Population Pharmacokinetic Drug-Drug Interaction Pooled Analysis of Existing Data for Rifabutin and HIV-Protease Inhibitors

Stefanie Hennig*[1,2], Elin M Svensson[2], Ronald Niebecker[2], Bernard Fourie[3], Marc H. Weiner[4], Stefano Bonora[5], Charles A Peloquin[6], Keith Gallicano[7], Charles Flexner[8], Alex Pym[9], Peter Vis[10], Piero L Olliaro[11], Helen McIlleron[12], Mats O Karlsson[2]

1. School of Pharmacy, University of Queensland, Brisbane, Australia

2. Department of Pharmaceutical Bioscience, Uppsala University, Uppsala, Sweden

3. Department of Medical Microbiology, University of Pretoria, Pretoria, South Africa

4. Department of Medicine, University of Texas Health Science Center and Veterans Administration Medical Center, San Antonio, Texas, United States

5. Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy

6. College of Pharmacy and Emerging Pathogens Institute, University of Florida, Gainesville, Florida, United States

7. Novum Pharmaceutical Research Services, Murrieta, California, United States

8. Johns Hopkins Adult AIDS Clinical Trials Unit, Division of Clinical Pharmacology, Baltimore, Maryland, United States

9. Tuberculosis Research Unit, Medical Research Council and KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH), Durban, South Africa

[10.] Janssen Infectious Diseases BVBA, Beerse, Belgium (current affiliation: LAP&P Consultants BV, Leiden, The Netherlands)

[11.] Special Program for Research and Training in Tropical Diseases (TDR), World Health Organization (WHO), Geneva, Switzerland

[12.] Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa

Words: 4600

Tables: 7

Figures: 2

References: 77

Appendix: 2 tables, 1 figure

***Corresponding author**: Stefanie Hennig, School of Pharmacy, Pharmacy Australia Centre of Excellence (PACE), University of Queensland, 20 Cornwall Street, Woolloongabba QLD 4102, Australia

Phone: +61 7 334 61970 **Fax**: +61 7 334 61999 **E-mail**: s.hennig@uq.edu.au

Running title: Rifabutin Drug-Drug Interaction Pharmacokinetics

Keywords: rifabutin, pharmacometrics, tuberculosis, ritonavir, mixed-effect model

Synopsis

Objectives: Extensive but fragmented data from existing studies were used to describe the drug-drug interaction between rifabutin and HIV-protease inhibitors, and predict doses achieving recommended therapeutic exposure for rifabutin in patients with HIV-associated tuberculosis, with concurrently administered protease inhibitors.

Materials and Methods: Individual level data from 13 published studies were pooled, and a population analysis approach was used to develop a pharmacokinetic model for rifabutin, its main active metabolite 25-O-desacetyl rifabutin (des-rifabutin), and drug-drug interaction with protease inhibitors in healthy volunteers and patients who had HIV and tuberculosis (TB/HIV).

Results: Key parameters of rifabutin affected by drug-drug interaction in TB/HIV were clearance to routes other than des-rifabutin (reduced by 76%-100%), formation to the metabolite (increased by 224% in patients), volume of distribution (increased by 606%), and distribution to the peripheral compartment (reduced by 47%). For des-rifabutin, the clearance was reduced by 35% to 76% and volume of distribution increased by 67% to 240% in TB/HIV. These changes resulted in overall increased exposure to rifabutin in TB/HIV patients by 210% because of the effects of protease inhibitors and 280% with ritonavir-boosted protease inhibitors.

Conclusion: Given together with nonboosted or ritonavir-boosted protease inhibitors, rifabutin at 150 mg once daily results in similar or higher exposure compared with rifabutin at 300 mg once daily without concomitant protease inhibitors, and may achieve peak concentrations within acceptable therapeutic range. Although 300 mg

rifabutin every three days with boosted protease inhibitor achieves an average equivalent exposure, intermittent doses of rifamycins are not supported by current guidelines.

Introduction

Tuberculosis (TB) and human immunodeficiency virus (HIV) are major causes of mortality worldwide. In HIV-associated TB, concurrent antiretroviral treatment and TB treatment is associated with substantially reduced mortality compared to TB treatment alone.[1] However, for patients requiring HIV-protease inhibitors, combined treatment for HIV and TB is complicated by drug-drug interactions with the anti-TB rifamycins. Anti-TB regimens are better when they include a rifamycin, especially in HIV-infected patients,[2] and rifampicin is established in TB treatment programs worldwide. However, rifampicin potently induces the metabolism of protease inhibitors, necessitating dose adjustments, and there are concerns about the safety and efficacy of the currently used approaches.[3-10] The potential for drug interactions is high in HIV-infected patients who are treated with multiple drugs.

Rifabutin, an alternative to rifampicin, has the important advantage of not substantially affecting the concentrations of protease inhibitors[11]. Although rifabutin may be an effective anti-TB agent in patients treated concurrently with protease inhibitor-based antiretroviral therapy, the optimal dose and dose interval for rifabutin are unknown. Based on limited evidence,[12-15] a 50% to 75% dose reduction has been recommended when rifabutin is given concurrent with ritonavir-boosted protease inhibitors.[3] Furthermore, rifabutin concentrations may be lower in patients than healthy volunteers.[14,16] However, rifabutin has dose-related toxicity.[17,18] Serious toxicity including uveitis, polyarthralgia, polymyalgia, and neutropenia may occur in patients treated with high doses, especially in association with enzyme inhibitors that may cause

disproportionate increase in the concentrations of rifabutin metabolites such as 25-O-desacetyl rifabutin (des-rifabutin).[11,19,20]

Des-rifabutin predominates among several metabolites of rifabutin, is formed by arylacetamide deacetylase, and has activity similar to the parent compound.[21] In healthy volunteers, plasma des-rifabutin:rifabutin area under the curve (AUC) ratio is 0.1 in the absence of inhibitors.[22,23] Rifabutin is extensively distributed to the tissues because it has a wide volume of distribution and long half-life (> 30 h) in HIV-infected patients.[24] Rifabutin also has high between-subject variability (BSV) in its pharmacokinetics (coefficient of variation (CV)% for clearance, 32%).[25] Therefore, the impact of dose interval and inhibition of its metabolism by protease inhibitors on the steady state pharmacokinetics of the drug in plasma and tissues is of relevance to understand pharmacokinetic-pharmacodynamic relations.

A population pharmacokinetic analysis approach can be used to analyze retrospectively collected data in a pooled analysis (meta-analysis) [26-28] and relations between demographics and parameter can be identified. The purpose of the present study was to characterize the pharmacokinetics of rifabutin and its main metabolite des-rifabutin in the presence of several different protease inhibitors, using a population pooled analysis approach to combine extensive but fragmented information from existing studies to model the pharmacokinetics of rifabutin concentrations in TB/HIV patients treated concurrently with protease inhibitors, and to determine the optimal dose and dose interval of rifabutin for prospective studies.

Patients and Methods

Data collection

In October 2009, a search was performed on PubMed and Google that identified 29 publications (abstracts and peer-reviewed papers)[11,14,16-19,24,25,29-49] for a global analysis of rifabutin pharmacokinetics. In 14 publications (48%), the interactions with protease inhibitors were studied. To evaluate the difference in pharmacokinetics and interaction with protease inhibitors between TB and/or HIV patients and healthy volunteers, 8 publications were identified that established the pharmacokinetics of rifabutin in healthy volunteers[11,19,32,35,37,38,44,49] and 16 publications were identified that reported the pharmacokinetics of rifabutin in TB patients with HIV (TB/HIV) or without HIV infection, or HIV patients without TB infection.[14,16,24,25,30,31,33,34,36,37,39-43,50] Parent-metabolite relations between rifabutin and des-rifabutin were evaluated in 6 publications including healthy volunteers[11,19,35,37,38,49] and 9 publications including TB and/or HIV patients[30,33,34,36,40-43,47]. The authors of the 29 identified publications were approached in 2009 and 2010 to contribute data to this pooled analysis. Pharmaceutical companies also were approached to contribute data from drug-drug interaction studies that were not published in the public domain. Raw data from all individuals who participated in the existing studies were requested from the collaborating authors and companies. All studies previously had undergone ethical review and had been approved by institutional review boards. Information about identity of participants of the previous studies was removed to make the data anonymous before data were transferred to our analysts (SH, ES, RN). From these data sets, we extracted rifabutin and des-rifabutin concentrations, doses and times of drug administration, patient characteristics, and information about

coadministration with protease inhibitors. Observations were defined as either a rifabutin or des-rifabutin concentration measurement after a given dose and all observations within the same dosing interval were grouped as one occasion. Subsequent literature searches were performed until May 2015 for additional data sources, but data inclusion was stopped in 2011 to enable consistent model building.

Population pharmacokinetic pooled analysis

The population approach pooled analysis was based on collection of individual patient data from the different studies pooled into a single database. This enabled analysis of the combined data in a new population pharmacokinetic model.

A nonlinear mixed-effect modeling approach was performed with software (NONMEM 7.2.0 to 7.3.0, ICON, Dublin, Ireland;[51] Perl-speaks-NONMEM , PsN, Uppsala, Sweden, version 4.2.0 to 4.2.2, http: //psn.sourceforge.net[52]) to derive population mean and variance for all pharmacokinetic parameters. Pharmacokinetic models were fitted to concentration-time data with standardized population pharmacokinetic methods.[53] NONMEM analyses were performed using the first-order method to increase speed of model development and the first-order conditional estimation method with interaction for the final stages. Nested models were hypothesis-tested using the likelihood ratio test in which the change in objective function value (OFV) approximated the χ^2 distribution ($\chi^2_{1,0.001} > 10.828$) and non-nested models were compared with the Akaike information criterion. Visual predictive checks with prediction and variability correction (pvcVPC)[54] were used as a diagnostic tool throughout the analysis.

The model-building strategy was based on a previously published model that was developed from a smaller data set.[55] The initiating model for the present analysis used 2-compartment disposition for both rifabutin and des-rifabutin with first-order clearance parameterized in terms of apparent oral clearance of rifabutin by routes other than des-rifabutin (CL/F), apparent oral metabolism clearance of des-rifabutin (CL_e/F), apparent oral clearance of des-rifabutin ($CL_m/F/F_m$), volume of distribution of the central compartment and the peripheral compartment for rifabutin (V2 and V3) and des-rifabutin (V4 and V5), and intercompartmental clearance rate for rifabutin (Q) and des-rifabutin (Q_m). This model used first-order absorption parameterized as the rate constant of absorption (k_a) after a lag time and included a first-pass metabolism fraction (F_m) to des-rifabutin. The metabolism from parent to metabolite was included as apparent oral metabolism clearance of rifabutin into a metabolite compartment. The CL_m and V4 were adjusted with the molecular weight to account for the difference in size between the 2 molecules.

Between-subject variability terms, with covariance, were tested on all parameters using exponential models. The covariance terms were evaluated on a linearized version of the model and included in the nonlinear model when significant.[56] The relative bioavailability (F) varied for each individual between sampling occasions, given the same overall variance for each occasion.[57] The residual unexplained variability model was additive for logarithm-transformed concentration data, separately for rifabutin and des-rifabutin, corresponding to proportional error on untransformed data.

In the initial drug-drug-interaction model, the interaction with protease inhibitors was modeled as present or absent, depending on whether protease inhibitor

coadministration occurred. The changes to the model with protease inhibitor coadministration initially included a decrease in CL and CL_m, with both these interactions strengthened when an ritonavir -boosted protease inhibitor was given. Further parameter changes with protease inhibitor coadministration were evaluated, allowing additional effects of ritonavir -boosting and different effects for healthy volunteers and TB/HIV patients. Aside from protease inhibitor coadministration, other covariates available for testing included body weight (WT), age, and sex for TB/HIV subjects versus healthy volunteers. The WT was included on all disposition parameters a priori using allometric scaling.[58] All other covariate parameter relations were included as proportional on/off changes for categorical covariates or linear relations for continuous covariates. Parameter precision was obtained from a limited nonparametric bootstrap stratified by study, and for studies with several arms, stratified by arm.

Final estimated model parameters were used to calculate the expected average steady-state concentrations (C_{av_ss}) for rifabutin using equation 1 to identify dosing regimens that provided an exposure > 4.5 mg·h/L (AUC_{0-24})[30,34] or 0.187 mg/L (C_{av_ss}), which previously was associated with acquired rifamycin resistance. The parameter C_{av_ss} was calculated using equation 1 and was transformed to an AUC for specific dosing intervals (tau) using equation 2, where CL_e is the systemic metabolism clearance to des-rifabutin:

$$C_{av\_ss} = (F \cdot [1\text{-}F_m] \cdot [Dose/tau])/(CL+CL_e) \quad (1)$$

$$AUC_{tau} = C_{av\_ss} \cdot tau \quad (2)$$

Steady state peak concentration (C_{max_ss}) for rifabutin and des-rifabutin were predicted from the final model using software (Berkeley Madonna, Version 8.3.18, Kagi, Berkeley, CA, USA).

Results

Data obtained

There were 9 collaborator teams that contributed 13 data sets that were published previously.[14,16,17,19,29,34,36,37,59,60] Furthermore, 3 data sets that were described previously in internal reports or conference proceedings were contributed from pharmaceutical companies.[55,61-63]

The combined data set used for the pharmacokinetic analysis of rifabutin and des-rifabutin, with and without coadministration of protease inhibitors, contained data from 251 subjects (mean age, 36.4 years; 188 male [75%]; 163 HIV-infected [65%]; 144 HIV-infected patients who had TB [57.3%]), totaling 7749 pharmacokinetic observations. The demographic details available varied between different studies, but all studies provided information about whether the subject was a healthy volunteer, had HIV-infection, or had TB (Table 1). There was no information available about other concomitantly given drugs in TB patients who had HIV (TB/HIV) patients, such as azoles and clarithromycin with known interaction, except for protease inhibitors, and there were no toxicity data available.

Details of the design of the different studies that contributed data were available from the publications.[14,16,19,29,34,36,37,55,59,60,62-64] Data points were not included in the combined data set when details were missing about dose, time of observation, concentration, study arm, or protease inhibitor coadministration. Rifabutin and des-rifabutin pharmacokinetic observations were available after administration of rifabutin alone (without protease inhibitors) in 235 and 191 subjects, and varied numbers of patients contributed observations after administration of rifabutin with various protease

Table 1. Demographic Characteristics of the Study Subjects Who Had Rifabutin and 25-O-desacetyl Rifabutin Concentrations Measured, Total Number of Subjects in the Data Set was 251.

Characteristic	Number of Subjects n (%) out of 251 Subjects Who Had Missing Information on That Charateristic	Number of Subjects n (%) out of 251 Subjects in Data Set With This Characteristic
Tuberculosis	0 (0)	144 (57.3)
HIV	0 (0)	163 (65.3)
Healthy volunteer	0 (0)	87 (34.7)
TB/HIV		141 (56.2)
Sex (female/male)	14 (5.6)	48 (19.0) /188 (75.4)
Race (white/black/other/Hispanic)	76 (30.3)	57 (22.7) /75 (30.0) /4 (1.5) /39 (15.5)
Weight (kg)	33 (13.1)	68 ± 14 (40.8-119.7)
Age (y)	14 (5.6)	36 ± 9 (18.0-67.0)
Height (cm)	52 (20.7)	170 ± 11 (135.0-198.0)
CD4+ count in HIV patients (cells/μL)	139 (55.5)	217 ± 51 (11.0 - 928.0)

Data reported as number (% of total) or mean ± SD (range, minimum to maximum).
Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis; TB/HIV, tuberculosis and HIV.

Table 2. Patients and Rifabutin and 25-O-desacetyl Rifabutin Pharmacokinetic Measurements Contributing to the Pooled Analysis

Pharmacokinetic Observation	**Rifabutin, n (%)**	**Des-Rifabutin, n (%)**
Number of patients	251	235 (93.6)
Patients with data when rifabutin was not coadministered with protease inhibitor	235 (93.6)	191 (76.1)
Patients with data when rifabutin was coadministered with protease inhibitor	136 (54.1)	122 (48.6)
Yes	79 (31.4)	75 (29.8)
No	57 (22.7)	47 (18.7)
Protease inhibitor used		
Ritonavir	5 (1.9)	5 (1.9)
Darunavir/r	13 (5.1)	13 (5.1)
Saquinavir/r	19 (7.5)	18 (7.2)
Indinavir	22 (8.7)	22 (8.7)
Lopinovir/r	41 (16.3)	39 (15.5)
Nelfinavir	35 (13.9)	25 (9.9)
Amprenavir/r	1 (0.4)	0 (0)
Total number of observations	4168	3581 (85.9)
Observations when rifabutin was not coadministered with protease inhibitor	2046 (49.1)	1682 (40.4)
Observations when rifabutin was coadministered with protease inhibitor	2122 (50.9)	1899 (45.5)
Yes	1365 (32.7)	1299 (31.2)
No	757 (18.1)	600 (14.4)
Protease inhibitor used		
Ritonavir	60 (1.4)	60 (1.4)
Darunavir/r	178 (4.2)	178 (4.2)
Saquinavir/r	562 (13.5)	533 (12.7)
Indinavir	465 (11.2)	465 (11.2)
Lopinovir/r	558 (13.4)	528 (12.6)
Nelfinavir	292 (7.0)	135 (3.2)
Amprenavir/r	7 (0.2)	0 (0)

*Data reported as number of patients (% of total) and pharmacokinetic measurements.
Abbreviation: /r, ritonavir-boosted.

inhibitors (Table 2). Fewer subjects contributed rifabutin and des-rifabutin observations with than without coadministration with a protease inhibitor due to higher frequency of dropout in the coadministration arm of several studies. A total of four (2%) patients, 51 (1.2%) rifabutin and 155 (4.3%) des-rifabutin concentrations were removed from the contributing studies because of incomplete information.

Rifabutin alone was administered as a 150-mg dose once daily in 39 subjects and every three days in 1 subject, as a 300-mg dose once daily in 107 subjects, once off in 4 subjects, every second day in 10 subjects, once weekly in 11 subjects and every three days in 55 subjects, as a 450-mg dose every three days in 1 subject; and as a 600-mg dose every three days in 7 subjects. Rifabutin was administered as a 150-mg dose once daily in 42 subjects and every three days in 7 subjects together with either ritonavir, DRV/r, SQV/r, IND, or LPV/r; as a 300-mg dose once daily in 10 subjects, once weekly in 10 subjects, every two days in 8 subjects and every three days in 27subjects together with SQV/r, IND, LPV/r, NEF, or AMP/r; and as a 600-mg dose every three days in 1 subject together with IND and in 1 subject together with NEF. Observations were measured in patients mainly (89%) during 3 occasions.

Population pharmacokinetic pooled analysis

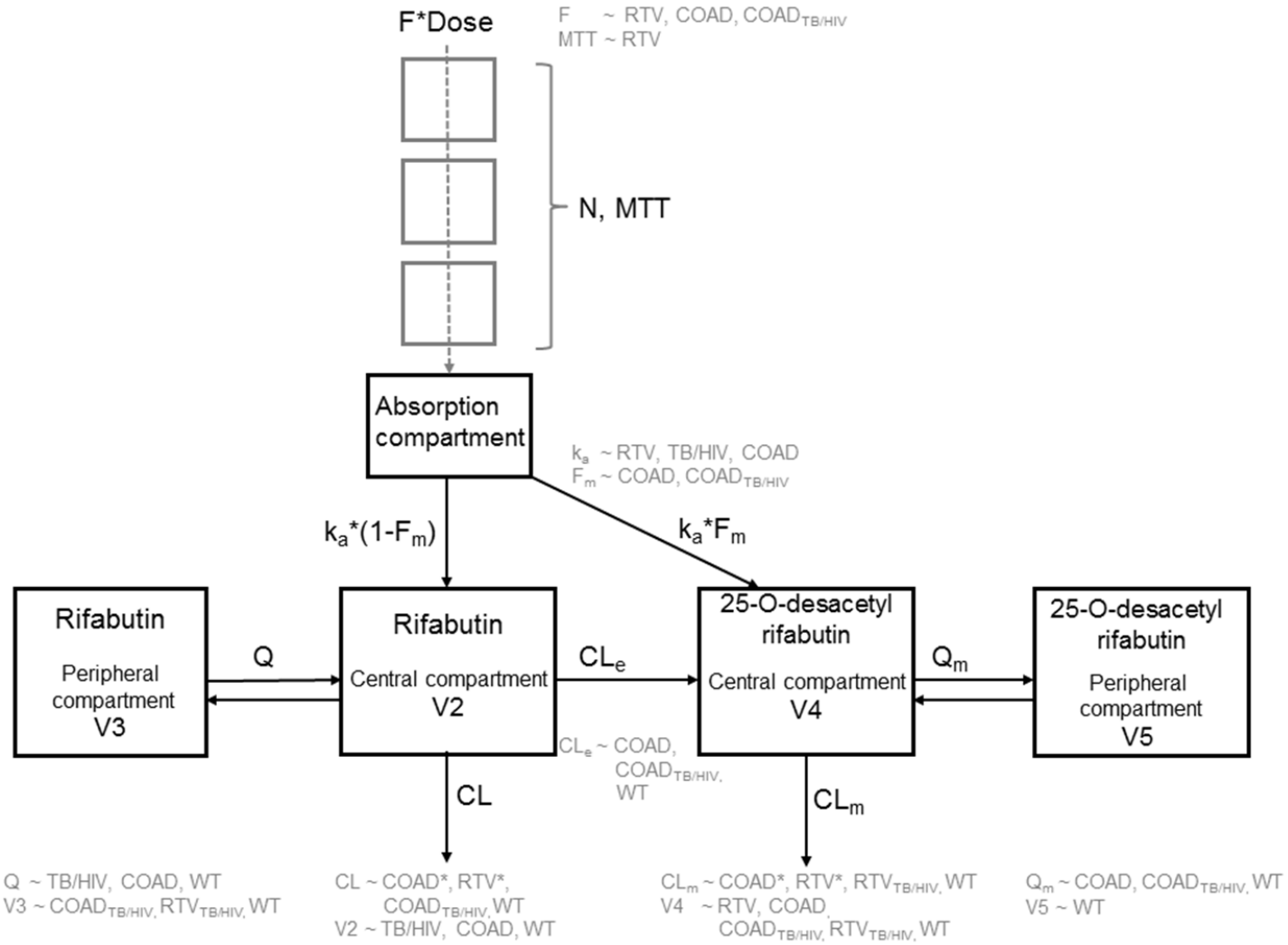
Structural and variance

For structural additions to the initial model (Figure 1), the main extension was the inclusion of a transit compartment model described by number of transit compartments (N) and mean transit time (MTT) instead of a lag-time parameter to describe the absorption of rifabutin (OFV drop, -637 points; degrees of freedom, 1). The variance structure was changed from a complex stochastic model with different between-subject

Figure 1: Schematic of the Final Pharmacokinetic Model For Rifabutin, Des-Rifabutin, and Protease Inhibitors, Including All Parameters and Covariates Associated With Specific Parameters. Parameters affected by drug interaction with protease inhibitors are highlighted in red. Covariate relations were included before performing lin-SCM. All disposition parameters were allometrically scaled with the factor $F_{CLWT} = (WT/70)^{0.75}$ on all clearance parameters and $F_{VWT} = WT/70$ on all volume parameters.

***Abbreviations*:** CL, systemic clearance of rifabutin to other routes than to des-rifabutin; CL_e, systemic metabolism to 25-O-desacetyl rifabutin; CL_m, systemic clearance of 25-O-desacetyl rifabutin; COAD, coadministration with a protease inhibitor; $COAD_{TB/HIV,}$ coadministration with a protease inhibitor in TB/HIV patients; F, bioavailability; F_m, fraction first-pass metabolism; TB/HIV, patients with HIV and TB; k_a, absorption rate constant; MTT, mean transit time; N, number of transit compartments; Q, intercompartmental clearance rate for rifabutin; Q_m, intercompartmental clearance rate for des-rifabutin; RTV, coadministration with ritonavir or ritonavir-boosted protease inhibitor; $RTV_{TB/HIV,}$ coadministration with ritonavir or ritonavir-boosted protease inhibitor in TB/HIV patients; TB, tuberculosis; V2, volume of distribution central compartment rifabutin; V3, volume of distribution peripheral compartment rifabutin; V4, volume of distribution central compartment des-rifabutin; V5, volume of distribution peripheral compartment des-rifabutin; WT, total body weight.

Figure 1


F*Dose
F ~ RTV, COAD, COAD$_{TB/HIV}$
MTT ~ RTV
N, MTT
Absorption compartment
k_a ~ RTV, TB/HIV, COAD
F_m ~ COAD, COAD$_{TB/HIV}$
$k_a*(1-F_m)$
k_a*F_m
Rifabutin
Peripheral compartment
V3
Q
Rifabutin
Central compartment
V2
CL_e
25-O-desacetyl rifabutin
Central compartment
V4
Q_m
25-O-desacetyl rifabutin
Peripheral compartment
V5
CL_e ~ COAD, COAD$_{TB/HIV}$, WT
CL
CL_m
Q ~ TB/HIV, COAD, WT
V3 ~ COAD$_{TB/HIV}$, RTV$_{TB/HIV}$, WT
CL ~ COAD*, RTV*, COAD$_{TB/HIV}$, WT
V2 ~ TB/HIV, COAD, WT
CL_m ~ COAD*, RTV*, RTV$_{TB/HIV}$, WT
V4 ~ RTV, COAD, COAD$_{TB/HIV}$, RTV$_{TB/HIV}$, WT
Q_m ~ COAD, COAD$_{TB/HIV}$, WT
V5 ~ WT

variability for different subpopulations (e.g. HIV patient data were more variable than data from healthy volunteers) to a full correlation matrix and between-subject variability on all structural model parameters, which resulted in a significantly improved model (OFV drop, -918; degrees of freedom, 65). Between-subject variability was not included for parameters describing parameter-covariate relations. The pharmacokinetics of rifabutin was highly variable, with between-subject variability on parameters usually > 50%.

Covariate and drug-drug interaction

The effect of coadministration with a protease inhibitor was retained from the initial model on CL and CL_m and extended by differentiating this effect for ritonavir-boosted and nonboosted protease inhibitors. Age and sex had no significant effect on any parameters during first lin-SCM. In second lin-SCM, the following covariates were tested on all structural parameters: coadministration with a protease inhibitor, ritonavir-boosting, and TB/HIV versus healthy volunteers, with some of these effects specific for TB/HIV patients compared with healthy volunteers, and covariate-parameter relations were included in the final model (Figure 1). The final parameter estimates and full variance-covariance matrix from the final model were determined (Table S1 and S2). To account for the complexity of the model and facilitate the interpretation of the parameters, estimates were translated into parameter values for healthy volunteers and TB/HIV patients when rifabutin was administered alone, together with a nonboosted protease inhibitor, or an ritonavir-boosted protease inhibitor (Table 3). The model described pharmacokinetic results comparable to results of previous studies[24,65] and predicted a terminal half-life of 34 h rifabutin in healthy volunteers and 29 h in TB/HIV

Table 3. Pharmacokinetic Parameter Estimates For Rifabutin and 25-O-desacetyl Rifabutin in the Final Model With and Without Drug-Drug-Interaction With Protease Inhibitors

Parameter	**Units**	**Rifabutin Alone**		**Rifabutin with Nonboosted Protease Inhibitor**		**Rifabutin with RTV-Boosted Protease Inhibitor**	
		Healthy Volunteer	**TB/HIV**	**Healthy Volunteer**	**TB/HIV**	**Healthy Volunteer**	**TB/HIV**
Rifabutin							
Apparent oral clearance to routes other than des-rifabutin, CL/F	L/h/70 kg	58.80	58.80	13.88	0.00	12.00	0.00
Apparent oral metabolism clearance to des-rifabutin, CL_e/F	L/h/70 kg	5.76	5.76	8.65	18.68	8.65	18.68
Central volume of distribution, V2/F	L/70 kg	6.55	4.59	46.30	32.44	46.30	32.44
Absorption rate constant, k_a	/h	0.25	0.23	0.28	0.26	0.14	0.13
Mean transit time, MTT	h	2.16	2.16	2.16	2.16	1.49	1.49
Number of transit compartments, N		7.15	7.15	7.15	7.15	7.15	7.15
Bioavailability, F		0.97	0.97	1.03	0.60	1.38	0.80
Peripheral volume of distribution, V3/F	L/70 kg	1580	1580	1580	571.9	1580	1395.6
Intercompartmental clearance, Q/F	L/h/70 kg	62.61	90.08	33.24	47.82	33.24	47.82

Des-rifabutin							
Apparent oral clearance, $CL_m/F/F_m$	L/h/70 kg	122.00	122.00	79.06	79.06	8.78	28.81
Central volume of distribution, $V4/F/F_m$	L/70 kg	37.30	37.30	91.01	126.78	31.58	62.56
Intercompartmental clearance, $Q_m/F/F_m$	L/h/70 kg	71.80	71.80	25.06	74.17	25.06	74.17
Peripheral volume of distribution, $V5/F/F_m$	L/70 kg	1220	1220	1220	1220	1220	1220
First-pass metabolism fraction, F_m		0.09	0.09	0.05	0.10	0.05	0.10

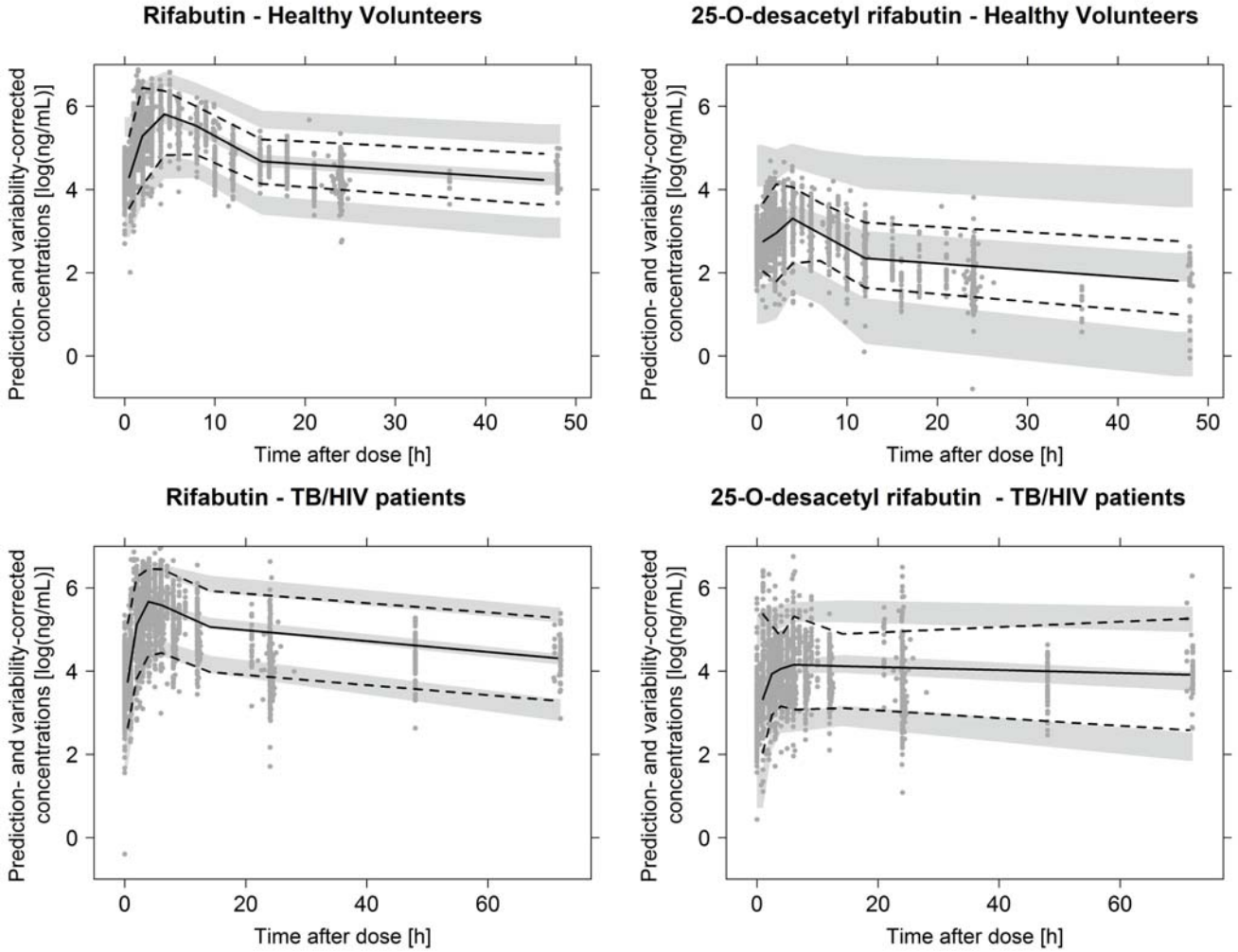
Abbreviations: CL, systemic clearance of rifabutin to routes other than des-rifabutin; CL_e systemic metabolism to 25-O-desacetyl rifabutin; CL_m, systemic clearance of 25-O-desacetyl rifabutin; F, bioavailability; F_m, fraction first-pass metabolism; TB/HIV, patients with HIV and TB infection (yes, 1; no, 0); k_a, absorption rate constant; MTT, mean transit time; N, number of transit compartments; Q, intercompartmental clearance rate for rifabutin; Q_m, intercompartmental clearance rate for des-rifabutin; TB, tuberculosis; V2, volume of distribution central compartment rifabutin; V3, volume of distribution peripheral compartment rifabutin; V4, volume of distribution central compartment des-rifabutin; V5, volume of distribution peripheral compartment des-rifabutin.
All disposition parameter were allometrically scaled with the factor $F_{CLWT} = (WT/70)^{0.75}$ on all clearance parameters and $F_{VWT} = WT/70$ on all volume parameters.

patients. The effects of the drug-drug interaction with protease inhibitors on rifabutin and des-rifabutin pharmacokinetic parameters were converted to percent reduction or increase of the parameter value compared with the parameter values without protease inhibitor coadministration (Table S3). Pharmacokinetic parameters for rifabutin and des-rifabutin were similar between healthy volunteers and TB/HIV patients when rifabutin was taken alone, except for a smaller volume of distribution for the patient population. When rifabutin was coadministered with a protease inhibitor, most parameters were changed by > 20% (comparison of parameters in Table 3, Table S3). Most importantly, rifabutin coadministration with a protease inhibitor caused a CL decrease by > 76%, V2 increase 6-fold, Q decrease by 47%, and transformation to des-rifabutin increase by 50% in healthy volunteers and 224% in patients. The increase in apparent oral metabolism clearance to des-rifabutin could be caused by a reduced sequential metabolism in the presence of PIs. Des-rifabutin had a decrease in CL_m by 35% when rifabutin was coadministered with a nonboosted protease inhibitor and > 76% when rifabutin was given with an ritonavir-boosted protease inhibitor; an increase in V4 by > 67% for patients; and decrease in Q_m and F_m.

Model evaluation

The pvcVPC for the final model was stratified to present data for healthy volunteers and patients separately (Figure 2). The pvcVPC showed that the model adequately described the average exposure over time for both rifabutin and des-rifabutin. The description of rifabutin and des-rifabutin pharmacokinetics and variability in TB/HIV patients was adequate. A more detailed pvcVPC stratified for coadministration with nonboosted and ritonavir-boosted protease inhibitors showed that the model

Figure 2: Prediction- and variability-corrected visual predictive check (pvcVPC) for rifabutin (left) and 25-O-desacetyl rifabutin (right) for the final model. The pvcVPC was stratified to present data separately for healthy volunteers (top panels) and patients (TB/HIV, bottom panels). The raw data are represented as grey dots. The upper, middle, and lower red lines represent the 95th, 50th, and 5th percentile of the observations. The grey shaded areas are the 90% confidence interval for the 95th, 50th, and 5th percentile of the simulated data.



adequately described the average exposure over time of all subgroups; patient data were better characterized by the model than healthy volunteer data, in which model-predicted variability exceeded observed variability (Figure S1).

Estimates of parameter precision for the final model were obtained using a limited bootstrap method. The analysis was limited to 13 bootstrap samples owing to long runtimes (1 estimation parallelized on 32 cores obtained stable OFV in 10 days). The relative standard errors for most parameters were < 20%, except for some covariate-parameter relation parameters such as V2 and HIV, k_a and coadministration with protease inhibitors and HIV, F and coadministration with protease inhibitors, F and coadministration with ritonavir-boosted protease inhibitors, Cl_e and coadministration with protease inhibitors, F_m and coadministration with protease inhibitors in HIV, and V4 and coadministration with protease inhibitors (Table S1).

Dose recommendations

The final model parameters were used to calculate the expected average steady-state concentration (C_{av_ss} [mg/L]) for rifabutin (Table 4) and model-predicted steady-state peak concentrations (C_{max_ss}) for rifabutin and des-rifabutin (Table 5) for a selection of dosing regimens when administered alone or together with protease inhibitors. These parameters were compared with reported pharmacokinetic values for rifabutin and the applied dosing schedules (Table S4)[11-16,19,20,25,31,33-38,49,55,65-70]. The expected C_{av_ss} after rifabutin (300 mg once daily) alone determined with the model was 0.17 mg/L for a typical patient or healthy volunteer, corresponding to an AUC_{0-24} of 4.08 mg·h/L. The rifabutin dosing regimen that matched the exposure of a 300-mg daily dose without protease inhibitor was 150 mg once daily for patients (300 mg every 3 days for healthy

Table 4. Relation Between Rifabutin Dosing Regimen, Use of Protease Inhibitors, and Expected Average Steady-State Rifabutin Concentration*

Rifabutin Dosing Regimen	Rifabutin Alone		Rifabutin With Nonboosted Protease Inhibitor		Rifabutin With RTV-Boosted Protease Inhibitor	
	Healthy Volunteer	TB/HIV	Healthy Volunteer	TB/HIV	Healthy Volunteer	TB/HIV
300 mg QD	0.17	0.17	0.55	0.36	0.80	0.48
150 mg QD	0.08	0.08	0.27	0.18	0.40	0.24
150 mg Q2D	0.04	0.04	0.14	0.09	0.20	0.12
300 mg Q3D	0.06	0.06	0.18	0.12	0.27	0.16
Alternating 150 mg & 300 mg Q2D	0.06	0.06	0.20	0.13	0.30	0.18

*Data reported as average steady-state rifabutin concentration, C_{av_ss} (mg/L). ***Abbreviations***: TB/HIV, patients with HIV and TB infection (yes, 1; 0, no); QD, once daily; Q2D, every 2 days; Q3D, every 3 days; RTV, ritonavir; TB, tuberculosis.

volunteers) when coadministered with a nonboosted protease inhibitor and 300 mg every 3 days for patients (150 mg every 2 days for healthy volunteers) when given with an ritonavir-boosted protease inhibitor. A target $C_{av\_ss} \geq 0.187$ mg/L ($AUC_{ss,0\text{-}24}$, 4.5 mg·h/L)[30,34] for the typical patient was best achieved using a dosage of 150 mg once daily when given together with a nonboosted protease inhibitor or alternating doses of 150 and 300 mg every second day when given together with an ritonavir-boosted protease inhibitor.

Model-predicted steady-state peak concentrations (C_{max_ss}) for rifabutin and des-rifabutin after rifabutin 300 mg once daily alone were 0.43 mg/L and 0.37 mg/L for the typical healthy volunteer and patient (Table 5), consistent with results of published reports (Table S4).[71] To reach a similar C_{max_ss} when administered with a nonboosted protease inhibitor or an ritonavir-boosted protease inhibitor, a 50% reduction in the daily dose of rifabutin to 150 mg once daily would be required. The time to achieve the C_{max_ss} was 3.5-fold longer with ritonavir-boosted protease inhibitor coadministration than with nonboosted protease inhibitors. Substantial accumulation of des-rifabutin was noted with the rifabutin C_{max_ss} to des-rifabutin C_{max_ss} ratio decreasing from 10:1 with rifabutin alone, to 5:1 when coadministered with a nonboosted protease inhibitor, and 2:1 when coadministered with an ritonavir-boosted protease inhibitor. A combined rifabutin and des-rifabutin $C_{max\_ss} > 1$ mg/L,[40] the suggested threshold for greater risk of adverse drug reactions, would be uncommon in TB/HIV patients unless the dosage was 300 mg once daily together with ritonavir-boosted protease inhibitors (Table 5).

Table 5. Relation Between Rifabutin Dosing Regimen, Use of Protease Inhibitors, and Expected Steady-State Rifabutin and 25-O-desacetyl Rifabutin Peak Concentration*

Rifabutin Dosing Regimen	Rifabutin Alone				Rifabutin With Nonboosted Protease Inhibitor				Rifabutin With RTV-Boosted Protease Inhibitor			
	Rifabutin		Des-Rifabutin		Rifabutin		Des-Rifabutin		Rifabutin		Des-Rifabutin	
	Healthy Volunteer	TB/HIV	Healthy Volunteer	TB/HIV	Healthy Volunteer	TB/HIV	Healthy Volunteer	TB/HIV	Healthy Volunteer	TB/HIV	Healthy Volunteer	TB/ HIV
300 mg QD	0.43	0.37	0.04	0.04	1.16	0.64	0.13	0.13	1.26	0.69	0.97	0.39
150 mg QD	0.22	0.18	0.02	0.02	0.58	0.32	0.06	0.07	0.63	0.35	0.48	0.20
150 mg Q2D	0.19	0.16	0.02	0.02	0.50	0.25	0.05	0.05	0.49	0.25	0.29	0.11
300 mg Q3D	0.38	0.30	0.04	0.03	0.94	0.47	0.10	0.08	0.89	0.44	0.46	0.17

*Data reported as average steady-state rifabutin or des-rifabutin peak concentration, C_{max_ss} (mg/L). ***Abbreviations***: des-rifabutin, 25-O-desacetyl rifabutin; TB/HIV, patients with HIV and TB infection (yes, 1; 0, no); QD, once daily; Q2D, every 2 days; Q3D, every 3 days; RTV, ritonavir; TB, tuberculosis.

Discussion

The results showed a successful pharmacokinetic model for rifabutin and des-rifabutin including covariates together with a drug-drug interaction model for coadministration with protease inhibitors using the extensive but fragmented data from existing studies. The model-based population pooled analysis successfully described the pharmacokinetics and the variability of rifabutin and des-rifabutin exposure in patients with HIV-associated TB and healthy volunteers. The pharmacokinetics of rifabutin and des-rifabutin were found to be highly variable between subjects, and WT was the only patient characteristic that explained some of the variability. The pharmacokinetic parameters were more variable in patients than healthy volunteers (Figure S1). Wide pharmacokinetic variability has been reported previously (Table S4). The reported pharmacokinetic values varied between studies. Reports of differences in exposure between healthy volunteers and TB/HIV patients had caused uncertainty in optimal drug dosing in patients who required concomitant anti-TB and HIV treatment. We have here presented results for both healthy volunteers and TB/HIV coinfected patients (Table 3-5, Table S3), which should support decisions for future clinical trials.

This pooled analysis showed that the average exposure was similar in patients and healthy volunteers when rifabutin was given alone. When protease inhibitors or ritonavir-boosted protease inhibitors were coadministered with rifabutin, the exposure in patients to rifabutin was decreased by 65% and 60% compared with exposure in healthy volunteers (Table 4). Literature review showed no previous study that evaluated the pharmacokinetics of rifabutin simultaneously in healthy volunteers and TB/HIV patients, but this pooled analysis of data from both groups enabled estimation of the differences.

The present model predicted that a decrease of 50% or 67% rifabutin dose is required when rifabutin is coadministered with a nonboosted or an ritonavir-boosted protease inhibitor, consistent with previous studies. The dosing regimens suggested for coadministration with a protease inhibitor matched the exposure after rifabutin 300 mg once daily alone. A typical patient receiving rifabutin 300 mg daily without protease inhibitors would have exposure slightly below the suggested lower limit ($AUC_{0\text{-}24} > 4.5$ mg/L).[30,34] However, half of the patients may have rifabutin exposure below the exposure required to avoid acquired rifamycin resistance. Similarly, both suggested doses, when given together with a protease inhibitor, would provide exposure slightly below the target minimum exposure. To recommend alternative dosages, new formulations and strengths of rifabutin need to be made available. Other studies have reported average exposures below $AUC_{0\text{-}24} > 4.5$ mg/L after rifabutin 300 mg once daily in patients[13,15,16,31,37] (Table S4). The predicted C_{max_ss} for the average TB/HIV patient after the typical adult dose of rifabutin 300 mg once daily is slightly below the proposed lower limited of 0.45 mg/L.[30,71] The same was predicted for a dosage of rifabutin 150 mg once daily together with nonboosted or ritonavir-boosted protease inhibitors. Achieving peak concentrations within the range 0.45 to 0.9 mg/L in more than half of the patients would require new formulations, such as 100-mg or 200-mg capsules, and additional studies would be required to evaluate new dosages or formulations.

There is clinical concern about intermittent dosing for rifabutin because of the risk of therapeutic failure caused by selection of resistance in patients who have low CD4 counts and disseminated bacillary burden such as HIV-positive patients, which is markedly higher than in HIV-negative patients with pulmonary TB. Therefore, rifabutin

exposure requirements may not be the same in these two patient groups: a higher number of bacilli may be associated with a higher probability of selection of naturally resistant mutants. Furthermore, HIV patients frequently present with low compliance owing to the complexity of their treatment. Dosing complexity increases with intermittent rifabutin dosing, and risk of resistance may increase therapeutic failure in sicker patients compared with patients who have more immune system support or patients during maintenance treatment. Intermittent dosing may be more adequate in HIV-negative patients to avoid adverse events. Dosing of rifabutin may be adapted to the disease status of the patients.

The clinical concern about intermittent dosing of rifabutin is matched by current guidelines from the United States Centers for Disease Control and Prevention,[3] which recommend that rifabutin 150 mg once daily should be given with an ritonavir-boosted protease inhibitor in adults. However, there are limited safety data with this dosage and combination, and it is unknown whether the increase in concentration of rifabutin and des-rifabutin that may result from this dosage may cause increased risk of developing uveitis, neutropenia, or hepatotoxicity; patients taking this combination should be monitored for rifabutin-related toxicities.[19] Limited data are available about the exposure-toxicity relationship, suggesting that the dosage should be decreased when peak concentrations (or the combined concentration of rifabutin and des-rifabutin) are > 1 mg/L.[40,71] The present model predicts that this potentially toxic peak concentration may occur for patients who receive rifabutin 300 mg once daily together with an ritonavir-boosted protease inhibitor (Table 5), and may be problematic for healthy volunteers in future clinical trials under several protease inhibitors coadministered dosing regimens. The upper boundary has not been confirmed, and serious toxicity may be common with

rifabutin dosages 150 mg 3 times/week to daily.[13,72] When considering the suggested dosages, which aim to match the exposure after a 300 mg once daily rifabutin dose alone and the minimum exposure target proposed previously[30,34], 50% patients will achieve an exposure above these targets. Rifabutin exposure increases with coadministration of protease inhibitors, and a disproportionate increase in des-rifabutin exposure also occurs. The increased des-rifabutin exposure may further contribute to efficacy and toxicity when rifabutin is given together with a protease inhibitor; however this relation has not yet been adequately evaluated.

The method of using a pooled analysis was cumbersome but successful. Pooled population analysis is an established statistical technique closely associated with meta-analysis and systematic reviews of the literature. The concepts of statistical meta-analysis are increasingly applied to pharmacometric analysis (model-based meta-analysis).[28,73,74] This method enables the evaluation of new or additional questions compared with the original studies, and it is cost effective because no new subjects are recruited. The coalescing of data at the individual subject level may increase precision of pharmacokinetic parameters and provide more power for effect and/or covariate detection.[28] Limitations of this approach are similar to limitations of traditional meta-analysis, including the analysis only of selective available studies ("file drawer problem"), and also include reliance on source data of individual subjects in published studies. The present method is time-consuming and may introduce errors because of increased variability observed during the analysis. Furthermore, addition of information from multiple studies may increase heterogeneity. We considered adding interstudy

variability, but this was not feasible because of the prohibitive runtimes of the model. Similarly, estimation of within-subject variability was considered, however not feasible.

Limitations of the present study include insufficient data to describe all subpopulations sufficiently, especially because of the model complexity, multiple effects of drug-drug interactions, and large variability. We were unable to differentiate pharmacokinetic differences between patients who had TB alone versus TB/HIV; despite the large population, there were few patients who had TB only, and we could not differentiate between the effects of different protease inhibitors. Furthermore, the data were sparse for many concomitant protease inhibitors, necessitating broadly categorizing these drugs into 2 groups (nonboosted and ritonavir-boosted protease inhibitors). Each protease inhibitor may have different interaction potential, especially the nonboosted protease inhibitors. However, this limitation may be less relevant because protease inhibitors boosted with ritonavir 100 mg likely have an equivalent interaction potential to each other, and nonboosted protease inhibitors are infrequently used in areas where TB is endemic.

Further research is important because rifabutin is now on the World Health Organization Essential Medicines List[75] for TB therapy in HIV-infected patients. Rifabutin also is important for treatment and prevention of atypical mycobacteria, especially *Mycobacterium avium*, in HIV-coinfected patients. The safety of regimens that combine protease inhibitors and rifamycins must be evaluated in comparison with other available therapeutic options.

In conclusion, we showed that drug-drug interaction between rifabutin and protease inhibitors may cause increased exposure to rifabutin by 210% for TB/HIV

patients with nonboosted protease inhibitors and 280% with ritonavir-boosted protease inhibitors; for healthy volunteers, the increase was > 300% and > 400%. The dosing regimens that result in similar exposure (C_{av_ss}, C_{max_ss}) to a rifabutin 300-mg dose given alone are rifabutin 150 mg given once daily with a nonboosted protease inhibitor or rifabutin 300 mg every 3 days when given together with an ritonavir-boosted protease inhibitor. Predicted peak concentrations suggested that with dosages of rifabutin 150 mg daily with ritonavir-boosted protease inhibitors, the average patient is unlikely to experience rifabutin exposure > 1 mg/L, which is a concentration limit that has been associated with toxicity. Therefore, daily instead of intermittent dosing with rifabutin 150 mg in TB/HIV coinfected patients may be appropriate in patients who are monitored adequately for toxicity. New formulations or strengths of rifabutin may be required for more optimized dosing regimens.

Acknowledgements

We thank all collaborators in this project who invested time and effort into retrieving data. We are grateful to Pfizer, Tibotec (Janssen), Roche, and Abbott (Abbvie) for their time and effort in contributing data to this study. Martin Agback at UPPMAX provided assistance about technical aspects of making NONMEM run on the UPPMAX resources.

Funding

This project was supported by the Special Program for Research and Training in Tropical Diseases (TDR) of the World Health Organization (WHO). HM was supported in part by the National Research Foundation of South Africa (Grant Number 90729). Support for 1 data set[37] that was contributed to this study was received from Award Number U01AI068636 from the National Institute of Allergy and Infectious Diseases, National Institute of Mental Health (NIMH), and National Institute of Dental and Craniofacial Research (NIDCR); 2 other data sets were supported by the United States Government Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention. AIDS CTU Grant # AI69464, or the NCT (National Clinical Trials) number for ACTG 365, NCT00000877.

EMS and MOK were supported by the Swedish Research Council (grant number 521-2011-3442). The NONMEM license used was supported in part by the Australian Centre of Pharmacometrics. A portion of the computations was performed on resources provided by the Swedish National Infrastructure for Computing (SNIC) at UPPMAX.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health, the Centers for Disease Control and Prevention, Johns Hopkins Adult.

Transparency declaration

SH, EMS, RN, MOK, HM, BF, MHW, SB, CP, KG, CF, AP, PV, PLO do not have an association that might pose a conflict of interest to this work, such as pharmaceutical stock ownership, consultancy, advisory board membership, relevant patents, or research funding.

Potential conflicts of interest: SH and MOK have received consulting fees for a project from Tibotec (now Janssen) in 2009. During the analysis, PV was a paid employee of Janssen.

Author contribution:

SH collected data, performed the analysis, interpreted results, and drafted the manuscript;
EMS, RN contributed to data analysis and manuscript review;
HM, MOK developed study concept, interpreted study results, reviewed the manuscript;
BF, MHW, SB, CP, KG, CF, AP, PV, PLO contributed data and reviewed the manuscript.

References

1. Lawn SD, Meintjes G, McIlleron H, et al. Management of HIV-associated tuberculosis in resource-limited settings: a state-of-the-art review. *BMC Med.* 2013;**11**:253.
2. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. *Lancet.* 2004;**364**:1244-1251.
3. Centers for Disease Control and Prevention. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. September 22, 2014; http://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/recommendations03.htm. Accessed 09/06/2015, 2015.
4. Nijland HM, L'Homme R F, Rongen GA, et al. High incidence of adverse events in healthy volunteers receiving rifampicin and adjusted doses of lopinavir/ritonavir tablets. *AIDS.* 2008;**22**:931-935.
5. Ren Y, Nuttall JJ, Egbers C, et al. Effect of rifampicin on lopinavir pharmacokinetics in HIV-infected children with tuberculosis. *J. Acquir. Immune Defic. Syndr.* 2008;**47**:566-569.
6. la Porte CJ, Colbers EP, Bertz R, et al. Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifampin in healthy volunteers. *Antimicrob. Agents Chemother.* 2004;**48**:1553-1560.
7. Grange S, Schutz M, Schmitt C, et al. Unexpected hepatotoxicity observed in a healthy volunteer study on the effects of multiple dose rifampicin on the steady-state pharmacokinetics of ritonavir-boosted saquinavir and vice versa. Paper

presented at: *6th International Workshop on Clinical Pharmacology of HIV Therapy 2005*; Quebec, Canada, Abstract 35, p.27.

8. Rolla V, Vieira A, Pereira-Pinto D. Safety, efficacy and pharmacokinetics of ritonavir 400mg-saquinavir 400mg and rifampicin combined therapy in HIV patients with tuberculosis. Paper presented at: *3rd IAS Conference on HIV Pathogenesis and Treatment 2005.* Abstract no. WePe3.3C0. Rio de Janeiro, Brasil.
9. Regazzi M, Carvalho AC, Villani P, et al. Treatment optimization in patients co-infected with HIV and Mycobacterium tuberculosis infections: focus on drug-drug interactions with rifamycins. *Clin. Pharmacokinet.* 2014;**53**:489-507.
10. McIlleron H, Ren Y, Nuttall J, et al. Lopinavir exposure is insufficient in children given double doses of lopinavir/ritonavir during rifampicin-based treatment for tuberculosis. *Antivir. Ther.* 2011;**16**:417-421.
11. Polk RE, Brophy DF, Israel DS, et al. Pharmacokinetic Interaction between amprenavir and rifabutin or rifampin in healthy males. *Antimicrob. Agents Chemother.* 2001;**45**:502-508.
12. Lan NT, Thu NT, Barrail-Tran A, et al. Randomised pharmacokinetic trial of rifabutin with lopinavir/ritonavir-antiretroviral therapy in patients with HIV-associated tuberculosis in Vietnam. *PLoS ONE.* 2014;**9**:e84866.
13. Naiker S, Connolly C, Wiesner L, et al. Randomized pharmacokinetic evaluation of different rifabutin doses in African HIV- infected tuberculosis patients on lopinavir/ritonavir-based antiretroviral therapy. *BMC pharmacology & toxicology.* 2014;**15**:61.

14. Boulanger C, Hollender E, Farrell K, et al. Pharmacokinetic evaluation of rifabutin in combination with lopinavir-ritonavir in patients with HIV infection and active tuberculosis. *Clin. Infect. Dis.* 2009;**49**:1305-1311.

15. Tanuma J, Sano K, Teruya K, et al. Pharmacokinetics of rifabutin in Japanese HIV-infected patients with or without antiretroviral therapy. *PLoS ONE.* 2013;**8**:e70611.

16. Bonora S, Boffito M, D'Avolio A, et al. Pharmacokinetics of Rifabutin coadministered with Lopinavir/Ritonavir in HIV patients affected by Tuberculosis. Paper presented at: *2nd IAS Conference on HIV Pathogenesis and Treatment;* 2003;8 Suppl 1:S427-8. Abstract 863. Paris, France.

17. McGregor MM, Olliaro P, Wolmarans L, et al. Efficacy and safety of rifabutin in the treatment of patients with newly diagnosed pulmonary tuberculosis. *Am. J. Respir. Crit. Care Med.* 1996;**154**:1462-1467.

18. Gonzalez-Montaner LJ, Natal S, Yongchaiyud P, et al. Rifabutin for the treatment of newly-diagnosed pulmonary tuberculosis: a multinational, randomized, comparative study versus Rifampicin. Rifabutin Study Group. *Tuber. Lung Dis.* 1994;**75**:341-347.

19. Cato A, Cavanaugh J, Shi H, et al.The effect of multiple doses of ritonavir on the pharmacokinetics of rifabutin. *Clin. Pharmacol. Ther.* 1998;**63**:414-421.

20. Moultrie H, McIlleron H, Sawry S, et al. Pharmacokinetics and safety of rifabutin in young HIV-infected children receiving rifabutin and lopinavir/ritonavir. *J. Antimicrob. Chemother.* 2015;**70**:543-549.

21. Nakajima A, Fukami T, Kobayashi Y, et al. Human arylacetamide deacetylase is responsible for deacetylation of rifamycins: rifampicin, rifabutin, and rifapentine. *Biochem. Pharmacol.* 2011;**82**:1747-1756.

22. FDA. Label and Approval History MYCOBUTIN. 2008.

23. Blaschke TF, Skinner MH. The clinical pharmacokinetics of rifabutin. *Clin. Infect. Dis.* 1996;**22 Suppl 1**:S15-21; discussion S21-12.

24. Gatti G, Di Biagio A, De Pascalis CR, et al. Pharmacokinetics of rifabutin in HIV-infected patients with or without wasting syndrome. *Br. J. Clin. Pharmacol.* 1999;**48**:704-711.

25. Gatti G, Papa P, Torre D, et al. Population pharmacokinetics of rifabutin in human immunodeficiency virus-infected patients. *Antimicrob. Agents Chemother.* 1998;**42**:2017-2023.

26. Wilkins JJ, Langdon G, McIlleron H, et al. Variability in the population pharmacokinetics of pyrazinamide in South African tuberculosis patients. *Eur. J. Clin. Pharmacol.* 2006;**62**:727-735.

27. Wilkins JJ, Savic RM, Karlsson MO, et al. Population pharmacokinetics of rifampin in pulmonary tuberculosis patients, including a semimechanistic model to describe variable absorption. *Antimicrob. Agents Chemother.* 2008;**52**:2138-2148.

28. Laporte-Simitsidis S, Girard P, Mismetti P, et al. Inter-study variability in population pharmacokinetic meta-analysis: when and how to estimate it? *J. Pharm. Sci.* 2000;**89**:155-167.

29. Burman W, Benator D, Vernon A, et al. Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *Am. J. Respir. Crit. Care Med.* 2006;**173**:350-356.

30. Weiner M, Benator D, Burman W, et al. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. *Clin. Infect. Dis.* 2005;**40**:1481-1491.

31. Moyle GJ, Buss NE, Goggin T, et al. Interaction between saquinavir soft-gel and rifabutin in patients infected with HIV. *Br. J. Clin. Pharmacol.* 2002;**54**:178-182.

32. Breda M, Benedetti MS, Bani M, et al. Effect of rifabutin on ethambutol pharmacokinetics in healthy volunteers. *Pharmacol. Res.* 1999;**40**:351-356.

33. Benator DA, Weiner MH, Burman WJ, et al. Clinical evaluation of the nelfinavir-rifabutin interaction in patients with tuberculosis and human immunodeficiency virus infection. *Pharmacotherapy.* 2007;**27**:793-800.

34. Weiner M, Benator D, Peloquin CA, et al. Evaluation of the drug interaction between rifabutin and efavirenz in patients with HIV infection and tuberculosis. *Clin. Infect. Dis.* 2005;**41**:1343-1349.

35. Ford SL, Chen YC, Lou Y, et al. Pharmacokinetic interaction between fosamprenavir-ritonavir and rifabutin in healthy subjects. *Antimicrob. Agents Chemother.* 2008;**52**:534-538.

36. Gallicano K, Khaliq Y, Carignan G, et al. A pharmacokinetic study of intermittent rifabutin dosing with a combination of ritonavir and saquinavir in patients infected with human immunodeficiency virus. *Clin. Pharmacol. Ther.* 2001;**70**:149-158.

37. Hamzeh FM, Benson C, Gerber J, et al. Steady-state pharmacokinetic interaction of modified-dose indinavir and rifabutin. *Clin. Pharmacol. Ther.* 2003;**73**:159-169.

38. Kraft WK, McCrea JB, Winchell GA, et al. Indinavir and rifabutin drug interactions in healthy volunteers. *J. Clin. Pharmacol.* 2004;**44**:305-313.

39. Narita M, Stambaugh JJ, Hollender ES, et al. Use of rifabutin with protease inhibitors for human immunodeficiency virus-infected patients with tuberculosis. *Clin. Infect. Dis.* 2000;**30**:779-783.

40. Hafner R, Bethel J, Power M, et al. Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. *Antimicrob. Agents Chemother.* 1998;**42**:631-639.

41. Hafner R, Bethel J, Standiford HC, et al. Tolerance and pharmacokinetic interactions of rifabutin and azithromycin. *Antimicrob. Agents Chemother.* 2001;**45**:1572-1577.

42. Jordan MK, Polis MA, Kelly G, et al. Effects of fluconazole and clarithromycin on rifabutin and 25-O-desacetylrifabutin pharmacokinetics. *Antimicrob. Agents Chemother.* 2000;**44**:2170-2172.

43. Trapnell CB, Narang PK, Li R, et al.Increased plasma rifabutin levels with concomitant fluconazole therapy in HIV-infected patients. *Ann. Intern. Med.* 1996;**124**:573-576.

44. Krishna G, Parsons A, Kantesaria B, et al. Evaluation of the pharmacokinetics of posaconazole and rifabutin following co-administration to healthy men. *Curr. Med. Res. Opin.* 2007;**23**:545-552.

45. Schwander S, Rusch-Gerdes S, Mateega A, et al. A pilot study of antituberculosis combinations comparing rifabutin with rifampicin in the treatment of HIV-1 associated tuberculosis. A single-blind randomized evaluation in Ugandan patients with HIV-1 infection and pulmonary tuberculosis. *Tuber. Lung Dis.* 1995;**76**:210-218.

46. Sirgel FA, Botha FJ, Parkin DP, et al. The early bactericidal activity of rifabutin in patients with pulmonary tuberculosis measured by sputum viable counts: a new method of drug assessment. *J. Antimicrob. Chemother.* 1993;**32**:867-875.

47. Chan SL, Yew WW, Ma WK, et al. The early bactericidal activity of rifabutin measured by sputum viable counts in Hong Kong patients with pulmonary tuberculosis. *Tuber. Lung Dis.* 1992;**73**:33-38.

48. Hong Kong Chest Service/British Medical Research Council. A controlled study of rifabutin and an uncontrolled study of ofloxacin in the retreatment of patients with pulmonary tuberculosis resistant to isoniazid, streptomycin and rifampicin. *Tuber. Lung Dis.* 1992;**73**:59-67.

49. Agarwala S, Mummaneni V, Geraldes M, et al. Pharmacokinetic effects of Rifabutin on Atazanavir with and without Ritonavir in healthy subjects. Paper presented at: 9th Conference on Retroviruses and Opportunistic Infections2002; Seattle, USA.

50. Skinner MH, Hsieh M, Torseth J, et al. Pharmacokinetics of rifabutin. *Antimicrob. Agents Chemother.* 1989;**33**:1237-1241.

51. *NONMEM User's Guides. (1989-2009)*. Version 7. Ellicott City, MD, USA: Icon Development Solutions; 2009.

52. Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit--a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. *Comput. Methods Programs Biomed.* 2005;**79**:241-257.

53. Ette EI, Williams PJ, eds. *Pharmacometrics: The Science of Qunatitative Pharmacology.* Hoboken, NJ: John Wiley & Sons, Inc.; 2007.

54. Bergstrand M, Hooker AC, Wallin JE, et al.Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J.* 2011;**13**:143-151.

55. Hennig S, Karlsson MO. Rifabutin and Darunavir/rtv Drug-Drug Interaction Modelling and Simulation - *Report for Sponsor:Tibotec Pharmaceuticals, Belgium.* Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden;2009.

56. Svensson EM, Karlsson MO. Use of a linearization approximation facilitating stochastic model building. *J. Pharmacokinet. Pharmacodyn.* 2014;**41**:153-158.

57. Karlsson MO, Sheiner LB. The importance of modeling interoccasion variability in population pharmacokinetic analyses. *J. Pharmacokinet. Biopharm.* 1993;**21**:735-750.

58. Holford NH. A size standard for pharmacokinetics. *Clin. Pharmacokinet.* 1996;**30**:329-332.

59. Weiner M, Burman W, Vernon A, et al. Low isoniazid concentrations and outcome of tuberculosis treatment with once-weekly isoniazid and rifapentine. *Am. J. Respir. Crit. Care Med.* 2003;**167**:1341-1347.

60. Naiker S, Conolly C, Weisner L, et al. Pharmacokinetic Evaluation of Different Rifabutin Dosing Strategies in African TB Patients on Lopinavir/ritonavir-based

ART 18th Conference on Retroviruses and Opportunistic Infections, ; 27 Feb- 2 Mar 2011, 2011; Boston, USA.

61. Sekar V, Lavreys L, De Paepe E, et al. Pharmacokinetic interaction between darunavir in combination with low-dose ritonavir and rifabutin. Joint meeting of the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy, and the 46th meeting of the Infectious Diseases Society of America; 2008; Washington, DC, USA.

62. Agouron Pharmaceuticals. *Project RBD Analytical Report HPLC Analysis of AG1343-523 in Human Plasma.* 1996.

63. Ng J, Nada A, Freeman S, et al. Pharmacokinetics of rifabutin 150 mg TIW plus LPV/r 400/100 mg BID administered in healthy adult subjects. Paper presented at: 10th International Workshop on Clinical Pharmacology of HIV Therapy2009; Amsterdam, The Netherlands.

64. Sekar VJ, Lefebvre E, De Pauw M, et al.Pharmacokinetics of darunavir/ritonavir and ketoconazole following co-administration in HIV-healthy volunteers. *Br. J. Clin. Pharmacol.* 2008;**66**:215-221.

65. Hennig S, Naiker S, Reddy T, et al. The effect of SLCO1B1 polymorphisms on the pharmacokinetics of rifabutin in African HIV-infected patients with tuberculosis. *Antimicrob. Agents Chemother.* 2015.

66. Ramachandran G, Bhavani PK, Hemanth Kumar AK, et al. Pharmacokinetics of rifabutin during atazanavir/ritonavir co-administration in HIV-infected TB patients in India. *Int. J. Tuberc. Lung Dis.* 2013;**17**:1564-1568.

67. la Porte CJ, Sabo JP, Elgadi M, et al. Interaction studies of tipranavir-ritonavir with clarithromycin, fluconazole, and rifabutin in healthy volunteers. *Antimicrob. Agents Chemother.* 2009;**53**:162-173.

68. Sekar V, Lavreys L, Van de Casteele T, et al. Pharmacokinetics of darunavir/ritonavir and rifabutin coadministered in HIV-negative healthy volunteers. *Antimicrob. Agents Chemother.* 2010;**54**:4440-4445.

69. Zhang J, Zhu L, Stonier M, et al. Determination of rifabutin dosing regimen when administered in combination with ritonavir-boosted atazanavir. *J. Antimicrob. Chemother.* 2011;**66**:2075-2082.

70. Zhang X, Fettner S, Zwanziger E, et al. Pharmacokinetic interaction study of ritonavir-boosted saquinavir in combination with rifabutin in healthy subjects. *Antimicrob. Agents Chemother.* 2011;**55**:680-687.

71. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. *Drugs.* 2014;**74**:839-854.

72. McIlleron H, Meintjes G, Burman WJ, et al. Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. *J. Infect. Dis.* 2007;**196 Suppl 1**:S63-75.

73. Kerbusch T, Milligan PA, Karlsson MO. Assessment of the relative in vivo potency of the hydroxylated metabolite of darifenacin in its ability to decrease salivary flow using pooled population pharmacokinetic-pharmacodynamic data. *Br. J. Clin. Pharmacol.* 2004;**57**:170-180.

74. Olsson-Gisleskog P, Jacqmin P, Perez-Ruixo JJ. Population pharmacokinetics meta-analysis of recombinant human erythropoietin in healthy subjects. *Clin. Pharmacokinet.* 2007;**46**:159-173.

75. World Health Organization. 19th WHO Model List of Essential Medicines (April 2015). 2015; http://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf?ua=1. Accessed 22/07/2015, 2015.

SUPPLEMENTARY DATA

Methods

Population pharmacokinetic pooled analysis

All covariate models were tested for statistical significance using a stepwise covariate model-building procedure. Repeatedly significant covariates were tested collectively using a linearized stepwise covariate model (lin-SCM) building method implemented in the software (PsN).[76] The linearization was used to reduce runtimes and enable an extensive search for possible relations. The statistical significance of including covariate relations into the model was assessed on the linearized version of the base model by comparing the OFVs before and after inclusion. All relations with continuous covariates were tested centered to the median covariate value or median of the weighted average of the covariate value (latter for time-varying covariates [continuous and categorical]) (http: //psn.sourceforge.net/docs.php). Additions to the model were retained in the model in the forward step when the decrease in OFV was significant (change in OFV > -3.84; $P < .05$) and their removal significantly increased OFV (change in OFV > 6.64; $P < .01$). The final model including the covariates identified in the lin-SCM was re-estimated in the nonlinear form.

Results

Table S1: Structural Model Parameter Estimates and Variability Estimates For Rifabutin and 25-O-desacetyl Rifabutin in the Final Model With and Without Drug-Drug-Interaction With Protease Inhibitors and Covariate Effect. The parameter values present a hypothetical average individual in the data set.

Parameter	**Units**	**Estimate Value [RSE%]**	**BSV (%) RSE%**
Rifabutin			
Apparent oral clearance to routes other than des-rifabutin, CL/F	L/h/70 kg	58.8 [8.5]	54.0 [10.5]
Metabolism clearance to des-rifabutin, CL_e/F	L/h/70 kg	7.29 [9.9]	51.5 [14.6]
Central volume of distribution,V2/F	L/70 kg	17.1 [15.9]	169.1 [9.4]
Absorption rate constant, k_a	/h	0.24 [4.7]	31.0 [37.5]
Mean transit time, MTT	h	2.16 [4.0]	51.8 [6.8]
Number of transit compartments, N		7.15 [6.1]	-
Bioavailability, F		Fixed to 1	26.8 [13.2] BOV
Peripheral volume of distribution, V3/F	L/70 kg	1580 [8.9]	65.6 [12.2]
Intercompartmental clearance, Q/F	L/h/70 kg	69.6 [10.8]	60.2 [14.5]
Des-rifabutin			
Clearance, $CL_m/F/F_m$	L/h/70 kg	122 [8.0]	78.3 [8.8]
Central volume of distribution, $V4/F/F_m$	L/70 kg	37.3 [15.5]	111.4 [18.9]
Intercompartmental clearance , $Q_m/F/F_m$	L/h/70 kg	71.8 [11.7]	60.8 [18.9]
Peripheral volume of distribution, $V5/F/F_m$	L/70 kg	1220 [16.4]	117.0 [8.0]
First-pass metabolism fraction, F_m		0.08 [9.8]	
Residual unexplained variability			
Rifabutin	%	22.7 [4.4]	-
Des-rifabutin	%	24.2 [6.4]	-

Drug-drug-interaction parameters		
Parameter	**Covariate-Parameter Relations**	**Estimate Value [RSE%]**
CL~COAD	1+CL~COAD	-0.764 [4.9]
CL~RTV	1+CL~RTV	-0.796 [2.4]
$CL\sim COAD_{TB/HIV}$	$1+ CL\sim COAD_{TB/HIV}$	-1 fixed
V2~COAD	1+V2~COAD*(FLAG - 0.37)	1.87 [8.6]
V2~ TB/HIV	$1+V2\sim TB/HIV *(0.653-FLAG_{TB/HIV})$	0.372 [39.2]
k_a~COAD	$1+ k_a\sim COAD*(FLAG-0.26))$	0.13 [69.5]
k_a~RTV	$1+ k_a\sim RTV)$	-0.489 [5.9]
k_a~ TB/HIV	$1+ k_a\sim TB/HIV *(0.653- FLAG_{TB/HIV})$	0.062 [65.2]
MTT~RTV	1+ MTT~RTV	-0.308 [17.3]
F~COAD	(1+ F~COAD)*(FLAG - 0.5)	0.062 [177.1]
$F\sim COAD_{TB/HIV}$	$1+ F\sim COAD_{TB/HIV}$	-0.422 [11.6]
F~RTV	1+ F~RTV	0.337 [35.5]
$V3\sim COAD_{TB/HIV}$	$1+ V3\sim COAD_{TB/HIV}$	-0.638 [14.3]
$V3\sim RTV_{TB/HIV}$	$1+ V3\sim RTV_{TB/HIV}$	1.44 [26.2]
Q~COAD	1+Q~COAD*(FLAG-0.29)	-0.543 [13.7]
Q~ TB/HIV	$1+Q\sim TB/HIV *(0.653- FLAG_{TB/HIV}))$	-0.341 [17.7]
CL_e~COAD	$1+ CL_e \sim COAD*(FLAG - 0.53))$	0.396 [45.9]
$CL_e\sim COAD_{TB/HIV}$	$1+ CL_e \sim COAD_{TB/HIV}$	1.16 [17.4]
CL_m~COAD	$1+CL_m\sim COAD)$	-0.352 [17.1]
CL_m~RTV	$1+CL_m\sim RTV)$	-0.928 [0.7]
$CL_m\sim RTV_{TB/HIV}$	$1+CL_m\sim RTV_{HIV})$	2.28 [12.6]
V4~COAD	1+ V4~COAD	1.44 [53.8]
$V4\sim COAD_{TB/HIV}$	$1+ V4\sim COAD_{TB/HIV}$	0.393 [39.9]
$V4\sim RTV_{TB/HIV}$	$1+ V4\sim RTV_{TB/HIV}$	0.422 [25.6]
V4~RTV	1+ V4~RTV	-0.653 [5.5]
Q_m~COAD	$1+ Q_m\sim COAD$	-0.651 [6.6]
$Q_m \sim COAD_{TB/HIV}$	$1+ Q_m\sim COAD_{TB/HIV}$	1.96 [19.5]
F_m~COAD	$(1+ F_m\sim COAD)*(FLAG - 0.29)$	-0.615 [14.2]
$F_m\sim COAD_{TB/HIV}$	$1+ F_m\sim COAD_{TB/HIV}$	1.19 [31.7]

All disposition parameters were allometrically scaled with the factor $F_{CLWT} = (WT/70)^{0.75}$ on all clearance parameters and $F_{VWT} = WT/70$ on all volume parameters.
All covariate effects are multiplication with the typical parameter value for the parameters and if applicable relationships are multiplied on top of each other. For examples the apparent oral metabolism clearance for a TB/HIV patients during co-administration with a protease inhibitor can be calculated with : CLe *(1+ CLe ~COAD*(FLAG - 0.53)) *(1+ CLe ~$COAD_{TB/HIV}$).

Abbreviations: BSV, between-subject variability; BOV, between-occasion variability; CL, systemic clearance of rifabutin to routes other than 25-O-desacetyl rifabutin; CL_e, systemic metabolism to 25-O-desacetyl rifabutin; CL_m, systemic clearance of 25-O-desacetyl rifabutin; ~COAD; estimated covariate parameter value for a particular relationship under coadministration with a protease inhibitor , FLAG, flag (yes, 1; no, 0) for coadministration with a protease inhibitor; $FLAG_{TB/HIV}$, flag (yes, 1; no, 0) for patients with HIV and TB infection; ~$COAD_{TB/HIV,}$ estimated covariate parameter value for a particular relationship under coadministration with a protease inhibitor in TB/HIV patients; F, bioavailability; F_m, fraction first-pass metabolism; ~TB/HIV, estimated covariate parameter value for a particular relationship in patients with HIV and TB infection; k_a, absorption rate constant; MTT, mean transit time; N, number of transit compartments; Q, intercompartmental clearance rate for rifabutin; Q_m, intercompartmental clearance rate for des-rifabutin; RSE%, relative standard error (%); ~RTV, estimated covariate parameter value for a particular relationship under coadministration with ritonavir or ritonavir-boosted protease inhibitor; ~$RTV_{TB/HIV,}$ estimated covariate parameter value for a particular relationship under coadministration with ritonavir or ritonavir-boosted protease inhibitor in HIV patients; V2, volume of distribution central compartment rifabutin; V3, volume of distribution peripheral compartment rifabutin; V4, volume of distribution central compartment des-rifabutin; V5, volume of distribution peripheral compartment des-rifabutin.

Table S2: Full Variance-Covariance Matrix of the Final Model

Parameter	**Value (CV% or Correlation)**											
IIV k_a	**31.0%**											
IIV CL	36.2%	**54.0%**										
IIV CL_m	1.2%	63.8%	**78.3%**									
IIV V2	54.3%	40.1%	28.5%	**169.1%**								
IIV Q	43.5%	71.9%	6.2%	12.3%	**60.2%**							
IIV MTT	27.5%	3.2%	-4.1%	-28.8%	18.9%	**51.8%**						
IIV F_m	-37.6%	-65.3%	1.1%	-27.4%	-87.0%	-0.9%	**89.3%**					
IIV CL_e	0.4%	67.2%	72.9%	32.4%	33.9%	-12.3%	-16.2%	**51.5%**				
IIV V3	-4.0%	24.0%	21.4%	-2.1%	40.8%	-15.5%	-18.8%	41.2%	**65.6%**			
IIV Q_m	-17.8%	-62.4%	-6.3%	-38.2%	-57.8%	11.7%	84.7%	-16.1%	-6.7%	**60.8%**		
IIV V4	-0.9%	-36.1%	13.1%	48.9%	-65.3%	-21.5%	62.0%	0.1%	-30.0%	49.9%	**111.4%**	
IIV V5	2.3%	-31.1%	24.3%	-9.0%	-26.7%	2.0%	53.5%	22.4%	46.9%	74.0%	36.1%	**26.8%**
IOV F	**26.8%**											

Abbreviations: CL, systemic clearance of rifabutin to routes other than des-rifabutin; CL_e, systemic metabolism to 25-O-desacetyl rifabutin; CL_m, systemic clearance of 25-O-desacetyl rifabutin; CV, coefficient of variation (%); F, bioavailability; F_m, fraction first-pass metabolism; IIV, interindividual variability; IOV, interoccasion variability; k_a, absorption rate constant; MTT, mean transit time; Q, intercompartmental clearance rate for rifabutin; Q_m, intercompartmental clearance rate for des-rifabutin; V2, volume of distribution central compartment rifabutin; V3, volume of distribution peripheral compartment rifabutin; V4, volume of distribution central compartment 25-O-desacetyl rifabutin; V5, volume of distribution peripheral compartment 25-O-desacetyl rifabutin.

Table S3: Effect of Covariates and Drug-Drug-Interaction With Protease Inhibitors on Rifabutin and Des-Rifabutin Pharmacokinetic Parameters*

Parameter	Units	Rifabutin Alone, TB/HIV Compared With Healthy Volunteer	Rifabutin With Nonboosted Protease Inhibitor		Rifabutin With RTV-Boosted Protease Inhibitor	
			Healthy Volunteer	TB/HIV	Healthy Volunteer	TB/HIV
Rifabutin						
Apparent oral clearance to routes other than des-rifabutin, CL/F	L/h/70 kg	0	-76	-100	-80	-100
Apparent oral metabolism clearance to des-rifabutin, CL_e/F	L/h/70 kg	0	50	224	50	224
Central volume of distribution, V2/F	L/70 kg	-29	607	607	607	607
Absorption rate constant, k_a	/h	- 6	14	14	-42	-42
Mean transit time, MTT	h	0	0	0	-31	-31
Number of transit compartments, N						
Bioavailability, F		0	6	-39	42	-18
Peripheral volume of distribution, V3/F	L/70 kg	0	0	-64	0	-12
Intercompartmental clearance, Q/F	L/h/70 kg	44	-47	-47	-47	-47
Des-rifabutin						
Apparent oral clearance, $CL_m/F/F_m$	L/h/70 kg	0	-35	-35	-93	-76
Central volume of distribution, $V4/F/F_m$	L/70 kg	0	144	240	-15	68
Intercompartmental clearance, $Q_m/F/F_m$	L/h/70 kg	0	-65	3	-65	3
Peripheral volume of distribution, $V5/F/F_m$	L/70 kg	0	0	0	0	0
First-pass metabolism fraction, F_m		0	-52	5	-52	5

*****Data reported as percent (%) parameter value reduction (-) or increase (+) compared with the parameter values without protease inhibitor coadministration.

Abbreviations: CL, systemic clearance of rifabutin to routes other than des-rifabutin; CL_e, systemic metabolism to 25-O-desacetyl rifabutin; CL_m, systemic oral clearance of 25-O-desacetyl rifabutin; F, bioavailability; F_m, fraction first-pass metabolism; TB/HIV, patients with HIV and TB infection (yes, 1; no, 0); k_a, absorption rate constant; MTT, mean transit time; N, number of transit compartments; Q, intercompartmental clearance rate for rifabutin; Q_m, intercompartmental clearance rate for des-rifabutin; RTV, coadministration with ritonavir or ritonavir-boosted protease inhibitor (yes, 1; no, 0); V2, volume of distribution central compartment rifabutin; V3, volume of distribution peripheral compartment rifabutin; V4, volume of distribution central compartment des-rifabutin; TB, tuberculosis.

Table S4: Pharmacokinetic Parameters Reported From Studies Evaluating Changes in the Pharmacokinetics of Rifabutin and 25-O-desacetyl Rifabutin When Coadministered With a Protease Inhibitor[§]

	Reference	Subjects	No. of Subjects	Rifabutin Dosage (mg)		Protease Inhibitor (mg)	Rifabutin Administration Only				Rifabutin and Protease Inhibitor Coadministration			
							Rifabutin		Des-Rifabutin		Rifabutin		Des-Rifabutin	
				Without Protease Inhibitor	With Protease Inhibitor		AUC_{0-24} (mg·h/L)	C_{max} (mg/L)	AUC_{0-24} (mg·h/L)	C_{max} (mg/L)	AUC_{0-24} (mg·h/L)	C_{max} (mg/L)	AUC_{0-24} (mg·h/L)	C_{max} (mg/L)
	HIV Patients													
*	Benator (2007)[33]	TB/HIV	7	300 Q2W	300 Q2W	NEF (1250 BD)	4.10 (3.18, 5.27)[«]	0.43 (0.34, 0.56)	0.57 (0.31, 1.02)[«]	0.06 (0.04, 0.09)	501 (3.25, 7.71)[«]	0.42 (0.24, 0.75)	1.96 (1.26, 3.04)[«]	0.14 (0.08, 0.23)
*	Bonora (2003)[16]	TB/HIV	4	300 QD	150 QD	LPV/r (400/100 BD)	2.129	0.214	-	-	2.79	0.20	-	-
*	Boulanger (2009)[14]	TB/HIV	10	300 Q3W	300 Q3W 150 Q3W	LPV/r (400/100 BD)	2.70 (1.39-3.98)	0.30 (0.15-0.55)	0.49 (0.07-1.52)	0.06 (0.01-0.17)	4.36 (1.73-6.09) 2.97 (0.60-4.67)	0.37 (0.09-0.58) 0.23 (0.04-0.32)	2.54 (1.08-3.69) 1.54 (0.91-2.35)	0.14 (0.07-0.21) 0.09 (0.05-0.12)
*	Gallicano (2001)[36 ◊]	HIV	19	-	300 QW (n=10), 150 Q3D (n=9)	SQV/r (400/400 bd)	-	-	-	-	14.2[#] ± 5.3 19.4[#] ± 7.3	0.51 ± 0.14 0.34 ± 0.13	10.80[#] ± 2.40 12.70[#] ± 3.80	0.13 ± 0.037 0.11 ± 0.036
	Lan (2014)[12]	HIV	12+13	300 QD	150 QD 150 Q3W	LPV/r	5.64 (2.72–8.88)	0.79 (0.34–1.11)	0.70 (0.25–10.25)	0.08 (0.025-0.60)	7.29 (3.52–12.51) 7.34°(1.43–10.90)	0.67 (0.25–1.15) 0.54 (0.06–0.96)	4.13 (1.77–8.62) 3.81° (0.87–7.63)	0.22 (0.09–0.54) 0.14 (0.03–0.31)
	Moultrie	HIV	6	-	5 mg/kg						5.36 (2.33 –	0.39	3.34 (1.62–	0.17

(2015)[20]				Q3W						6.29)	(0.19–0.46)	5.95)	(0.08–0.32)
Reference	**Subjects**	**No. of Subjects**	**Rifabutin Dosage (mg)**		**Protease Inhibitor (mg)**	**Rifabutin Administration Only**				**Rifabutin and Protease Inhibitor Coadministration**			
						Rifabutin		**Des-Rifabutin**		**Rifabutin**		**Des-Rifabutin**	
			Without Protease Inhibitor	**With Protease Inhibitor**		**AUC_{0-24} (mg·h/L)**	**C_{max} (mg/L)**	**AUC_{0-24} (mg·h/L)**	**C_{max} (mg/L)**	**AUC_{0-24} (mg·h/L)**	**C_{max} (mg/L)**	**AUC_{0-24} (mg·h/L)**	**C_{max} (mg/L)**
HIV Patients													
Moyle (2002)[31]	TB/HIV	14	300 QD	300 QD	SQV/r (120 mg TDS)	3.01 (28.0)	0.31 (32.8)	-	-	4.34 (19.6)	0.45 (20.5)	-	-
* Naiker (2014)[13,]	TB/HIV	16	300 QD	150 QD 150 Q3W	LPV/r (400/100 BD)	3.05 [2.65-3.43]	0.29 [0.25-0.38]	-	-	4.77 [3.95-6.10] 2.31 [1.77-3.88]	0.31 [0.26-0.38] 0.17 [0.09-0.30]	-	-
Ramachandran (2013)[66]	HIV	16		150 Q3W	ATV/r (330/100 QD)	-	-	-	-	4.61 [2.07–5.34]	0.33 [0.19–0.48]	-	-
Tanuma (2013)[15]	HIV	9/7	300 QD	150 Q3W	LPV/r (NR)	2.79 (1.32 – 15.7)	0.46 (0.15 – 0.86)	0 (0-3.69)	0 (0-0.3)	3.00 (1.13 – 5.43)	0.28 (0.10 – 0.44)	1.52 (0.44 – 3.64)	0.13 (0.05–0.23)
* Weiner (2005)[34]	TB/HIV	15	300 QD	600 Q2W	EFV (600 QD)	4.32 ± 1.37	0.44 ± 0.16	0.85 ± 0.80	0.12 ± 0.08	5.46 ± 2.73	0.70 ± 0.26	0.59 ± 0.69	0.07 ± 0.05
Healthy Volunteers													
Agarwala (2002)[49]	HVT	30	-	150 QD	ATV (400 QD & 600 QD & 400/100 RTV QD)	-	-	-	-	7.69 (20.3)/ 6.29 (19.7)/ 7.39 (19.5)	0.55 (20.9)/ 0.41 (23.3)/ 0.50 (22.4)	4.38 (18.2)/ 3.61 (21.9)/ 5.66 (6.8)	0.23 (16.1)/ 0.19 (24.7)/ 0.29 (10.1)

*	Cato (1998)[19]	HVT	24	150 QD	150 QD	RTV (300, 400, 500 BD)	1.84 ± 0.39	0.19 ± 0.03	0.17 ± 0.08	0.02 ± 0.00	8.36 ± 2.23	0.60 ± 0.18	6.29 ± 0.84	0.31 ± 0.03
	Reference	**Subjects**	**No. of Subjects**	**Rifabutin Dosage (mg)**		**Protease Inhibitor (mg)**	**Rifabutin Administration Only**				**Rifabutin and Protease Inhibitor Coadministration**			
							Rifabutin		**Des-Rifabutin**		**Rifabutin**		**Des-Rifabutin**	
				Without Protease Inhibitor	**With Protease Inhibitor**		**AUC_{0-24} (mg·h/L)**	**C_{max} (mg/L)**	**AUC_{0-24} (mg·h/L)**	**C_{max} (mg/L)**	**AUC_{0-24} (mg·h/L)**	**C_{max} (mg/L)**	**AUC_{0-24} (mg·h/L)**	**C_{max} (mg/L)**
	Ford (2008)[35]	HVT	15	300 QD	150 QOD	FPV/r (700/100 BD)	6.11° (5.33, 7.01)	0.31 (0.27, 0.37)	0.41° (0.34, 0.49)	0.02 (0.02, 0.03)	5.81° (5.04, 6.68)	0.27 (0.23, 0.32)	4.60° (4.17, 5.06)	0.14 (0.12, 0.16)
*	Hamzeh (2003)[37] ‡	HVT/HIV	17	300 QD	150 QD	IND (1000 Q8H)	3.37 ± 0.86	0.40 ± 0.14	0.34 ± 0.12	0.04 ± 0.03	5.75 ± 2.28	0.50 ± 0.2	0.73 ± 0.30	0.06 ± 0.03
	Kraft (2004)[38] ~	HVT	10 14	300 QD	300 QD 150 QD	IND (800 Q8H)	2.56 2.87	0.29 0.29	0.17 0.13	0.02 0.02	7.01 4.42	0.69 0.37	0.79 0.53	0.08 0.05
	la Porte (2009)[67]	HVT	20	150 s.d.	150 s.d.	TPV/r (500 /200 BD)	2.26 (0.90-6.03)	0.16 (0.06-0.44)	0.18 (0.06-0.56)	0.02 (0.00-0.04)	6.21 (4.16-10.43)	0.28 (0.17-0.46)	3.72 (2.52-6.41)	0.06 (0.03-0.11)
	Polk (2001)[11]	HVT	24	300 QD	300 QD	AMP (1200 mg BD)	3.39 (2.84, 4.03)	0.38 (0.30, 0.48)	0.23 (0.19, 0.28)	0.03 (0.03, 0.04)	9.92 (8.07, 12.20)	0.84 (0.64, 1.10)	3.06 (2.35, 3.98)	0.23 (0.18, 0.29)
*	Sekar (2010)[68]	HVT	15	300 QD	150 QOD	DRV/r (600/100 BD)	4.66 ± 0.97	0.57 ± 0.13	0.34 ± 0.12	0.04 ± 0.02	10.79° ± 3.17	0.62 ± 0.24	7.50° ± 2.04	0.24 ± 0.08
	Zhang (2011)[69]	HVT	15+18	150 QD	150 Q2W	ATV/r (300/100 QD)	1.56 (32)	0.16 (30)	0.12 (42)	0.01 (32)	2.31 (22)	0.40 (14)	1.28 (20)	0.10 (20)
	Zhang (2011)[70]	HVT	25	150 QD	150 Q3D 150 Q4D	SQV/r (1000/100 BD)	1.80 ± 0.40	0.19 ± 0.05	0.13 ± 0.06	0.02 ± 0.00	8.10 ± 1.70¢ 7.40 ± 1.70¥	0.35 ± 0.11 0.33 ± 0.11	5.10 ± 1.50¢ 5.20 ± 1.10¥	0.12 ± 0.04 0.12 ± 0.03

	Population Pharmacokinetic studies						
	Reference	**Subjects**	**No. of Subjects**	**Rifabutin Dosage (mg)**		**Protease Inhibitor (mg)**	**Pharmacokinetic Parameter Values**
				Without Protease Inhibitor	**With Protease Inhibitor**		
	Gatti (1998)[25]	HIV	40	150 BD, 150 TDS, 300 QD, 450 QD, 600 QD	-	-	CL/F(L/h)=60.9 (IIV=32%), Vc/F(L)=231, Q/F(L/h)=60.3, Vp/F(L)=1050, ka=0.201
*	Company report (Tibotec)[55]	HVT	32	300 QD	150 QOD	DRV/r (600/100 BD)	CL/F(L/h)=50.4 (IIV=30.8%), CLr/F(L/h)=1.1, CLe/F(L/h)=20.3 (IIV=81.1%), Vc/F(L)=76.2 (IIV=14.9%), Q/F(L/h)=40 Vp/F(L)=1570, ka=0.195 (IIV=35.6%), lag-time=0.8 (IIV=57.7%) CLm/F/Fm(L/h)=325 (IIV=9.6%), Vm/F/Fm (L)=144, Q4/F/Fm =1.34, V5/F/Fm (L)=330, Fm=0.0535 CL decrease with protease inhibitor: 97.5% (IIV=10.4%), CLm decrease with protease inhibitor: 91.9% (IIV=10.4%), F increase with protease inhibitor: 46% (IIV=13.4%), Q4 increase with protease inhibitor: 2410% (IIV=10.4 %)
*	Hennig (2015)[65]	TB/HIV	44	300 QD	150 QD 150 O3W	LPV/r (400/100 BD)	CL/F(L/h)=116.5 (IIV=12.0%), CLe/F(L/h)=21.2, Vc/F(L) (females) =117.8 *1.84 (male) (IIV=49.0%), Q/F(L/h)= 123.8, Vp/F(L)=4897.8, ka=0.24 (IIV=23.9%), lag-time=1.59 (IIV=24.7%), F= 1 fixed (IIV= 33.0%), CLm/F/Fm(L/h)=196.7 (IIV=30.0%), Vm/F/Fm (L)=3.86, Q4/F/Fm =0.15, V5/F/Fm (L)=536.8, F increase for rs11045819 genotype = 30.4%

§ Values are reported as in the original publication as mean ± SD, median (range), mean (CV%), median [IQR], or mean **(**90% CI**)**. ***Abbreviations***: des-rifabutin, 25-O-desacetyl rifabutin; BD, twice daily; HIV, human immunodeficiency virus (HIV)-infected patients, HVT, healthy volunteers; NR, not reported; QD, once daily; QOD, every other day; QW, once weekly; Q2W, twice weekly; Q3W, thrice weekly; Q3D, every 3 days; Q8H, every 8 hours; s.d., single dose; TB, patients with tuberculosis; TDS, three times a day. * Data contributed to this pooled analysis.

◊ Pharmacokinetic parameters from 4 weeks after starting rifabutin dosing.

‡ Results reported in μmol/L and μmol/·h, converted to ng/mL and ng·h/mL using the molecular weight of rifabutin (847.0 Da) and des-rifabutin (820.0 Da);

+ Noncompartmental analysis from day 15.

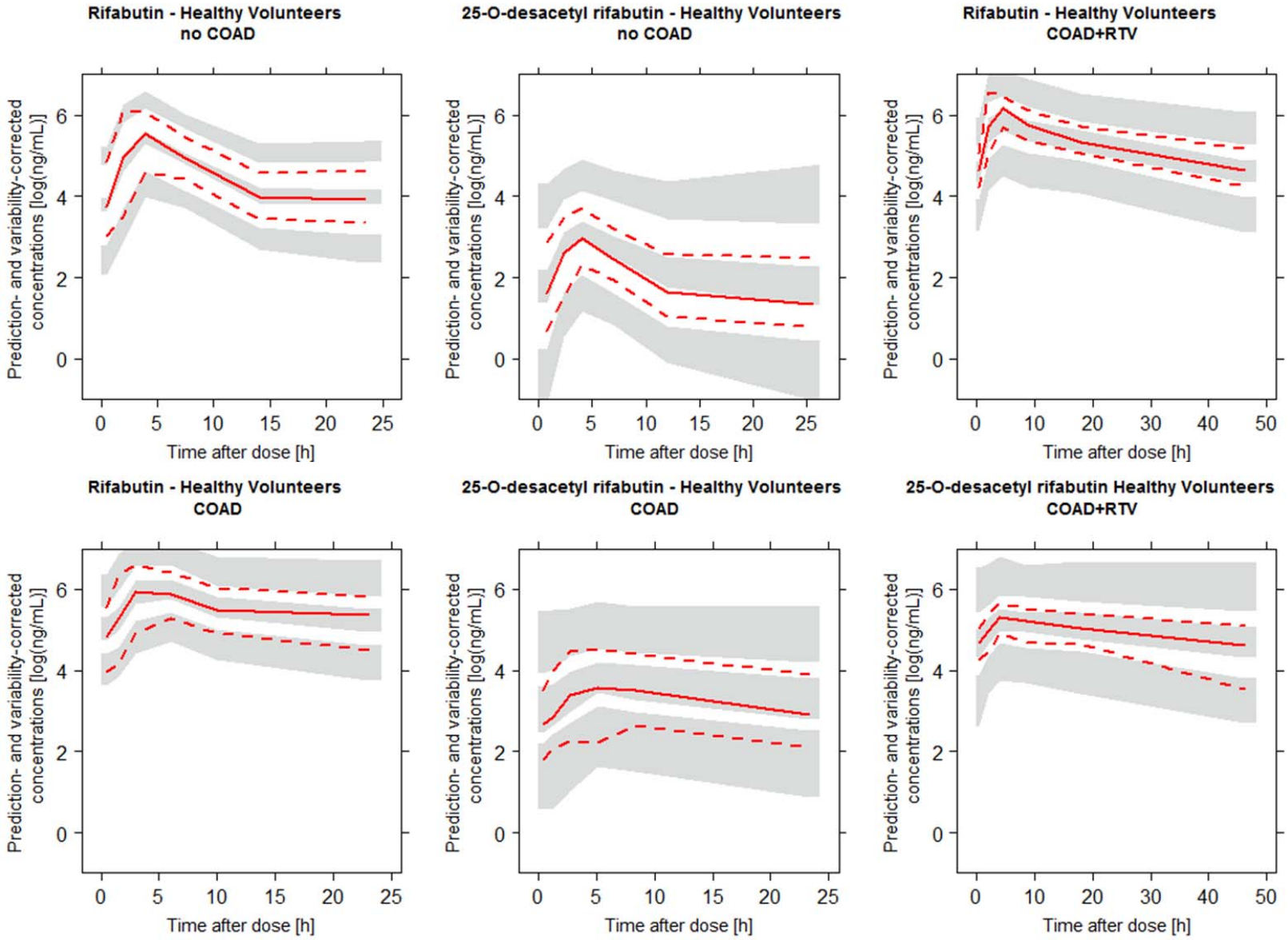
~ Did not report SD, CI, CV%, or IQR.

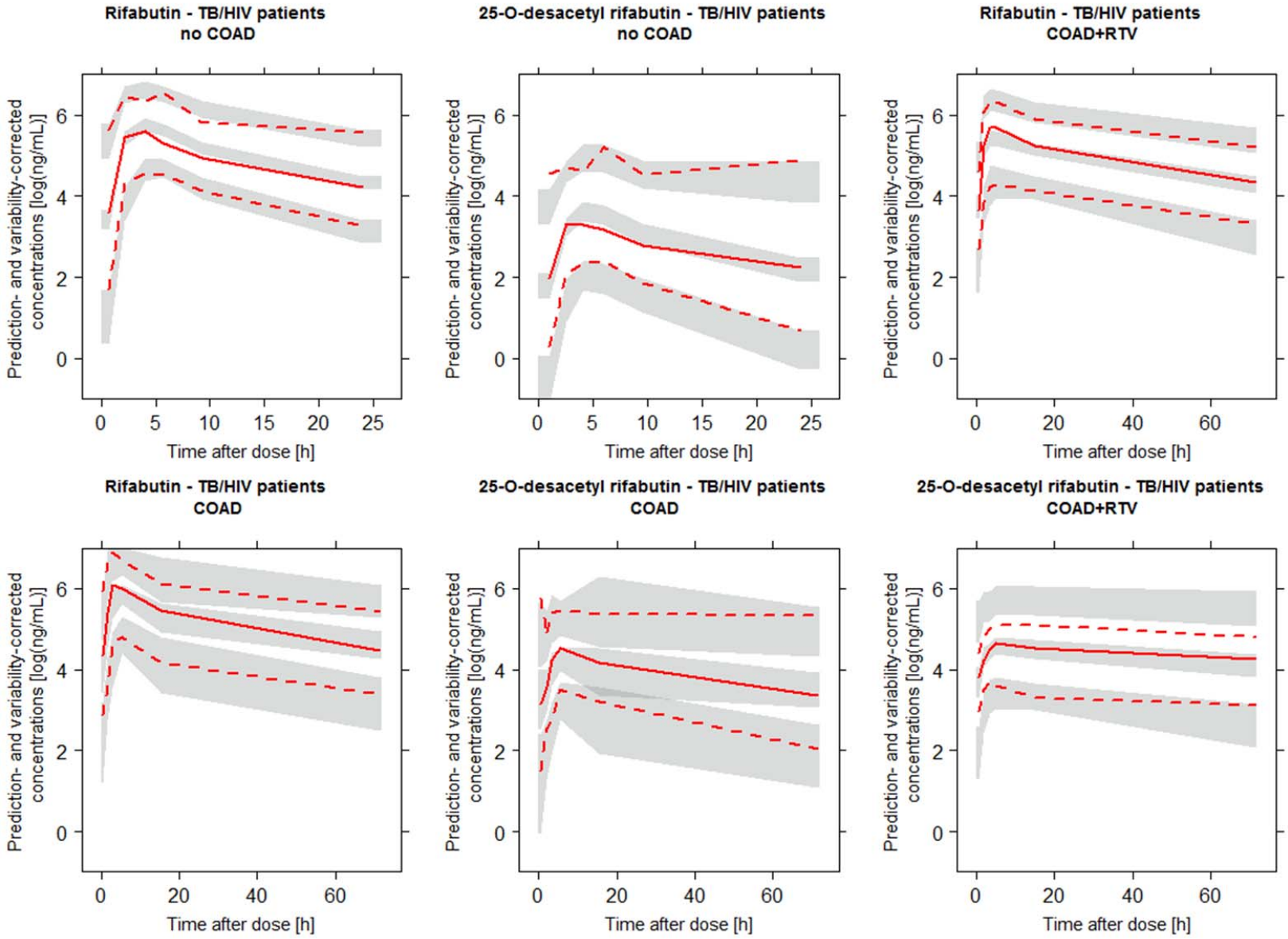
° AUC_{0-48}, « AUC_{0-21}, # AUC_{0-168}, † $AUC_{0-\infty}$, ¢ AUC_{0-72}, ¥ AUC_{0-96}.

Protease inhibitors: ATV, atazanavir; ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; EFV, efavirenz; FPV/r, fosamprenavir/ritonavir; IND, indinavir; LPV/r, lopinavir/ritonavir; NEF, nelfinavir; TPV/r, tipranavir/ritonavir; RTV, ritonavir.
Rifabutin parameters: CL, systemic clearance of rifabutin; CLe, systemic metabolism clearance to 25-O-desacetyl rifabutin; F, bioavailability; IIV, interindividual variability; k_a, absorption rate constant; Q, intercompartmental clearance; Vc, volume of distribution of central compartment; Vp, volume of distribution of peripheral compartment.
25-O-desacetyl rifabutin parameters: CLm, systemic clearance of 25-O-desacetyl rifabutin; Fm, First-pass metabolism; Q4, intercompartmental clearance; Vm, volume of distribution of central compartment; V5, volume of distribution of peripheral compartment.

Figure S1: Prediction- and Variability-Corrected Visual Predictive Check (pvcVPC) for Rifabutin and 25-O-desacetyl Rifabutin in the Final Model. The pvcVPC was stratified to present data for healthy volunteers (top 6 panels) and patients (TB/HIV, bottom 6 panels) and coadministration with and without protease inhibitor and ritonavir-boosted protease inhibitor. The upper, middle, and lower red lines represent the 95th, 50th, and 5th percentile of the observations, and the grey shaded areas are the 90% confidence interval for the simulated data percentiles for each bin.

Abbreviations: COAD, coadministration with protease inhibitor; COAD+RTV, coadministration with ritonavir-boosted protease inhibitor; TB/HIV, patients with HIV and TB infection; TB, tuberculosis.


Rifabutin - Healthy Volunteers
no COAD
25-O-desacetyl rifabutin - Healthy Volunteers
no COAD
Rifabutin - Healthy Volunteers
COAD+RTV
Rifabutin - Healthy Volunteers
COAD
25-O-desacetyl rifabutin - Healthy Volunteers
COAD
25-O-desacetyl rifabutin Healthy Volunteers
COAD+RTV
Prediction- and variability-corrected concentrations [log(ng/mL)]
Time after dose [h]


Rifabutin - TB/HIV patients
no COAD
25-O-desacetyl rifabutin - TB/HIV patients
no COAD
Rifabutin - TB/HIV patients
COAD+RTV
Rifabutin - TB/HIV patients
COAD
25-O-desacetyl rifabutin - TB/HIV patients
COAD
25-O-desacetyl rifabutin - TB/HIV patients
COAD+RTV
Prediction- and variability-corrected concentrations [log(ng/mL)]
Time after dose [h]

References

1. Lawn SD, Meintjes G, McIlleron H, Harries AD, Wood R. Management of HIV-associated tuberculosis in resource-limited settings: a state-of-the-art review. *BMC Med.* 2013;**11**:253.
2. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. *Lancet.* 2004;**364**:1244-1251.
3. Centers for Disease Control and Prevention. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. September 22, 2014; http://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/recommendations03.htm. Accessed 09/06/2015, 2015.
4. Nijland HM, L'Homme R F, Rongen GA, et al. High incidence of adverse events in healthy volunteers receiving rifampicin and adjusted doses of lopinavir/ritonavir tablets. *AIDS.* 2008;**22**:931-935.
5. Ren Y, Nuttall JJ, Egbers C, et al. Effect of rifampicin on lopinavir pharmacokinetics in HIV-infected children with tuberculosis. *J. Acquir. Immune Defic. Syndr.* 2008;**47**:566-569.
6. la Porte CJ, Colbers EP, Bertz R, et al. Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifampin in healthy volunteers. *Antimicrob. Agents Chemother.* 2004;**48**:1553-1560.
7. Grange S, Schutz M, Schmitt C, Riek M, Gaudeul-Ehrhart E. Unexpected hepatotoxicity observed in a healthy volunteer study on the effects of multiple dose rifampicin on the steady-state pharmacokinetics of ritonavir-boosted saquinavir and vice versa. Paper presented at: 6th International Workshop on Clinical Pharmacology of HIV Therapy 2005; Quebec, Canada, Abstract 35, p.27.
8. Rolla V, Vieira A, Pereira-Pinto D. Safety, efficacy and pharmacokinetics of ritonavir 400mg-saquinavir 400mg and rifampicin combined therapy in HIV patients with tuberculosis. Paper presented at: 3rd IAS Conference on HIV Pathogenesis and Treatment2005; Rio de Janeiro, Brasil.
9. Regazzi M, Carvalho AC, Villani P, Matteelli A. Treatment optimization in patients co-infected with HIV and Mycobacterium tuberculosis infections: focus on drug-drug interactions with rifamycins. *Clin. Pharmacokinet.* 2014;**53**:489-507.
10. McIlleron H, Ren Y, Nuttall J, et al. Lopinavir exposure is insufficient in children given double doses of lopinavir/ritonavir during rifampicin-based treatment for tuberculosis. *Antivir. Ther.* 2011;**16**:417-421.
11. Polk RE, Brophy DF, Israel DS, et al. Pharmacokinetic Interaction between amprenavir and rifabutin or rifampin in healthy males. *Antimicrob. Agents Chemother.* 2001;**45**:502-508.
12. Lan NT, Thu NT, Barrail-Tran A, et al. Randomised pharmacokinetic trial of rifabutin with lopinavir/ritonavir-antiretroviral therapy in patients with HIV-associated tuberculosis in Vietnam. *PLoS ONE.* 2014;**9**:e84866.
13. Naiker S, Connolly C, Wiesner L, et al. Randomized pharmacokinetic evaluation of different rifabutin doses in African HIV- infected tuberculosis patients on lopinavir/ritonavir-based antiretroviral therapy. *BMC pharmacology & toxicology.* 2014;**15**:61.
14. Boulanger C, Hollender E, Farrell K, et al. Pharmacokinetic evaluation of rifabutin in combination with lopinavir-ritonavir in patients with HIV infection and active tuberculosis. *Clin. Infect. Dis.* 2009;**49**:1305-1311.
15. Tanuma J, Sano K, Teruya K, et al. Pharmacokinetics of rifabutin in Japanese HIV-infected patients with or without antiretroviral therapy. *PLoS ONE.* 2013;**8**:e70611.
16. Bonora S, Boffito M, D'Avolio A, et al. Pharmacokinetics of Rifabutin coadministered with Lopinavir/Ritonavir in HIV patients affected by Tuberculosis. Paper presented at: IAS Conference on HIV Pathogenesis and Treatment2003; Paris, France.

17. McGregor MM, Olliaro P, Wolmarans L, et al. Efficacy and safety of rifabutin in the treatment of patients with newly diagnosed pulmonary tuberculosis. *Am. J. Respir. Crit. Care Med.* 1996;**154**:1462-1467.
18. Gonzalez-Montaner LJ, Natal S, Yongchaiyud P, Olliaro P. Rifabutin for the treatment of newly-diagnosed pulmonary tuberculosis: a multinational, randomized, comparative study versus Rifampicin. Rifabutin Study Group. *Tuber. Lung Dis.* 1994;**75**:341-347.
19. Cato A, Cavanaugh J, Shi H, Hsu A, Leonard J, Granneman R. The effect of multiple doses of ritonavir on the pharmacokinetics of rifabutin. *Clin. Pharmacol. Ther.* 1998;**63**:414-421.
20. Moultrie H, McIlleron H, Sawry S, et al. Pharmacokinetics and safety of rifabutin in young HIV-infected children receiving rifabutin and lopinavir/ritonavir. *J. Antimicrob. Chemother.* 2015;**70**:543-549.
21. Nakajima A, Fukami T, Kobayashi Y, Watanabe A, Nakajima M, Yokoi T. Human arylacetamide deacetylase is responsible for deacetylation of rifamycins: rifampicin, rifabutin, and rifapentine. *Biochem. Pharmacol.* 2011;**82**:1747-1756.
22. FDA. Label and Approval History MYCOBUTIN. 2008.
23. Blaschke TF, Skinner MH. The clinical pharmacokinetics of rifabutin. *Clin. Infect. Dis.* 1996;**22 Suppl 1**:S15-21; discussion S21-12.
24. Gatti G, Di Biagio A, De Pascalis CR, Guerra M, Bassetti M, Bassetti D. Pharmacokinetics of rifabutin in HIV-infected patients with or without wasting syndrome. *Br. J. Clin. Pharmacol.* 1999;**48**:704-711.
25. Gatti G, Papa P, Torre D, et al. Population pharmacokinetics of rifabutin in human immunodeficiency virus-infected patients. *Antimicrob. Agents Chemother.* 1998;**42**:2017-2023.
26. Wilkins JJ, Langdon G, McIlleron H, Pillai GC, Smith PJ, Simonsson US. Variability in the population pharmacokinetics of pyrazinamide in South African tuberculosis patients. *Eur. J. Clin. Pharmacol.* 2006;**62**:727-735.
27. Wilkins JJ, Savic RM, Karlsson MO, et al. Population pharmacokinetics of rifampin in pulmonary tuberculosis patients, including a semimechanistic model to describe variable absorption. *Antimicrob. Agents Chemother.* 2008;**52**:2138-2148.
28. Laporte-Simitsidis S, Girard P, Mismetti P, Chabaud S, Decousus H, Boissel JP. Inter-study variability in population pharmacokinetic meta-analysis: when and how to estimate it? *J. Pharm. Sci.* 2000;**89**:155-167.
29. Burman W, Benator D, Vernon A, et al. Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *Am. J. Respir. Crit. Care Med.* 2006;**173**:350-356.
30. Weiner M, Benator D, Burman W, et al. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. *Clin. Infect. Dis.* 2005;**40**:1481-1491.
31. Moyle GJ, Buss NE, Goggin T, Snell P, Higgs C, Hawkins DA. Interaction between saquinavir soft-gel and rifabutin in patients infected with HIV. *Br. J. Clin. Pharmacol.* 2002;**54**:178-182.
32. Breda M, Benedetti MS, Bani M, et al. Effect of rifabutin on ethambutol pharmacokinetics in healthy volunteers. *Pharmacol. Res.* 1999;**40**:351-356.
33. Benator DA, Weiner MH, Burman WJ, et al. Clinical evaluation of the nelfinavir-rifabutin interaction in patients with tuberculosis and human immunodeficiency virus infection. *Pharmacotherapy.* 2007;**27**:793-800.
34. Weiner M, Benator D, Peloquin CA, et al. Evaluation of the drug interaction between rifabutin and efavirenz in patients with HIV infection and tuberculosis. *Clin. Infect. Dis.* 2005;**41**:1343-1349.
35. Ford SL, Chen YC, Lou Y, et al. Pharmacokinetic interaction between fosamprenavir-ritonavir and rifabutin in healthy subjects. *Antimicrob. Agents Chemother.* 2008;**52**:534-538.
36. Gallicano K, Khaliq Y, Carignan G, Tseng A, Walmsley S, Cameron DW. A pharmacokinetic study of intermittent rifabutin dosing with a combination of ritonavir and saquinavir in patients infected with human immunodeficiency virus. *Clin. Pharmacol. Ther.* 2001;**70**:149-158.

37. Hamzeh FM, Benson C, Gerber J, et al. Steady-state pharmacokinetic interaction of modified-dose indinavir and rifabutin. *Clin. Pharmacol. Ther.* 2003;**73**:159-169.
38. Kraft WK, McCrea JB, Winchell GA, et al. Indinavir and rifabutin drug interactions in healthy volunteers. *J. Clin. Pharmacol.* 2004;**44**:305-313.
39. Narita M, Stambaugh JJ, Hollender ES, Jones D, Pitchenik AE, Ashkin D. Use of rifabutin with protease inhibitors for human immunodeficiency virus-infected patients with tuberculosis. *Clin. Infect. Dis.* 2000;**30**:779-783.
40. Hafner R, Bethel J, Power M, et al. Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. *Antimicrob. Agents Chemother.* 1998;**42**:631-639.
41. Hafner R, Bethel J, Standiford HC, et al. Tolerance and pharmacokinetic interactions of rifabutin and azithromycin. *Antimicrob. Agents Chemother.* 2001;**45**:1572-1577.
42. Jordan MK, Polis MA, Kelly G, Narang PK, Masur H, Piscitelli SC. Effects of fluconazole and clarithromycin on rifabutin and 25-O-desacetylrifabutin pharmacokinetics. *Antimicrob. Agents Chemother.* 2000;**44**:2170-2172.
43. Trapnell CB, Narang PK, Li R, Lavelle JP. Increased plasma rifabutin levels with concomitant fluconazole therapy in HIV-infected patients. *Ann. Intern. Med.* 1996;**124**:573-576.
44. Krishna G, Parsons A, Kantesaria B, Mant T. Evaluation of the pharmacokinetics of posaconazole and rifabutin following co-administration to healthy men. *Curr. Med. Res. Opin.* 2007;**23**:545-552.
45. Schwander S, Rusch-Gerdes S, Mateega A, et al. A pilot study of antituberculosis combinations comparing rifabutin with rifampicin in the treatment of HIV-1 associated tuberculosis. A single-blind randomized evaluation in Ugandan patients with HIV-1 infection and pulmonary tuberculosis. *Tuber. Lung Dis.* 1995;**76**:210-218.
46. Sirgel FA, Botha FJ, Parkin DP, et al. The early bactericidal activity of rifabutin in patients with pulmonary tuberculosis measured by sputum viable counts: a new method of drug assessment. *J. Antimicrob. Chemother.* 1993;**32**:867-875.
47. Chan SL, Yew WW, Ma WK, et al. The early bactericidal activity of rifabutin measured by sputum viable counts in Hong Kong patients with pulmonary tuberculosis. *Tuber. Lung Dis.* 1992;**73**:33-38.
48. Hong Kong Chest Service/British Medical Research Council. A controlled study of rifabutin and an uncontrolled study of ofloxacin in the retreatment of patients with pulmonary tuberculosis resistant to isoniazid, streptomycin and rifampicin. *Tuber. Lung Dis.* 1992;**73**:59-67.
49. Agarwala S, Mummaneni V, Geraldes M, Stoltz R, Mara EO. Pharmacokinetic effects of Rifabutin on Atazanavir with and without Ritonavir in healthy subjects. Paper presented at: 9th Conference on Retroviruses and Opportunistic Infections2002; Seattle, USA.
50. Skinner MH, Hsieh M, Torseth J, et al. Pharmacokinetics of rifabutin. *Antimicrob. Agents Chemother.* 1989;**33**:1237-1241.
51. *NONMEM User's Guides. (1989-2009)*. Version 7. Ellicott City, MD, USA: Icon Development Solutions; 2009.
52. Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit--a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. *Comput. Methods Programs Biomed.* 2005;**79**:241-257.
53. Ette EI, Williams PJ, eds. *Pharmacometrics: The Science of Qunatitative Pharmacology.* Hoboken, NJ: John Wiley & Sons, Inc.; 2007.
54. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J.* 2011;**13**:143-151.
55. Hennig S, Karlsson MO. *Rifabutin and Darunavir/rtv Drug-Drug Interaction Modelling and Simulation - Report for Sponsor:Tibotec Pharmaceuticals, Belgium.* Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden;2009.
56. Svensson EM, Karlsson MO. Use of a linearization approximation facilitating stochastic model building. *J. Pharmacokinet. Pharmacodyn.* 2014;**41**:153-158.

57. Karlsson MO, Sheiner LB. The importance of modeling interoccasion variability in population pharmacokinetic analyses. *J. Pharmacokinet. Biopharm.* 1993;**21**:735-750.
58. Holford NH. A size standard for pharmacokinetics. *Clin. Pharmacokinet.* 1996;**30**:329-332.
59. Weiner M, Burman W, Vernon A, et al. Low isoniazid concentrations and outcome of tuberculosis treatment with once-weekly isoniazid and rifapentine. *Am. J. Respir. Crit. Care Med.* 2003;**167**:1341-1347.
60. Naiker S, Conolly C, Weisner L, et al. Pharmacokinetic Evaluation of Different Rifabutin Dosing Strategies in African TB Patients on Lopinavir/ritonavir-based ART 18th Conference on Retroviruses and Opportunistic Infections, ; 27 Feb- 2 Mar 2011, 2011; Boston, USA.
61. Sekar V, Lavreys L, De Paepe E, et al. Pharmacokinetic interaction between darunavir in combination with low-dose ritonavir and rifabutin. Joint meeting of the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy, and the 46th meeting of the Infectious Diseases Society of America; 2008; Washington, DC, USA.
62. Agouron Pharmaceuticals. *Project RBD Analytical Report HPLC Analysis of AG1343-523 in Human Plasma.* 1996.
63. Ng J, Nada A, Freeman S, et al. Pharmacokinetics of rifabutin 150 mg TIW plus LPV/r 400/100 mg BID administered in healthy adult subjects. Paper presented at: 10th International Workshop on Clinical Pharmacology of HIV Therapy2009; Amsterdam, The Netherlands.
64. Sekar VJ, Lefebvre E, De Pauw M, Vangeneugden T, Hoetelmans RM. Pharmacokinetics of darunavir/ritonavir and ketoconazole following co-administration in HIV-healthy volunteers. *Br. J. Clin. Pharmacol.* 2008;**66**:215-221.
65. Hennig S, Naiker S, Reddy T, et al. The effect of SLCO1B1 polymorphisms on the pharmacokinetics of rifabutin in African HIV-infected patients with tuberculosis. *Antimicrob. Agents Chemother.* 2015.
66. Ramachandran G, Bhavani PK, Hemanth Kumar AK, et al. Pharmacokinetics of rifabutin during atazanavir/ritonavir co-administration in HIV-infected TB patients in India. *Int. J. Tuberc. Lung Dis.* 2013;**17**:1564-1568.
67. la Porte CJ, Sabo JP, Elgadi M, Cameron DW. Interaction studies of tipranavir-ritonavir with clarithromycin, fluconazole, and rifabutin in healthy volunteers. *Antimicrob. Agents Chemother.* 2009;**53**:162-173.
68. Sekar V, Lavreys L, Van de Casteele T, et al. Pharmacokinetics of darunavir/ritonavir and rifabutin coadministered in HIV-negative healthy volunteers. *Antimicrob. Agents Chemother.* 2010;**54**:4440-4445.
69. Zhang J, Zhu L, Stonier M, et al. Determination of rifabutin dosing regimen when administered in combination with ritonavir-boosted atazanavir. *J. Antimicrob. Chemother.* 2011;**66**:2075-2082.
70. Zhang X, Fettner S, Zwanziger E, Rowell L, Salgo M. Pharmacokinetic interaction study of ritonavir-boosted saquinavir in combination with rifabutin in healthy subjects. *Antimicrob. Agents Chemother.* 2011;**55**:680-687.
71. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. *Drugs.* 2014;**74**:839-854.
72. McIlleron H, Meintjes G, Burman WJ, Maartens G. Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. *J. Infect. Dis.* 2007;**196 Suppl 1**:S63-75.
73. Kerbusch T, Milligan PA, Karlsson MO. Assessment of the relative in vivo potency of the hydroxylated metabolite of darifenacin in its ability to decrease salivary flow using pooled population pharmacokinetic-pharmacodynamic data. *Br. J. Clin. Pharmacol.* 2004;**57**:170-180.
74. Olsson-Gisleskog P, Jacqmin P, Perez-Ruixo JJ. Population pharmacokinetics meta-analysis of recombinant human erythropoietin in healthy subjects. *Clin. Pharmacokinet.* 2007;**46**:159-173.
75. World Health Organization. 19th WHO Model List of Essential Medicines (April 2015). 2015; http://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf?ua=1. Accessed 22/07/2015, 2015.
76. Khandelwal A, Harling K, Jonsson EN, Hooker AC, Karlsson MO. A fast method for testing covariates in population PK/PD Models. *AAPS J.* 2011;**13**:464-472.