 30 minutes later in those subjects. The relationship between choice of formulation type and \(CL/F\) was modelled as in Equation 7.

\[
(CL/F)_{ij} = [TV(CL/F) \cdot (1 + \theta_{SDF-CL/F} \cdot SDF)] \cdot \exp(\eta_{CL/F,i} + \kappa_{CL/F,j})
\]  

(7)
In Equation 7, \((CL/F)_{ij}\) is apparent oral clearance in individual \(i\) at occasion \(j\), \(TV(CL/F)\) is the value of \(CL/F\) in the population assuming administration of an FDC, \(\theta_{SDF}\) is the model parameter describing the effect of single-drug formulation use on oral clearance, \(SDF\) is formulation type (0 for FDC, 1 for single-drug formulation), \(\eta_{CL/F,i}\) is IIV on oral clearance in individual \(i\), and \(\kappa_{CL/F,ij}\) is IOV on oral clearance in individual \(i\) at occasion \(j\). The relationship between \(MTT\) and formulation type was expressed similarly. The impact of covariate effects on rifampin pharmacokinetics are illustrated in Figure 2.

Final estimates of the parameters are presented in Table III, together with bootstrap estimates of standard errors and parameter confidence intervals. Goodness-of-fit plots (Figure 3) indicated a good fit of the model to the data, although the plot of observed concentrations against population predictions reveals that approximately 175 points (approximately 5% of observations) were being underpredicted by the population model (individual predictions < 0.2 mg·L\(^{-1}\)). The distribution of the weighted residuals was unbiased with respect to time, indicating that this was probably not attributable to a systematic problem in the structural model. Plots of the observations, individual predictions and population predictions of representative individuals (Figure 4) confirmed that the final model adequately described the data, even when the ‘worst’ fits, characterized by high individual (IWRES) and population weighted residuals (WRES), were selected for display. A visual predictive check of the final model appears as Figure 5. Model-based predictions of \(AUC_{0-24}\) had a mean of 30.7 ± 13.2 mg·h·L\(^{-1}\) across all subjects and sampling occasions.
DISCUSSION

The population pharmacokinetics of rifampin in the studied patients were highly variable. The drug exhibited more variability in its population pharmacokinetics in the study group than has been reported in healthy volunteers (50). Loos et al reported CL/F in a small German patient population to be $14.2 \pm 9.70 \text{ L} \cdot \text{h}^{-1}$ (31), but few other reports of rifampin pharmacokinetics in similar patient groups have been reported in terms of CL/F and V/F in the literature. It is helpful, therefore, to look at exposure metrics instead. Model-derived estimates of $AUC_{0-24}$ were generally lower than published reports in other populations of fully-induced pulmonary tuberculosis patients (see Table IV), although they were consistent with those calculated in a separate noncompartmental analysis of the BKH subset of this data (36). Our results are similar to those collected during studies of HIV patient populations (16, 51), although less than 15% of the subjects included in our analysis were seropositive for the disease (Table I).

Subpopulations with different absorption characteristics were evident from plots of the raw data, and had also been previously described in healthy volunteers (50). Most commonly, these differences appeared to be related to the rate and extent of absorption. Several potential causes for this variability may be immediately discounted. No food intake was allowed until two hours post-dose, eliminating food effects as a possible source (46, 73), and no significant correlation was found with HIV co-infection (11, 16, 17, 47, 49, 58, 64). Other sources might be attributed to the fact that the studies were conducted during clinical treatment in a hospital setting. While concomitant drug intake was carefully monitored, the combinations of medications involved were too numerous ($n=41$), and their frequencies within the population too low, to allow any effective investigation of their potential influence. None were previously reported to have influenced the pharmacokinetics of rifampin. The
influence of delayed gastric emptying, alterations in gastric pH (1, 44) and poor nutritional status (37) could not be determined using our study design. Other covariate effects, however, were available for model-based analysis, and we shall discuss these further on.

The core one-compartment model with linear elimination was similar to one used previously to model rifampin in healthy volunteers (50). The transit compartment model provided a better fit to the data than the other absorption models tested and it was chosen, therefore, as the most appropriate model for fitting the unusual absorption profiles seen in our data (Figure 4). Previously, transit model (‘tanks-in-series’) approaches have been used to describe signal transduction (62, 71), and similar approaches have been used to model absorption (12, 66). Weiss used the gamma distribution to model drug residence times (67), and since then, similar approaches have been applied to other areas (26, 55). The transit model assumes a gradual increase in the absorption rate, which results in a smoother initial rise in the plasma concentration towards the maximum. This is considered to be a better approximation of the underlying physiology than the use of first or zero order absorption models which include a lag time parameter (T_{lag}). The lag time parameter, which assumes an instantaneous shift from no absorption to maximal absorption, is physiologically implausible and is associated with computational difficulties. The transit compartment model offers advantages from a numerical point of view, since partial derivatives are defined for the predicted concentrations from the entire absorption profile (59). Here, we have extended this approach to account for multiple dosing. Addition of the transit model, while providing a better fit, did not, however, affect predictions of CL/F and V/F, which were largely independent of the method used to model absorption. Increasing the complexity of the absorption model was, however, offset by a proportional improvement in the model’s ability to explain variability in the key structural parameters, justifying the additional computation overhead (Table II).
Some caveats apply to the extended transit model for repeated doses that we present in this article. Our implementation assumes that the entirety of the bioavailable dose has completely reached the absorption compartment before the next dose is administered, as the system is reset at each dosing event. In this case, given once-daily dosing, this assumption was valid and was supported by the data. The utility of the method may be enhanced where subjects are fasted, owing to the increased rate of gastric emptying under these conditions.

The data did not support the inclusion of an enzyme turnover model for autoinduction, despite the fact that this phenomenon is well-known in rifampin; repeated daily administration leads to accelerated clearance and decreased plasma concentrations (3, 31, 32, 74). The most likely explanation is that subjects were uniformly at a steady-state for induction, having been recruited after at least 10 days of regular rifampin treatment, and the weekend drug holiday was insufficiently large an interruption to produce a change in elimination-related enzyme levels significant enough to produce a significant signal in the data. Literature reports indicate that a maximal state of induction is typically achieved within 7-10 days (2, 31, 54), and takes between 3 and 7 days to return to normal levels (21, 61).

A significant within-subject, between-occasion contribution to overall variability in $CL/F$ and $MTT$ was noted. While in the former, IOV was relatively small (22.5%), IOV in $MTT$ was significantly larger (67.9%). Since little time-varying covariate data was available, no conclusions could be drawn regarding the origin of this component of variability in the sample population. However, allowing $CL/F$ and $MTT$ to vary according to sampling occasion significantly improved the fit, and the model’s predictive ability. The transit model parameters $MTT$, and especially $n$ (estimated to be 7.13
in the population, but with a CV of 156%) exhibited substantial variability. While there is no physiological explanation for the value of \( n \), which is purely empirical, variability in the overall shape of the absorption curve may be linked to both gastric pH and the rates of release of rifampin from each of the specific formulations used. Indeed, formulation type was a critical predictor of rifampin pharmacokinetics in this patient population, as we shall see.

A strong correlation (0.947) between \( CL/F \) and \( V/F \) was noted in the data. This was in all likelihood driven by variability in \( F \). Rifampin is well-known for displaying variability in both rate and extent of absorption when dosed orally (27, 35, 36, 41, 43, 52, 65), particularly where FDC and single-drug formulations are compared. A variety of potential reasons for this have been investigated in the literature. It had long been speculated that this behaviour was related to formulation dissolution and disintegration properties of oral formulations (45, 46), and recent work suggests that this is indeed the case (4). The structure of the final model, however, was unable to support the direct estimation of IIV on \( F \), owing to numerical issues related to the large number of model parameters (although, in principle, there is no reason why this should not work in other implementations of this model). No significant correlations were noted between \( CL/F \) and any of the absorption parameters (\( k_a, MTT \) or \( n \)).

There was evidence in our data to support a formulation effect on bioavailability, in the form of a strong covariate relationship between \( CL/F \) and formulation type. The use of single-drug formulations was associated with a statistically significant increase in \( CL/F \) (23.6%) relative to the typical value of the parameter in subjects in whom FDCs were used. The reasons for this are probably related to \( F \), rather than \( CL \), since it is unlikely that formulation would exert a direct effect
on elimination processes, and given the large quantity of clinical evidence for the relationship between $F$ and formulation. With larger quantities of data, it may be possible confirm this directly.

Rifampin has an acidic pKa of 1.7 and a basic pKa of 7.9 (7). Consequently, it is highly soluble but poorly permeable at gastric pH (1-3) and physiological conditions, but its solubility varies by 100-fold in this range. Solubility at duodenal pH (4-6) is moderate to high and permeability is high, and in the colon, both solubility and permeability are high. In formulations in which release rate is high, most of the dose is dissolved by the time gastric emptying occurs, resulting in rapid uptake from the duodenum. However, where release rate is slower, or gastric pH is not optimal, less substrate is available at the absorption site, limiting uptake and producing a different shape (4), and adding to variability of both $n$ and $MTT$, as well as $F$, which we have already discussed. This is supported by the selection of a significant covariate effect linking rifampin formulation type and $MTT$ during the model-building process. According to the model, when rifampin was administered as a single-drug formulation, $MTT$ was 104% longer (at 0.865 h) than the typical value for the population. This relationship in our data appears to delay the time of peak concentration ($T_{\text{max}}$) in single-drug formulation users (see Figure 2) and, while probably not clinically relevant, explains a portion, but not all, of the variability seen in the absorption phase.

In addition to the effect on $T_{\text{max}}$, the choice of a single-drug formulation appears to reduce the peak plasma concentration ($C_{\text{max}}$, through its effect on $CL/F$). The effect on $CL/F$ also produces a net decrease in exposure, represented by the area under the concentration-time curve ($AUC$ – see Figure 2). It is, however, important to temper these findings with a brief discussion of potential confounders. The BKH subgroup was treated almost uniformly with single-drug formulations, while the DPM1 and DPM2 subgroups were mostly administered FDCs. In a further complication, 51 of
the included BKH subjects (contributing 13.1% of the total number of observations) were treated with formulations later found to be of inferior quality (35). Excluding these individuals, or including the use of the inferior formulations as a covariate on any of the model parameters, failed to produce a significant difference in the model fit or the parameter estimates, indicating that the majority of the observed formulation effect did not result from this source. Dosing in the studied patients was routinely carried out by body weight, explaining the absence of a significant weight effect on any of the model parameters despite previously-published evidence of this relationship (50).

The distribution of \( n \), the number of transit compartments, was significantly skewed (see Table III). This appears to be a natural characteristic of this parameter, and was present in all stages of model development. If one considers that the final estimate of \( n \) is theoretically an optimum, higher values of which would make little difference to the fit in comparison to lower, this behaviour is not unexpected.

The visual predictive check (Figure 5) indicated that the model slightly overpredicted the variability of the data. This can probably be explained in terms of the significant proportion of the population made up by patients with atypical absorption, which led to the large estimates of absorption-related variability we have observed and a concomitant overall increase in the variability of model-derived predictions (see Figure 4 for examples). Also, greater than 75% of the observations were recorded at 6 hours post-dose or less, concentrating the information content in this region. Given the degree of variability in the data, the increased uncertainty at times greater than 8 hours post-dose, where observations were sparser, is not unexpected. The median values of the observations and the predictions matched very closely, confirming that the model adequately captured the central trend. The poor agreement of the lower intervals at the 480 mg dose level is probably attributable to the
a relatively low number of observations in this group (approximately 10.5% of the total). We may therefore conclude that the model is suitable for simulation in patient populations similar to those studied here, as long as it is borne in mind that simulations may overemphasize variability to a small degree, and that one assumes that simulated subjects have been dosed by weight, as was the case here.

It has been reported previously that rifampin’s antimicrobial killing properties are related to the ratio of the area under the concentration-time curve (AUC) to the minimum inhibitory concentration (MIC) (22). This means that the effectiveness of rifampin treatment is strongly related to $F$ and $CL$, and as we have seen, both are somewhat variable. More recent research by Gumbo and colleagues (15) has suggested that the ratio of the peak plasma concentration ($C_{\text{max}}$) to the MIC is important in preventing the emergence of resistance. Assuming a range of MICs of rifampin, with respect to drug-susceptible clinical isolates of *Mycobacterium tuberculosis*, of between 0.125 mg·L$^{-1}$ and 0.250 mg·L$^{-1}$ (19, 53), plasma concentrations in some individuals may not reach high enough levels to prevent the emergence of resistance, or be maintained at high enough levels to ensure optimal bactericidal effect. As an illustration, the lowest measured peak concentration in the studied patients was 0.716 mg·L$^{-1}$, which when one considers that approximately 84-88% of rifampin in blood is protein-bound (8), translates to an estimated maximal unbound concentration of about 0.1 mg·L$^{-1}$. In addition to oft-cited causes of treatment failure, such as poor compliance (14, 72), it follows that inadequate exposure to the drug may be playing a role in the poor cure rates seen in South African patients; low rifampin exposures have been also reported by van Crevel and colleagues in a demographically similar group of Indonesian patients (65). While a highly variable rate of absorption is expected to have little effect on total exposure, its effect on $C_{\text{max}}$ is considerable – slower absorption leads to lower peak plasma concentrations. These data add further support to the
mounting clinical evidence that higher doses may be more effective, although the safety implications of increased exposure remain unclear (13, 22, 25, 30, 39, 48).

While the multidrug treatment strategy currently employed to combat pulmonary tuberculosis is undeniably effective in the majority of South African patients, the variability in rifampin pharmacokinetics and generally lower exposures we have observed in our South African study population suggests that some patients routinely receive low concentrations of the drug. It is therefore vitally important in this context that further research be carried out in order to more clearly characterize the PK/PD relationship, and thereby to enable the definition of the most appropriate dosing strategy in South African pulmonary tuberculosis patients, and indeed other populations as well.
ACKNOWLEDGMENTS

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We thank Jean van Dyk, Rudy Onia, Afia Fredericks and Alicia Evans for their invaluable technical and logistical assistance. We also wish to thank Dr Bernard Fourie, Director, Medical Research Council Tuberculosis Research Unit, South Africa, for allowing the use of some of the PK data included in this study. The authors have identified no conflicts of interest.
REFERENCES


FIGURE LEGENDS

**Figure 1.** Diagrammatic representation of the final model for RIF pharmacokinetics. $A_1 =$ amount of rifampin in the depot compartment (mg); $A_2 =$ amount of RIF in the central compartment (mg); $k_{tr} =$ transit rate constant; $n =$ estimated number of transit compartments; $MTT =$ mean transit time; $V =$ volume of distribution.

**Figure 2.** Simulations illustrating the effect of the use of a single-drug formulation, compared to the same model assuming that an FDC was used. The effects of the covariate relationship on $CL/F$ and $MTT$ alone are also represented. All other demographic parameters were assumed to be the population median.

**Figure 3.** Goodness-of-fit plots for the final model for RIF pharmacokinetics in South African pulmonary tuberculosis patients. $DV =$ observed RIF concentration; $PRED =$ population predicted RIF concentration; $IPRED =$ individual predicted RIF concentration; $|IWRES|$ =$ $absolute individual weighted residual; $WRES =$ weighted residual.

**Figure 4.** Plots of the observations (open circles), individual predictions (solid lines) and population predictions (dotted lines) from the final model, to illustrate goodness-of-fit for different classes of individual (typical individuals, individuals with low rifampin exposure, and individuals with atypical absorption profiles. ‘Poor fit’, ‘Typical fit’ and ‘Best fit’ denote goodness-of-fit, categorized by inspection of weighted individual residuals (IWRES) and population residuals (WRES).
**Figure 5.** A visual predictive check of the model’s ability to predict the data. The predictive check was conditional on dose (450 mg, 480 mg, and 600 mg). The open circles are the observed data points, solid lines are loess smooths of the 5th, 50th and 95th percentiles of the observations, the dashed line is a loess smooth through the median of the simulations, and the dashed outer lines represent the 90% prediction interval obtained from the simulations (also loess smooths). Typically, one would expect the simulated data to match the observations – the central tendencies should match, and approximately 10% of the observations should be distributed equally above and below the 90% prediction limits.
Table I. Patient demographics, covariates and study designs of the clinical studies of rifampin pharmacokinetics in the South African pulmonary tuberculosis patients included in the rifampin pharmacokinetic model. Continuous variables are given as median (interquartile range).

<table>
<thead>
<tr>
<th></th>
<th>DPM1</th>
<th>DPM2</th>
<th>BKH</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>91</td>
<td>31</td>
<td>139</td>
<td>261</td>
</tr>
<tr>
<td>Study site</td>
<td>D P Marais SANTA</td>
<td>D P Marais SANTA</td>
<td>Brewelskloof Hospital, Centre, Retreat, Western Cape, South Africa</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Centre, Retreat, Western Cape, South Africa</td>
<td>Centre, Retreat, Western Cape, South Africa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>36 (30 - 43)</td>
<td>37 (31 - 41)</td>
<td>36 (28 - 44)</td>
<td>36 (29 - 44)</td>
</tr>
<tr>
<td>Gender</td>
<td>25/66</td>
<td>2/29</td>
<td>75/64</td>
<td>102/159</td>
</tr>
<tr>
<td>(female/male)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>52.5 (47.3 - 58.3)</td>
<td>59 (55 - 63)</td>
<td>46 (40 - 51)</td>
<td>50 (43.7 - 56)</td>
</tr>
<tr>
<td>BMI</td>
<td>19.6 (18.1 - 21)</td>
<td>20.6 (19.6 - 22.9)</td>
<td>17.7 (16.2 - 19.8)</td>
<td>18.7 (17.1 - 20.7)</td>
</tr>
<tr>
<td>HIV Infection*</td>
<td>21 (25.3%)</td>
<td>3 (9.7%)</td>
<td>13 (9.5%)</td>
<td>37 (14.2%)</td>
</tr>
<tr>
<td>Formulation type</td>
<td>4/87</td>
<td>105/34</td>
<td>0/31</td>
<td></td>
</tr>
<tr>
<td>(single-drug/FDC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study length (weeks)</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Typical number of samples/subject</td>
<td>12</td>
<td>13-52</td>
<td>9</td>
<td>2,913†</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----</td>
<td>-------</td>
<td>---</td>
<td>--------</td>
</tr>
<tr>
<td><strong>Sampling schedule</strong></td>
<td>Pre-dose and random between 0-12 h post-dose</td>
<td>Pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 h post-dose</td>
<td>Pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 h post-dose</td>
<td></td>
</tr>
</tbody>
</table>

* n = 251 subjects

† Total number of samples
Table II. Comparison of parameter estimates and objective function values from competing absorption models. ∆OFV = change in NONMEM objective function value; df = degrees of freedom; $CL/F = \text{apparent clearance, } \text{L·h}^{-1}$; $V/F = \text{apparent volume of distribution, } \text{L}$; $k_a = \text{absorption rate constant, } \text{h}^{-1}$; $\epsilon_{\text{add}} = \text{additive residual error, } \text{mg·L}^{-1}$; $\epsilon_{\text{ccv}} = \text{proportional residual error}; \text{IIV} = \text{interindividual variability (variance).}$

<table>
<thead>
<tr>
<th>Absorption Model</th>
<th>∆OFV (df)</th>
<th>$CL/F$ (IIV)</th>
<th>$V/F$ (IIV)</th>
<th>$k_a$ (IIV)</th>
<th>$\epsilon_{\text{add}}$</th>
<th>$\epsilon_{\text{ccv}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-order</td>
<td>0 (0)</td>
<td>19.4 (0.321)</td>
<td>52.8 (0.427)</td>
<td>1.61 (2.39)</td>
<td>0.256</td>
<td>0.302</td>
</tr>
<tr>
<td>First-order and lag time</td>
<td>-83.026 (1)</td>
<td>20.2 (0.387)</td>
<td>53.4 (0.415)</td>
<td>1.64 (0.689)</td>
<td>0.409</td>
<td>0.255</td>
</tr>
<tr>
<td>Sequential zero- and first-order</td>
<td>-270.703 (2)</td>
<td>19.2 (0.314)</td>
<td>51.5 (0.384)</td>
<td>1.23 (0.787)</td>
<td>0.254</td>
<td>0.259</td>
</tr>
<tr>
<td>Transit compartments</td>
<td>-391.939 (3)</td>
<td>19.2 (0.279)</td>
<td>53.2 (0.188)</td>
<td>1.15 (0.439)</td>
<td>0.093</td>
<td>0.222</td>
</tr>
</tbody>
</table>
Table III. Final parameter values estimated by the model. %RSE = relative standard error. %CV = coefficient of variation. FDC = fixed-dose combination; CI = confidence interval.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical value</th>
<th>%RSE*</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral clearance ($CL/F$, L·h$^{-1}$)</td>
<td>19.2</td>
<td>1.29%</td>
<td>18.4 – 20.0</td>
</tr>
<tr>
<td>Volume of distribution ($V/F$, L)</td>
<td>53.2</td>
<td>1.16%</td>
<td>51.1 – 54.3</td>
</tr>
<tr>
<td>Absorption rate constant ($k_a$, h$^{-1}$)</td>
<td>1.15</td>
<td>3.91%</td>
<td>1.05 – 1.25</td>
</tr>
<tr>
<td>Mean transit time ($MTT$, h)</td>
<td>0.424</td>
<td>3.82%</td>
<td>0.400 – 0.459</td>
</tr>
<tr>
<td>Number of transit compartments ($n$)</td>
<td>7.13</td>
<td>8.42%</td>
<td>5.17 – 7.13</td>
</tr>
<tr>
<td>Effect of the use of a single-drug formulation on oral clearance ($\theta_{SDF-CL/F}$)</td>
<td>0.236</td>
<td>9.63%</td>
<td>0.160 – 0.283</td>
</tr>
<tr>
<td>Effect of the use of a single-drug formulation on mean transit time ($\theta_{SDF-MTT}$)</td>
<td>1.04</td>
<td>8.78%</td>
<td>0.791 – 1.24</td>
</tr>
<tr>
<td>Interindividual Variability (IIV, variances &amp; %CV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral clearance ($\eta_{CL/F}$)</td>
<td>0.279 (52.8%)</td>
<td>5.97%</td>
<td>0.242 – 0.347</td>
</tr>
<tr>
<td>Apparent volume of distribution ($\eta_{V/F}$)</td>
<td>0.188 (43.4%)</td>
<td>10.9%</td>
<td>0.154 – 0.250</td>
</tr>
<tr>
<td>Absorption rate constant ($\eta_{k_a}$)</td>
<td>0.439 (66.3%)</td>
<td>11.0%</td>
<td>0.324 – 0.506</td>
</tr>
<tr>
<td>Mean transit time ($\eta_{MTT}$)</td>
<td>0.361 (60.1%)</td>
<td>7.87%</td>
<td>0.266 – 0.411</td>
</tr>
<tr>
<td>Number of transit compartments ($\eta_n$)</td>
<td>2.44 (156%)</td>
<td>13.7%</td>
<td>1.84 – 3.39</td>
</tr>
<tr>
<td>Covariance $\eta_{CL/F} \sim \eta_{V/F}$ (covariance &amp; correlation)</td>
<td>0.217 (0.947)</td>
<td>7.45%</td>
<td>0.186 – 0.267</td>
</tr>
</tbody>
</table>
### Interoccasional Variability (IOV, variances & %CV)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (Mean)</th>
<th>%CV</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral clearance ($k_{CL/F}$)</td>
<td>0.0508</td>
<td>22.5%</td>
<td>0.0413 – 0.0724</td>
</tr>
<tr>
<td>Mean transit time ($k_{MTT}$)</td>
<td>0.461</td>
<td>67.9%</td>
<td>0.401 – 0.590</td>
</tr>
</tbody>
</table>

### Residual variability

<table>
<thead>
<tr>
<th>Type</th>
<th>Value (Mean)</th>
<th>%CV</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additive error ($\varepsilon_{\text{add}}$, mg·L(^{-1}))</td>
<td>0.0923</td>
<td>5.41%</td>
<td>0.0790 – 0.103</td>
</tr>
<tr>
<td>Proportional error ($\varepsilon_{\text{ccv}}$)</td>
<td>0.222</td>
<td>2.89%</td>
<td>0.207 – 0.238</td>
</tr>
</tbody>
</table>

* Assessed by nonparametric bootstrap, $n=800$ iterations. Runs without successful conclusion (‘MINIMIZATION SUCCESSFUL’) omitted from analysis ($n=52$), 748 runs included in total.
Table IV. Comparison of model estimates of $AUC$ with reported values from the literature. PTB=pulmonary tuberculosis; $n$=sample size.

<table>
<thead>
<tr>
<th>Source</th>
<th>Population</th>
<th>Dosing</th>
<th>$n$</th>
<th>Type</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current study</td>
<td>South African PTB patients at steady state</td>
<td>Oral, by weight: 450/480 mg for $\leq 50$ kg, 600 mg for 50 kg+</td>
<td>261</td>
<td>$AUC_{0-24}$ (steady state model prediction, mg·h·L$^{-1}$)</td>
<td>30.7 (SD=13.2)</td>
</tr>
<tr>
<td>Choudhri et al, 1997</td>
<td>Kenyan PTB patients without HIV at steady state</td>
<td>Oral, by weight: 450 mg for $\leq 45$ kg, 600 mg for 45 kg+</td>
<td>15</td>
<td>$AUC_{0-12}$ (linear trapezoidal, mg·h·L$^{-1}$)</td>
<td>23.1 (SD=12.9)</td>
</tr>
<tr>
<td></td>
<td>Kenyan PTB patients with HIV at steady state</td>
<td>Oral, by weight: 450 mg for $\leq 45$ kg, 600 mg for 45 kg+</td>
<td>14</td>
<td>$AUC_{0-12}$ (linear trapezoidal, mg·h·L$^{-1}$)</td>
<td>19.6 (SD=10.6)</td>
</tr>
<tr>
<td>Gurumurthy et al, 2004</td>
<td>Indian PTB patients without HIV at steady state</td>
<td>Oral, 450 mg</td>
<td>13</td>
<td>$AUC_{0-\infty}$ (linear trapezoidal, mg·h·L$^{-1}$)</td>
<td>44.6 (range 36.3-52.9)</td>
</tr>
<tr>
<td></td>
<td>Indian PTB patients with HIV at steady state</td>
<td>Oral, 450 mg</td>
<td>15</td>
<td>$AUC_{0-\infty}$ (linear trapezoidal, mg·h·L$^{-1}$)</td>
<td>28.2 (range 18.1–38.4)</td>
</tr>
<tr>
<td>Loos et al, 1985</td>
<td>German PTB patients at steady state (mean weight</td>
<td>Oral, 600 mg</td>
<td>6</td>
<td>$AUC_{0-12}$ (linear trapezoidal, mg·h·L$^{-1}$)</td>
<td>60.3 (SD=33.4)</td>
</tr>
<tr>
<td></td>
<td>67 kg, range 50-82 kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perlman et al, 2005</td>
<td>North American PTB patients with HIV at</td>
<td>Oral, by weight: 450 mg for $\leq 50$ kg, 600 mg for 50</td>
<td>31</td>
<td>$AUC_{0-10}$ (3-point linear trapezoidal, mg·h·L$^{-1}$)</td>
<td>30.1 (CV=48.1%)</td>
</tr>
<tr>
<td>Study</td>
<td>Country/Region</td>
<td>Group Description</td>
<td>Dosage</td>
<td>AUC (0-24) AUC&lt;sub&gt;0-24&lt;/sub&gt; &lt;br&gt; (linear trapezoidal, mg·h·L&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>Reference</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------------------------</td>
<td>--------------------------------------------------------</td>
<td>----------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Ruslami et al, 2007 (57)</td>
<td>Indonesia</td>
<td>Indonesian PTB patients at steady state (mean weight 48.4 ± 6.9 kg)</td>
<td>Oral, 450 mg</td>
<td>24 48.5 (26.7–72.8) AUC&lt;sub&gt;0-24&lt;/sub&gt; &lt;br&gt; (linear trapezoidal, mg·h·L&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indonesian PTB patients at steady state (mean weight 47.3 ± 8.1 kg)</td>
<td>Oral, 600 mg</td>
<td>23 79.7 (38.7–138.1) AUC&lt;sub&gt;0-24&lt;/sub&gt; &lt;br&gt; (linear trapezoidal, mg·h·L&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td>Tappero et al, 2005 (63)</td>
<td>Botswana</td>
<td>Botswanan PTB patients without HIV at steady state</td>
<td>Oral, by weight: 450 mg for ≤ 50 kg, 600 mg for 50 kg+</td>
<td>20 34.7 (range 15.5-77.4) AUC&lt;sub&gt;0-12&lt;/sub&gt; &lt;br&gt; (extrapolated linear trapezoidal, mg·h·L&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Botswanan PTB patients with HIV at steady state</td>
<td>Oral, by weight: 450 mg for ≤ 50 kg, 600 mg for 50 kg+</td>
<td>41 36.3 (range 10.8-95.0) AUC&lt;sub&gt;0-12&lt;/sub&gt; &lt;br&gt; (extrapolated linear trapezoidal, mg·h·L&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td></td>
</tr>
</tbody>
</table>
$k_{tr} = (n + 1)/MTT$
Poor fit  Typical fit  Good fit

Time after dose (h)

Rifampin concentration (mg/L)

Typical individuals
Low $AUC_{0\rightarrow\infty}$
Atypical absorption
<table>
<thead>
<tr>
<th>Rifampicin concentration (mg/L)</th>
<th>Time after dose (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>450 mg</td>
<td>0 2 4 6 8 10 12</td>
</tr>
<tr>
<td>480 mg</td>
<td>0 2 4 6 8 10 12</td>
</tr>
<tr>
<td>600 mg</td>
<td>0 2 4 6 8 10 12</td>
</tr>
</tbody>
</table>

The graph shows the concentration of rifampicin over time for different doses of 450 mg, 480 mg, and 600 mg.