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3 **Title: Arylacetamide deacetylase (AADAC) gene polymorphism and HIV infection**  
4 **affect the exposure of Rifapentine: a population pharmacokinetics analysis.**

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34

35 **ABSTRACT**

36 Rifapentine is a rifamycin used to treat tuberculosis. As for rifampicin, plasma exposures of  
37 rifapentine are associated with treatment response. While concomitant food intake and HIV  
38 infection explain part of the pharmacokinetic variability associated with rifapentine, few  
39 studies have evaluated the contribution of genetic polymorphisms. We evaluated the effects  
40 of functionally significant polymorphisms of the genes encoding OATP1B1, PXR, CAR, and  
41 AADAC on rifapentine exposure. Two studies evaluating novel regimens amongst Southern  
42 African patients with drug-susceptible pulmonary tuberculosis were included in this analysis.  
43 In RIFAQUIN, rifapentine was administered in the continuation phase of antituberculosis  
44 treatment in 1200mg once-weekly or 900mg twice-weekly doses. In Daily-RPE 450 or  
45 600mg were given daily during the intensive-phase of treatment. Nonlinear mixed-effects  
46 modelling was used to describe the pharmacokinetics of rifapentine and to identify significant  
47 covariates. A total of 1144 drug-concentration measurements, from 326 patients, were  
48 included in the analysis. Pharmacogenetic information was available for 162 patients. A one-

49 compartment model with first-order elimination and transit compartment absorption  
50 described the data well. In a typical patient (body weight of 56kg, fat-free-mass of 45kg), the  
51 values of clearance and volume of distribution were 1.33L/h and 25L, respectively. Patients  
52 carrying the AA variant (65.4%) of *AADAC* rs1803155 were found to have 10.4% lower  
53 clearance. HIV+ infected patients had 21.9% lower bioavailability. Once weekly doses of  
54 1200 mg were associated reduced clearance (-13.2%), compared to more frequently  
55 administered doses. Bioavailability was 23.3% lower amongst patients participating in the  
56 Daily-RPE study compared to RIFAQUIN. This is the first study to report the effect of  
57 *AADAC* rs1803155AA on rifapentine clearance. The observed increase in exposure is modest  
58 and unlikely to be of clinical relevance. The difference in bioavailability between the two  
59 studies is probably related to the different food concomitant to the dose. HIV coinfecting  
60 patients had lower rifapentine exposures.

61

## 62 INTRODUCTION

63 Rifamycins play a key role in the multidrug treatment of tuberculosis. Their sterilizing  
64 activity is exposure-dependent (1-3). Rifapentine, was approved by the Food and Drug  
65 Administration (FDA) in 1998 for the treatment of pulmonary tuberculosis (3,4). Rifapentine  
66 pharmacokinetics are influenced by age, weight, dosing pattern, human immunodeficiency  
67 virus (HIV) infection, and sex (5,6). Rifapentine is less rapidly absorbed than rifampicin,  
68 with peak plasma concentrations reached within 5 hours. Concomitant food markedly  
69 increases its absorption; the extent of rifapentine absorption increased by 33-86% when given  
70 with meals (7). Rifapentine has a half-life of approximately 12 hours in humans (8,9). With  
71 its long half-life and excellent sterilizing activity, rifapentine is an attractive alternative to  
72 rifampicin and is increasingly used to treat active tuberculosis and latent infection. However,

73 there is marked interpatient variability in rifamycin pharmacokinetics (10). The primary  
74 metabolic pathways for rifapentine involve deacetylation to the primary enzymatic metabolite  
75 25-desacetyl rifapentine, which is mediated by human arylacetamide deacetylase (*AADAC*)  
76 and non-enzymatic hydrolysis resulting in formation of the secondary metabolites 3-formyl  
77 rifapentine and 3-formyldesacetyl rifapentine (11). Protein binding of rifapentine is estimated  
78 to be about 98% (3,12). Like other rifamycin's, rifapentine induces its own metabolism (9).

79 Previously published data indicate that single nucleotide polymorphisms (SNPs) in the solute  
80 carrier organic anion transporter 1B1 (*SLCO1B1*) gene encoding the OATP1B1  
81 transmembrane receptor affect rifampicin concentrations (13,14). *SLCO1B1* rs4149032 C>T  
82 polymorphism, found in 70% of South Africans with tuberculosis living in Cape Town, was  
83 associated with 20% and 28% reductions in rifampicin bioavailability in heterozygotes and  
84 homozygotes, respectively (14). Rifamycins are also substrates of the drug efflux pump P-  
85 glycoprotein coded for by the polymorphic *ABCB1* gene (15) and are metabolized mainly by  
86 polymorphic human arylacetamide deacetylase (*AADAC*) (16). Human rifamycin exposures  
87 are also modulated by the pregnane X receptor (*PXR*) and constitutive androstane (*CAR*)  
88 nuclear receptors (17). Since the development of resistance to rifamycins and their  
89 bactericidal effects are related to rifamycin concentrations, SNPs substantially influencing  
90 rifamycin concentrations may be of therapeutic importance. Little is known about the  
91 pharmacogenetic correlates of rifapentine pharmacokinetics, which may potentially help in  
92 finding the optimal dose of rifapentine. Therefore, the aim of this study was to determine the  
93 effect of polymorphisms of *SLCO1B1*, *PXR*, *CAR*, and *AADAC* on rifapentine  
94 pharmacokinetics.

## 95 **RESULTS**

96 A total of 326 patients were included in the study and contributed a total of 1151  
97 concentrations-time points. Only 7 concentrations were below the LLOQ and were omitted  
98 from the analysis. The median body weight and age of the study participants were 56 kg and  
99 32 years respectively. All demographic characteristics are summarized in Table 1.

100 The population pharmacokinetics of rifapentine was well described by a one-compartment  
101 model with first-order elimination and transit compartment absorption. Fat-free-mass(FFM)  
102 was found to be the best size descriptor for clearance ( $\Delta$ OFV 93 points,  $p < 0.001$  when  
103 including FFM for allometric scaling on clearance and 23 points better than using body  
104 weight) and total body weight for volume of distribution ( $\Delta$ OFV 20,  $p < 0.001$ ). The  
105 absorption of rifapentine was described using a series of transit compartments, which  
106 significantly improved the model with respect to simple first-order absorption ( $\Delta$ OFV 421,  
107  $p < 0.001$ ). In a typical patient (46 kg FFM and 56 kg weight), the values of clearance and  
108 volume of distribution were 1.33 L/h and 25 litres. Final parameter estimates (shown in Table  
109 3) were in agreement with the previously published results (6,18) and a VPC of the final  
110 model is shown in Figure 1.

111 Of 326 patients, pharmacogenetic data was available for 162 (49.7%) all of whom were  
112 enrolled from South African sites. The distribution of genotype and allele frequencies are  
113 presented in Table 2. *SLCO1B1* rs2306283 and *AADAC* rs1803155 variant alleles were  
114 found in 82% of patients whereas the *NR1I2* rs2472677 and *NR1I2* rs1523130 variant alleles  
115 existed at a low overall frequency of 33.5% and 16.4% respectively. In keeping with our  
116 previous findings among South Africans in Cape Town (14), the *SLCO1B1* rs4149032 variant  
117 allele frequency was found to be 0.75 (Table 2).

118 After screening and inclusion of genetic information (and imputation of missing genotype  
119 with a mixture model), patients homozygous for *AADAC* rs1803155 AA polymorphism were

120 found to have 10.4% lower clearance of rifapentine compared to subjects that were  
121 rs1803155 GG or GA ( $\Delta$ OFV 6.2,  $p=0.013$ ). Initially the three categories of rs1803155 (AA,  
122 GA, GG) were analysed as separate groups to estimate the respective effects of GA and GG.  
123 However, the estimated effects were similar for GG & GA, and when combined the model  
124 goodness of fit was not affected. Using the principle of parsimony, we decided to use the  
125 simpler model, as the effects of GG and GA were not statistically significant. The other  
126 pharmacogenetic variants did not affect the pharmacokinetic parameters.

127 Patients infected with HIV infection were found to have 21.9% lower bioavailability ( $\Delta$ OFV  
128 42,  $p<0.001$ ). The patients who were treated with high 1200 mg doses of rifapentine tended  
129 to have clearance reduced by 13.2% compared to other dose groups ( $\Delta$ OFV 17,  $p<0.001$ ).  
130 The pharmacokinetic differences between the two studies were explored and it was found that  
131 the bioavailability of rifapentine in the Daily RPE study was 23.3% lower than in the  
132 RIFAQUIN study ( $\Delta$  OFV 59,  $p<0.001$ ). The pharmacogenetic covariates other than *AADAC*  
133 rs1803155 polymorphism didn't have significant effects on the pharmacokinetic parameters.

#### 134 **DISCUSSION**

135 The present study is the first to investigate the influence of various plausible physiologically-  
136 relevant candidate gene polymorphisms on rifapentine pharmacokinetics. We developed a  
137 population pharmacokinetic model of rifapentine, which was consistent with previous reports,  
138 and tested the effect of genotype information on the pharmacokinetic parameters. We showed  
139 that the *AADAC* rs1803155 polymorphism is associated with rifapentine clearance. Subjects  
140 carrying the AA genotype had 10.4% lower clearance than those carrying AG or GG, thus  
141 leading to increased rifapentine exposure. The low clearance due to this polymorphism is  
142 consistent with previous studies reporting decreased activity of *AADAC* activity due to the  
143 presence of the variant allele (19). The majority of patients in our study had the *AADAC*

144 rs1803155 AA variant allele which occurred at a frequency of 0.82, and 65% were  
145 homozygous for the single nucleotide polymorphism, which could, in part, account for the  
146 relatively high rifapentine exposures described. The polymorphism occurs at lower  
147 frequencies of 0.50 to 0.64 in European American, African American, Korean, and Japanese  
148 populations (19). Another study identified lower rifapentine concentrations in black Africans  
149 but the influence of pharmacogenetic factors, which might account for the difference in the  
150 genotype frequencies between the populations, was not explored (20), whereas Sloan *et al.*,  
151 who explored the influence of *AADAC* gene polymorphisms on rifampicin pharmacokinetics  
152 in Malawian patients, did not identify a significant relationship (21). The prevalence of variant  
153 genotypes is different between African ethnic groups and may be the reason for this  
154 contrasting effect. As only 3 of 162 patients had rs1803155 GG, no meaningful separate  
155 estimate of clearance for this genotype could be obtained. In further attempts to explain  
156 variability in rifapentine pharmacokinetics, we explored the effects of several polymorphisms  
157 of drug transporters and transcriptional regulators. The choice of polymorphisms was based  
158 on those previously described to affect drug disposition, and also by previous  
159 pharmacogenetic studies conducted on rifampicin. Interestingly, we could not detect the  
160 effect *SLCO1B1* rs4149032 polymorphism on pharmacokinetics of rifapentine, even with a  
161 carrier, no carrier approach. The frequency of *SLCO1B1* in our cohort was 0.75, which is in  
162 agreement with previous finding in South African patients from the Cape Town region.  
163 Similarly, we did not find a statistically significant effect associated with *SLCO1B1*  
164 rs2306283, which existed in our study population at a frequency of 0.82. *SLCO1B1*  
165 polymorphisms have been reported to be associated with low rifampicin levels (13,14) and  
166 the lack of effect on rifapentine may suggest differences in the ADME of the two drugs. It  
167 may be that this transporter does not play a major role in the pharmacokinetics of rifapentine,  
168 or that the variant allele is associated with greater induction by rifampicin. We did not

169 observe an effect due to polymorphisms of the transcriptional regulators. This could be due to  
170 activation of PXR or CAR by rifapentine, which may have overridden any constitutive  
171 effects.

172 Additionally, we found that HIV infected patients have lower bioavailability of rifapentine.  
173 While the association of HIV infection with antituberculosis drug exposures is inconsistent,  
174 our findings for rifapentine are consistent with recent studies (22-24). The data available was  
175 not sufficient to identify potential drug-drug interactions with the various antiretroviral drugs  
176 prescribed concomitantly.

177 Patients in the higher dose group (1200 mg given once weekly) had increased exposure in the  
178 current study contrary to the findings by Savic *et al.*, which describes a decrease in the  
179 bioavailability of rifapentine with increased dose (6). The reduced dosing frequency in this  
180 group, may have led to reduced auto-induction and thus increased exposure.

181 Previous reports demonstrate that exposure to rifamycins is reduced in males due to a higher  
182 FFM: body weight ratio (25). The study by Langdon *et al.* described a 35% reduction in the  
183 clearance of 25-desacetyl rifapentine amongst females (5). In the present analysis, as  
184 allometric scaling with FFM accounted for the variability associated with sex, we did not  
185 observe any outstanding effects of sex. There was a difference in bioavailability between the  
186 two studies included in this analysis. This may be due to differences in food intake with the  
187 dose. Rifapentine absorption is strongly enhanced when it is administered with food (7). The  
188 finding that the Daily RPE study had a lower bioavailability may arise from the fact that  
189 meals with the dose were not standardized, in contrast to the RIFAQUIN study where a  
190 standard meal was provided throughout the study.

191 To conclude, our study is the first to show that the *AADAC* rs1803155 (AA) genotype is  
192 associated with lower rifapentine clearance, leading to increased rifapentine exposure. This

193 effect should be confirmed in a larger independent analysis. The pharmacogenetic association  
194 was modest compared to the study effect, which is likely linked to differences in the pattern  
195 of food use across the studies and highlights the importance of food recommendations both  
196 when the drug is used in a programmatic setting and when its pharmacokinetics is  
197 investigated. Additionally, we found that rifapentine exposure was lower in HIV infected  
198 patients, a finding consistent with previous studies and warranting further investigation to  
199 assess whether dose adjustment strategies should be considered. Lastly, patients dosed with  
200 1200 mg once weekly doses had lower clearance, possibly as a result of less pronounced  
201 autoinduction.

202

## 203 MATERIALS AND METHODS

204 **Study population:** This analysis was performed on patients diagnosed with pulmonary TB  
205 from two clinical studies: The Phase III RIFAQUIN study (ISRCTN44153044) (26) and two-  
206 stage activity-safety study of daily rifapentine (27), hereinafter “Daily RPE”  
207 (NCT00814671). A subset of participants from these studies provided their consent to assess  
208 the effect of genetic polymorphisms of nuclear receptors, drug metabolizing enzymes, and  
209 drug transporters on the pharmacokinetics of rifapentine.

210 The RIFAQUIN study included two experimental arms in which patients were dosed with  
211 daily moxifloxacin, rifampicin, pyrazinamide, and ethambutol for 2 months followed by a  
212 continuation phase with either 4 months of once weekly 1200 mg rifapentine together with  
213 400 mg moxifloxacin, or 2 months of 400 mg moxifloxacin twice weekly with 900 mg of  
214 rifapentine. The RIFAQUIN study was conducted at sites in the Western Cape and Gauteng  
215 regions of South Africa and in Harare, Zimbabwe. The doses of rifapentine and moxifloxacin  
216 were taken with 240 mL of water 15 minutes after a light meal of 2 hard-boiled eggs with

217 bread. During the 4<sup>th</sup> month of treatment, blood samples were drawn for determination of  
218 plasma rifapentine concentrations. The pharmacokinetic assessment involved rich (with a  
219 pre-dose and samples at 1, 2, 3, 5, 7, 10, 12, 26, and 50 h after dosing) or sparse sampling  
220 (samples drawn around 2, 5, and 24 or 48 h after dosing).

221 The Daily RPE study was open-label and had two experimental arms. Patients with  
222 pulmonary tuberculosis were randomized to 450 or 600 mg rifapentine daily, which replaced  
223 600 mg rifampicin during the intensive phase of standard therapy. The study participants  
224 were recruited in the Western Cape, South Africa. The patients were advised to take the  
225 required Rifapentine dose with food, but no standardised meal was provided during the study  
226 and no accurate details about food intake with the dose were recorded. Pharmacokinetic  
227 sampling was performed at approximately one month after starting therapy and samples were  
228 obtained either with intensive (with samples pre-dose and at 0.75, 1.5, 3.5, 5, 12, and 24 h  
229 after dose), or sparse sampling (0.5-2 h and 5-8 h after dose). Separate written informed  
230 consent for the pharmacogenetic study was obtained from participants retrospectively. The  
231 pharmacogenetic study was reviewed and approved the Research Ethics Committee of the  
232 University of Cape Town and the University of the Witwatersrand.

233 **Drug determination:** Plasma rifapentine concentrations were determined with a validated  
234 liquid chromatography-tandem mass spectrometry assay developed in the Division of Clinical  
235 Pharmacology, University of Cape Town. Samples were processed with a protein  
236 precipitation extraction method using rifaximin as internal standard, followed by high  
237 performance liquid chromatography with MS/MS detection using an AB SCIEX API 3200  
238 instrument. The analyte and internal standard were monitored at mass transitions of the  
239 protonated precursor ions  $m/z$  877.3 and  $m/z$  786.3 to the product ions  $m/z$  845.4 and  $m/z$   
240 754.1 for rifapentine and rifaximin, respectively. The calibration curves fit quadratic  
241 (weighted by 1/concentration) regressions over the ranges 0.156 – 40.0 mg/L for rifapentine.

242 The accuracies for the rifapentine assay were 103.9%, 102.8%, and 97.5% at the low,  
243 medium, and high QC levels, respectively, during inter-batch validation. The lower limit of  
244 quantification (LLOQ) was 0.156 mg/L.

245 **SNP genotyping:** Genomic DNA was extracted from 200  $\mu$ L whole blood using QIAamp  
246 DNA Mini Kit (Qiagen, Inc., Valencia, California) in accordance with the manufacturer's  
247 protocol. DNA was quantified spectrophotometrically using NanoDrop (Thermo Fisher  
248 Scientific Inc., Wilmington, Delaware) before storage at  $-20^{\circ}\text{C}$ . Genotyping was performed  
249 by real-time polymerase chain reaction (PCR) on a DNA Engine Chromo4 system (Bio-Rad  
250 Laboratories, Inc., Hercules, California). The PCR protocol involved an initial denaturation  
251 step at  $95^{\circ}\text{C}$  for 15 min, followed by 50 cycles of amplification at  $95^{\circ}\text{C}$  for 15 s and final  
252 annealing at  $60^{\circ}\text{C}$  for 1 min. TaqMan Genotyping Master Mix and assays for *SLCO1B1*  
253 rs2306283 (SNP ID: C\_1901697\_20), *SLCO1B1* rs4149032 (C\_1901709\_10), *NR1I2*  
254 rs2472677 (C\_26079845\_10), *NR1I2* rs1523130 (C\_9152783\_20), and *AADAC* rs1803155  
255 (C\_8911003\_1\_) were obtained from Thermo Fisher Scientific (Waltham, Massachusetts).  
256 Allelic discrimination plots and genotype assignments were performed using Opticon  
257 Monitor, version 3.1 from Bio-Rad Laboratories.

258 **Pharmacokinetic analysis:** Rifapentine plasma concentration-time data was analysed using a  
259 nonlinear mixed-effects model implemented in NONMEM 7.4.2 (28). The execution of runs  
260 was through Perl-speaks-NONMEM, Pirana and graphical diagnostics were created using  
261 Xpose 4.6.0 and R (29,30). Estimation of typical population pharmacokinetic parameters,  
262 along with their random inter-individual (IIV) and inter-occasion (IOV) variability was  
263 performed using first-order conditional estimation method with  $\epsilon$ - $\eta$  interaction (FOCE  
264 INTER). A lognormal distribution was assumed for IIV and IOV and a combined additive  
265 and proportional model for the residual unexplained variability (RUV) was evaluated.  
266 Various structural models were tested including one or two-compartment distribution with

267 first-order elimination and first-order absorption with or without lag time or transit  
268 compartment absorption (31). The influence of genetic polymorphisms on rifapentine  
269 pharmacokinetics for patients with unknown genotype was identified using mixture  
270 modelling (32). The effect of the genotype was first tested using method *EXTRA* which  
271 estimates the association only for the patients with available genetic information but also  
272 estimating an additional covariate effect for the unknown genotype. Subsequently, the *MIX*  
273 method to impute values using mixture modelling was applied to include the patient with  
274 unknown genotype to strengthen the robustness of the findings (32). Model selection was  
275 based on changes in the NONMEM objective function value ( $\Delta$ OFV), and visual inspection  
276 of conditional weighted residuals (CWRES) versus time, visual predictive checks (33), and  
277 basic goodness of fit plots (GOF). During model development, physiological plausibility and  
278 the precision of the parameter estimates were also considered. The model parameters of the  
279 final model were evaluated for their precision using sampling importance resampling method  
280 (SIR) (34).

281 Allometric scaling was applied on clearance (CL), and volume of distribution (V) to adjust  
282 for the effect of body size, according to Anderson and Holford (35). Fat-free mass (FFM),  
283 and fat mass (FAT) were tested as alternative size predictors through allometric scaling  
284 instead of total body weight (35,36). After the inclusion of allometric scaling, potential  
285 demographic, study site specific and pharmacogenetic covariates were screened inspecting  
286 parameter versus covariate plots and then tested in the model using drops in objective  
287 function value (assumed to be  $\chi$ -square distributed and thus using 3.84 points drop as  
288 significant at  $p < 0.05$  for the inclusion of a single parameter), while scrutinising the  
289 physiological plausibility of the effect (37).

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432 **Table 1: Demographic and clinical characteristics of patients**

Demographic & Clinical Characteristics	Daily RPE 450 mg group (N=44)	Daily RPE 600 mg group (N=41)	RIFAQUIN 900 mg group (N=116)	RIFAQUIN 1200 mg group (N=125)	Overall (N=326)
No. of PK samples	166	130	416	432	1144
Sex (male/female)	(33/11)	(32/9)	(72/44)	(81/44)	(218/108)
Number of HIV+ patients	6 (13.6%)	7 (17.1%)	30 (25.9%)	16(12.8%)	59(18.1%)
Median age, range (yrs)	29 (19-61)	29 (18-63)	31 (19-64)	34 (19- 80)	32 (18-80)
Median weight in kg (range)	55 (45-79)	55 (45-94)	55 (38-77)	57 (38- 78)	56 (38-94)
Median FFM in kg (range)	47 (32-58)	47 (32-56)	45 (27-62)	45 (27-60)	45 (27-62)

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442 **Table 2: Observed genotype and allele frequency of Single nucleotide polymorphisms in the**  
 443 **study (N=162)**

Genotype	Genotype frequency (%)			Allele frequencies	
	AA	AG	GG	A	G
SLCO1B1 A>G rs2306283	8 (4.94)	43 (26.5)	111 (68.5)	0.18	0.82
SLCO1B1 C>T rs4149032	15 (9.26)	52 (32.1)	95 (58.6)	0.25	0.75
*NR1I2 C>T rs2472677	71 (44.1)	72(44.7)	18 (11.2)	0.67	0.34
NR1I2 T>C rs1523130	116 (71.6)	39 (24.1)	7 (4.3)	0.84	0.16
AADAC G>A rs1803155	3 (1.85)	53 (32.7)	106 (65.4)	0.18	0.82

444 \*The data available only for 161 patients

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461 **Table 3:** Final parameter estimates for rifapentine population pharmacokinetic model

Parameter	Estimate	95% CI	IIV <sup>+</sup> or IOV <sup>++</sup>	95% CI
CL <sup>a</sup> (L/hr)	1.33	1.14;1.54	23.0% <sup>+</sup>	17.7;28.6
V <sup>a</sup> (L)	25	21.9;28.4	12.8% <sup>+</sup>	8.8;17.4
ka (hr <sup>-1</sup> )	0.814	0.568;1.26	48.9% <sup>++</sup>	36.4;59.8
MTT (hr)	1.47	1.20;1.78	37.4% <sup>++</sup>	28.3;48.6
NN	10.2	6.70;14.0	-	-
F	1 FIXED		20.3% <sup>++</sup>	14.9;26.4
Proportional residual error (%)	9.56	7.09;13.2	-	-
Additive residual error (mg/L)	0.247	0.143-0.401	-	-
HIV+ effect on F (%)	-21.9	-33.2; -6.64	-	-
Group on 1200 mg dose in RIFAQUIN study on CL (%)	-13.2	-22.8; -4.36	-	-
Daily RPE study on F (%)	-23.3	-35.6; -9.25	-	-
AADAC rs1803155 (AA) effect on CL (%)	-10.4	-17.3; -3.53	-	-

462 CL-oral clearance; V-apparent volume of distribution in the central compartment;  $k_a$ -first-  
463 order absorption rate constant; MTT- absorption mean transit time; NN- number of  
464 hypothetical transit compartments; F- oral bioavailability; HIV+ - Human immunodeficiency

465 virus positive; AADAC- arylacetamide deacetylase. IIV- inter-individual variability, and  
466 IOV- inter-occasional variability are expressed as percent coefficient of variation (% CV).

467 a The typical values of clearance and volume of distribution reported for a patient with body  
468 weight 56 kg and FFM of 46 kg.

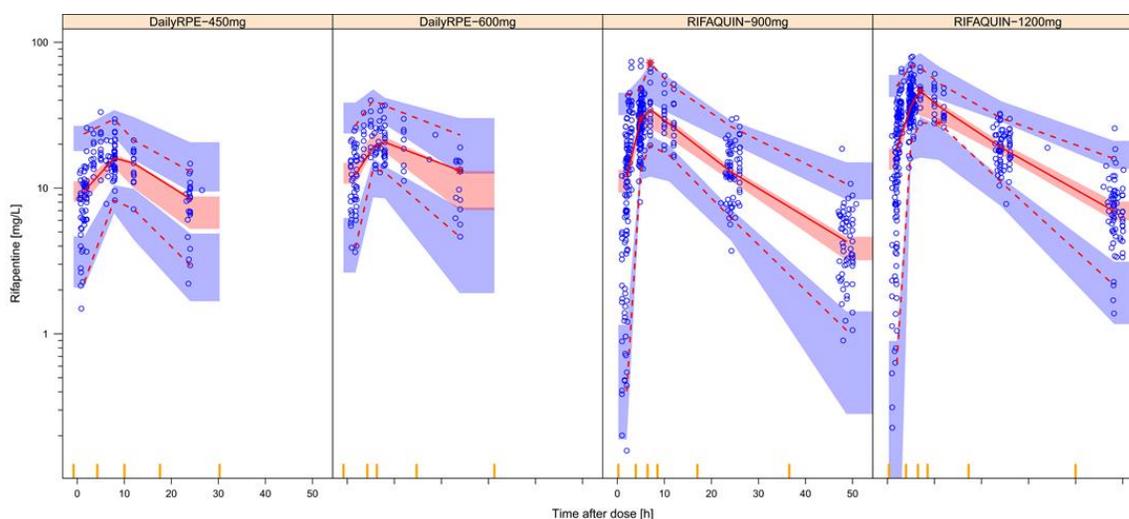
469 95% CI of parameter estimates obtained with Sampling importance resampling (SIR) n=1000  
470 of the final model.

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473 Figure 1: Visual predictive check (VPC) for the final rifapentine population pharmacokinetic

474 model in log scale, stratified according to different dose groups in the analysis.



475 The lower, middle, and upper solid lines are the 2.5<sup>th</sup>, 50<sup>th</sup>, and 97.5<sup>th</sup> percentiles of the  
476 observed plasma concentration. The shaded areas are the 95% confidence intervals for the  
477 same percentiles, obtained from re-simulations of the same trial.

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