

5-14-2020

Twice-Daily Doravirine Overcomes the Interaction Effect from Once-Weekly Rifapentine and Isoniazid in Healthy Volunteers.

Edwin Lam
Thomas Jefferson University

Joseph Schaefer
Thomas Jefferson University

Richard Zheng
Thomas Jefferson University

Tingting Zhan
Thomas Jefferson University

Follow this and additional works at: <https://jdc.jefferson.edu/petfp>
Walter K. Kraft

 Part of [Thomas Jefferson University Department of Pharmacology Commons](#)

[Let us know how access to this document benefits you](#)

Recommended Citation

Lam, Edwin; Schaefer, Joseph; Zheng, Richard; Zhan, Tingting; and Kraft, Walter K., "Twice-Daily Doravirine Overcomes the Interaction Effect from Once-Weekly Rifapentine and Isoniazid in Healthy Volunteers." (2020). *Department of Pharmacology and Experimental Therapeutics Faculty Papers*. Paper 120.

<https://jdc.jefferson.edu/petfp/120>

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's [Center for Teaching and Learning \(CTL\)](#). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Pharmacology and Experimental Therapeutics Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: JeffersonDigitalCommons@jefferson.edu.

1 **Title:** Twice-Daily Doravirine Overcomes the Interaction Effect from Once-Weekly Rifapentine and
2 Isoniazid in Healthy Volunteers

3
4 **Authors:** Edwin Lam¹, Joseph Schaefer², Richard Zheng¹, Tingting Zhan¹, & Walter K. Kraft¹

5
6 **Affiliations:** Department of Pharmacology & Experimental Therapeutics¹ and Sidney Kimmel Medical
7 College², Thomas Jefferson University, Philadelphia, PA, USA

8
9 **Corresponding Author:**

10 Edwin Lam, PharmD
11 Department of Pharmacology & Experimental Therapeutics
12 Thomas Jefferson University
13 132 South 10th Street, 1170 Main Building
14 Tel: 215-955-9076
15 Email: Edwin.lam@jefferson.edu

16
17 **Conflicts of Interest:** All authors declared no competing interests for this work.

18
19 **Funding:** This work was supported by an Investigator Studies Program grant provided by Merck & Co,
20 Inc. [MISP58495]. Edwin Lam is supported by the National Institutes of Health institutional training grant
21 [T32GM008562].

22
23 **Keywords:** Human immunodeficiency virus; tuberculosis, non-nucleoside reverse transcriptase inhibitor;
24 rifamycin; drug interaction; doravirine

48 **Abstract:**

49 Doravirine (DOR) is a non-nucleoside reverse transcriptase inhibitor indicated for the treatment of human
50 immunodeficiency virus-1 (HIV-1). Its use in combination with rifapentine (RPT), an anti-tuberculosis
51 antibiotic, may reduce the exposure of DOR compromising viral suppression in those living with HIV-1 co-
52 infected with tuberculosis. We conducted a prospective, phase I, open label, two-period, fixed sequence,
53 drug interaction study to evaluate the effect of once-weekly RPT and isoniazid (INH) on the
54 pharmacokinetics of DOR in healthy volunteers. DOR 100 mg was administered alone twice-daily for 4
55 days in period 1. In period 2, once-weekly RPT+INH was co-administered with multiple doses of DOR 100
56 mg twice-daily for study days 7, 14, and 21. Plasma was obtained for DOR pharmacokinetics when given
57 alone and co-administered with RPT+INH. Eleven healthy volunteers enrolled and completed the study.
58 The geometric mean ratios and 90% confidence intervals for DOR AUC_{0-12} and C_{12} in the presence of
59 RPT+INH compared to DOR alone were 0.71 (0.60-0.85) and 0.69 (0.54-0.89), respectively. Although
60 exposures were moderately reduced in the presence of RPT+INH, trough DOR values were within the
61 concentration range associated with virological suppression. These results demonstrate that a modest
62 decrease in doravirine exposure would unlikely be clinically relevant in a virally suppressed patient co-
63 administered once-weekly RPT+INH.

64

65

66

67

68

69

70

71

72 **Introduction**

73 Doravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used in combination with
74 other antiretrovirals (ARV) for the treatment of HIV-1 infection in adults. It is non-inferior to current
75 standard of care ARV regimens with fewer adverse events.^{1,2} The elimination of doravirine is primarily
76 through metabolism via cytochrome P450 (CYP) 3A mediated oxidation to an M9 metabolite.³ In vitro
77 studies demonstrate low potential of interference from the parent or metabolite on phase I and II
78 metabolizing enzymes and drug transporters.³ Therefore, doravirine has a lower potential for drug-drug
79 interactions compared to other NNRTIs and does not impact the pharmacokinetics of other drugs.
80 Considering the predominant route of elimination is through CYP3A, co-administration with strong
81 inhibitors and inducers may alter the pharmacokinetic profile of doravirine.

82 The Centers for Disease Control and Prevention (CDC) currently recommends several latent
83 tuberculosis infection (LTBI) treatment options for persons with HIV and includes either once-daily
84 isoniazid for nine months, rifampin or rifabutin once-daily for four months, or once-weekly rifapentine
85 and isoniazid for three months.⁴ The rifamycin class of anti-tuberculosis agents are strong inducers of
86 CYP enzymes, including CYP3A, with rifabutin being the less potent inducer of the three. Co-
87 administration with multiple-doses of rifampin significantly reduced doravirine trough concentrations by
88 97% with multiple-dose rifabutin similarly reducing troughs by 68%.^{5,6} With the exception of rifabutin,
89 where twice-daily doses of doravirine are predicted to overcome the interaction⁶, the use of rifampin
90 and rifabutin together with once-daily doses of doravirine is contraindicated. A three month
91 rifapentine based regimen has comparable efficacy and safety compared to lengthy once-daily anti-
92 tuberculosis regimens.⁷ The magnitude of drug-drug interaction between doravirine when co-
93 administered with rifapentine and isoniazid has not been defined.

94 The objective of this study was to evaluate the effects of once-weekly rifapentine and isoniazid
95 on the steady-state pharmacokinetics of twice-daily doravirine, and to assess the safety and tolerability
96 of these co-administered drugs.

97 **Methods**

98 The study was approved by the Thomas Jefferson University Institutional Review Board and
99 registered on clinicaltrials.gov (NCT03886701). The study was conducted in accordance to Good Clinical
100 Practice standards and applicable federal and/or local regulatory requirements. All participants provided
101 written informed consent prior to beginning the study.

102 **Study population**

103 Healthy HIV and TB negative adult men or non-pregnant women between 18-60 years old with a
104 body mass index of 19-33 kg/m² weighing between 45-120 kg at screening were enrolled in the study.
105 Women of childbearing potential and their partners were required to use acceptable methods of
106 contraception during the time of the study and until four weeks after the last dose of drug. Women who
107 were postpartum for less than 12 months were excluded. Other exclusion criteria included any clinically
108 significant disease, current drug or alcohol abuse, known anaphylactic or systemic reactions to doravirine,
109 rifapentine, or isoniazid, and those who have received another study drug within four weeks or five half-
110 lives (whichever occurring first).

111 **Study design and treatments**

112 This was a phase I, prospective, open-label, two-period, fixed-sequence, drug-drug interaction
113 study conducted in healthy volunteers. (**Figure 1**) Subjects received doravirine 100 mg twice-daily for
114 four study days during the first period. In the second period, once-weekly weight based rifapentine and
115 isoniazid and pyridoxine 50 mg was co-administered with doravirine 100 mg twice-daily. The doses of
116 rifapentine were weight based and included 900 mg (≥ 50 kg) or 750 mg (32.1-49.9 kg) with a 900 mg
117 maximum dose. Isoniazid was given as a 15 mg/kg dose and rounded up to the nearest 50 or 100 mg

118 with a maximum dose of 900 mg. The doses and dosing schedule for rifapentine, isoniazid, and
119 pyridoxine were selected based on the Centers for Disease Control and Prevention treatment regimens
120 for LTBI.⁴ Subjects received a light meal prior to each doravirine dose for study days 1-4. For the morning
121 of study days 7, 14, and 21, isoniazid and pyridoxine was dosed following an overnight fast with
122 doravirine and rifapentine dosed after the subject received a meal. For days 8-13 and 15-20, subjects
123 received a light meal before each dose of doravirine. All subjects received 8 ounces of water with each
124 dose.

125 **Pharmacokinetic sampling and bioanalysis**

126 Plasma samples for doravirine were collected at pre-dose (0 hour), 0.5, 1, 1.5, 2, 3, 6, 12, 24, 36,
127 48 and 72 hours post dose on study days 4-7 (period one) and study days 21-24 (period two). A pre-dose
128 sample was taken for all subjects prior to starting period 1 and doravirine dosing to ensure no previous
129 doses of doravirine were taken. A doravirine trough concentration was collected on study days 15, 16,
130 and 20 prior to the administration of the second doravirine dose. Approximately 3 mL of blood was
131 collected into K2-EDTA vials and inverted 8-10 times before being centrifuged at 3000 rpm for 10
132 minutes. Plasma was aliquoted into a cryotube and was stored at -20°C before analysis. Plasma
133 doravirine concentrations were determined using a validated ultra-performance liquid chromatography
134 tandem mass spectrometry with a lower limit of quantification of 1 ng/mL over a calibration range of 1-
135 1000 ng/mL (developed and validated by Syneos Health Clinique, Quebec, QC, Canada).

136 **Safety and tolerability**

137 Safety and tolerability were assessed throughout the study and included monitoring for adverse events,
138 physical exams, vital signs, electrocardiograms, and laboratory safety tests (blood chemistry,
139 hematology, and urinalysis). Laboratory safety assessments were conducted in period 1 (study day 5)
140 and period 2 (study days 8, 15, and 22).

141 **Pharmacokinetic and statistical analysis**

142 Plasma doravirine pharmacokinetic parameters were estimated using a non-compartmental
143 analysis and performed on R version 3.6.1 with the PKNCA and ncappc packages. Doravirine
144 pharmacokinetic parameters included the area under the concentration-time curve during the dosing
145 interval (AUC_{0-12}), steady-state trough plasma concentration at the end of the dosing interval (C_{12}),
146 average steady-state plasma drug concentration during multiple dose administration (C_{avg}), peak plasma
147 concentration at steady-state (C_{max}), terminal elimination half-life ($t_{1/2}$), apparent clearance at steady-
148 state (CL_{ss}/F), and the accumulation ratio for both periods.

149 The parameters AUC_{0-12} , C_{12} , C_{avg} , and C_{max} were separately evaluated using a generalized estimating
150 equations (GEE) model with log-link with the primary predictor of period. Geometric means and
151 corresponding 95% confidence intervals were calculated for each treatment group. The 90% confidence
152 intervals were estimated from the GEE model for the geometric mean ratios for (doravirine + rifapentine
153 + isoniazid)/doravirine) alone. The statistical analysis was performed on R version 3.6.1 with the gee
154 package.⁸ Sample size was calculated from the reported variability in doravirine trough concentration in
155 HIV-infected men (1540 nmol/L and 95% CI: 1110-2140 nmol/L).⁹ Using a significance level of 5% with a
156 two-sided paired t-test, a sample size of 11 provided greater than 80% power to detect a change of 50%
157 in doravirine trough concentrations. The magnitude of change was selected on the assumption that a
158 50% change in trough concentrations would be clinically significant.

159

160 **Results**

161 **Subject demographics**

162 Eleven subjects (10 male and 1 female) were enrolled and completed the study with a mean (\pm SD) age of
163 46.4 (\pm 9.9) years old. Subjects were Black or African American (73%) or white (27%). Mean body
164 weights were 92.9 kg (range 75.5-109.4 kg) which allowed the maximum doses of rifapentine and

165 isoniazid (900 mg) for all subjects during the study. The mean (\pm SD) body mass index was 31.2 (\pm 2.6)
166 kg/m². All subjects were included in the PK and safety analysis.

167 **Doravirine plasma concentration time profile**

168 All pharmacokinetic data were included in the analysis and figures. All subjects had undetectable
169 doravirine concentrations in plasma at pre-dose prior to beginning study day 1. Two subjects had
170 undetectable doravirine concentrations in plasma at the 72-hour time point in the second period (study
171 day 24). Mean doravirine plasma concentration profiles alone and in combination with rifapentine and
172 isoniazid for all sampled points was plotted against time (**figure 2**). The mean doravirine plasma
173 concentration during the dosing interval for doravirine alone or in combination with rifapentine and
174 isoniazid is shown in **figure 3**. Co-administration with once-weekly rifapentine and isoniazid modestly
175 reduced the steady-state AUC₀₋₁₂, C₁₂, C_{avg}, and C_{max} by 29%, 31%, 29%, and 25%, respectively. **Figure 4**
176 displays the individual and geometric mean ratios for rifapentine + isoniazid + doravirine/doravirine
177 alone AUC₀₋₁₂, C₁₂, C_{avg}, and C_{max}. Rifapentine co-administration reduced doravirine half-life by 58% while
178 increasing the steady-state total plasma clearance by 41% (**table 1**).

179 **Safety and Tolerability**

180 Doravirine in combination with rifapentine and isoniazid was generally well tolerated with no
181 serious adverse events. Adverse events were mild in intensity with 9 out of 11 subjects (82%) reporting
182 at least one adverse event. The most common adverse event throughout the study was intravenous
183 catheter site pain and redness (45.5%) where blood sampling occurred. Nausea and vomiting was the
184 most common reported adverse event (9%) during period 1 where doravirine was dosed alone. During
185 the second period where doravirine was co-administered with weekly rifapentine and isoniazid, one
186 subject (9%) reported dysuria following the second week of rifapentine and isoniazid dosing. The same
187 subject reported chills, headache, and a fever following the third week of dosing rifapentine and

188 isoniazid. These symptoms subsided and were resolved two days after the report adverse event. All
189 laboratory parameters were within normal limits during the course of the study.

190

191 **Discussion**

192 In patients infected with HIV and LTBI, the current therapeutic options include daily rifampin or
193 rifabutin for 4 months or isoniazid daily for 9 months. Although both INH and rifamycin based regimens
194 are similarly effective in the treatment of LTBI in patients with HIV, patients are more likely to complete
195 shorter and convenient regimens. While rifapentine and isoniazid affords a shorter duration and dosing
196 frequency for treatment than INH monotherapy, drug interaction studies are infrequent to evaluate this
197 regimen co-administered with HIV antiretroviral therapies.

198 In this study, twice-daily doses of doravirine 100 mg dosed to steady-state was selected based
199 on nonparametric superposition predictions from a single dose drug interaction study with rifabutin.⁶
200 Furthermore, doravirine was generally well tolerated across multiple doses of up to 750 mg with robust
201 antiviral activity at 200 mg once-daily in patients with HIV-1 with a terminal half-life of approximately 15
202 hours.^{9,10} Therefore, a twice-daily dosing regimen for 4 days was selected in the first period for several
203 reasons: 1) given the safety profile of doravirine reported previously, a 100 mg twice-daily dose of
204 doravirine is expected to not be a safety concern, 2) it is expected that the 100 mg twice-daily doses of
205 doravirine should obtain the same level of virological efficacy as seen with patients dosed 200 mg once-
206 daily, and 3) steady-state exposure is expected within 3 days of dosing allowing steady-state doravirine
207 concentrations to be sampled by the fourth study day in the first period.

208 Doravirine is contraindicated when co-administered with drugs that are strong CYP3A inducers.
209 The current study evaluated the pharmacokinetics of steady-state doravirine in the presence of
210 rifapentine and isoniazid. Once-weekly doses of rifapentine and isoniazid moderately reduced doravirine
211 steady AUC_{0-12} and C_{12} following twice-daily doses of 100 mg doravirine in healthy volunteers. This

212 reduction in exposure is reflected by the increase in doravirine steady-state clearance (8.4 L/hour versus
213 5.9 L/hour) and a shortened half-life (15.2 hours versus 6.4 hours) in the presence of rifapentine and
214 isoniazid. Rifapentine is a potent inducer of CYP450 metabolizing enzyme specifically impacting CYP3A4,
215 CYP2C8, and CYP2C9 isoenzymes.¹¹ The potency of induction is 45% greater than rifabutin, with rifampin
216 being the most potent of the anti-tuberculosis rifamycins.¹² Therefore, this reduction in exposure with
217 subsequent increase in doravirine clearance was expected as seen in previous drug interaction studies,
218 where rifampin and rifabutin co-administration significantly reduced doravirine trough values following
219 once-daily dosing.^{5,6} This study reinforces the time-dependent change in the metabolic induction
220 capacity of once-weekly rifapentine. As seen in **figure 5**, mean doravirine C₁₂ concentrations reached a
221 nadir approximately 2 days following rifapentine dosing (study day 14).

222 In phase II studies doravirine doses of 25 mg and 200 mg have comparable virological efficacy in
223 patients with HIV-1 with geometric mean C₂₄ values at 107 ng/mL (77-149 ng/mL).⁹ While there is no
224 established therapeutic range that correlates with clinically sustained virological suppression and
225 efficacy, an NNRTI class-specific steady-state concentration 6-fold above the in vitro 50% inhibitory
226 concentration (IC₅₀) for wild type HIV would result in approximately 99% maximal viral reduction.¹⁵ In
227 the case of doravirine, the in vitro IC₅₀ is 5.1 ng/mL which results in a pharmacokinetic target of 31.5
228 ng/mL.¹⁶ Although doravirine mean steady-state trough values at the second week of rifapentine dosing
229 were below the observed C₂₄ in pivotal trials (**figure 5**), concentrations still remained 7.6-fold above the
230 values associated with maximal viral load reduction. Moreover, the nadir trough values seen at the
231 second week of rifapentine and isoniazid dosing were >50% of the values following a 25 mg dose in the
232 patient population where the antiviral activity was comparable to the higher dose levels. Based on the
233 strong correlation of doravirine trough values in the exposure-response relationship, trough
234 concentrations seen in this study are within the ranges associated with a ≥80% proportion of individuals
235 achieving HIV-1 RNA copies of <50 copies/mL.¹⁷

236 It should be noted that a true nadir cannot be defined given the absence of trough collections
237 on study days 17-19. Using the elimination rate and distribution volume of doravirine in the presence of
238 rifapentine observed in this study, trough values were predicted for study days 16-19 (**figure 6**). The
239 mean plasma trough concentrations at 12 and 24 hours was predicted to be 376.4 ng/mL suggesting
240 that concentrations of doravirine can be sustained above the IC_{50} during a once weekly course of
241 rifapentine. Although we observed a persistent reduction of up to 82% in doravirine C_{12} six days
242 following the last dose of rifapentine, the time-dependent metabolic induction is nonetheless similar to
243 reports in literature which observed up to 2-4 days of maximal induction following rifapentine
244 administration.^{13, 14}

245 There were minimal adverse events observed in this study. Compared to previous reports using
246 this regimen in drug interaction studies with other HIV-1 antiretrovirals,¹⁴ co-administration of
247 doravirine with once-weekly rifapentine and isoniazid at maximum doses was well tolerated. The most
248 common adverse event reported by 45.5% of subjects was intravenous catheter site pain and redness
249 which was unrelated to the study drugs. Only one female subject reported flu-like symptoms which
250 included fever, chills, and headache after the second dose of rifapentine, isoniazid, and doravirine. This
251 was anticipated, as a high incidence of flu-like symptoms have been reported following high dose
252 rifapentine and isoniazid, particularly in older aged white women.¹⁸ Furthermore, safety lab value trends
253 were within the normal ranges throughout the entirety of the study.

254 Several limitations should be noted. The study did not analyze the primary metabolite, M9,
255 which is a direct result of CYP-mediated oxidation. In the presence of an inducer such as rifapentine and
256 twice-daily dosing of doravirine, the exposure of M9 is expected to increase. The impact of the M9
257 metabolite on safety is unclear, as M9 is present as only 13% of parent dose, does not accumulate with
258 repeated dosing, and does not have activity against HIV reverse transcriptase.¹⁹ The study also enrolled
259 mostly male participants (10 male vs. 1 female). Although there was a gender imbalance in this study,

260 gender does not impact the pharmacokinetics of doravirine.¹⁷ Lastly, doravirine trough concentrations
261 were not collected for study days 17-19 during period two of the study. As such a true nadir cannot be
262 confirmed with certainty during that period where doravirine was co-administered with rifapentine and
263 isoniazid.

264 In summary, once-weekly oral rifapentine and isoniazid moderately reduced the AUC₀₋₁₂ and C₁₂
265 of twice-daily 100 mg doravirine by 29% and 31%, respectively. This reduction, however, was within the
266 trough values associated with virological efficacy seen in pivotal clinical studies. As a result, doravirine
267 100 mg administered twice-daily may be considered to mitigate the drug interaction effect of
268 rifapentine where the modest reduction in doravirine exposure is unlikely to be clinically relevant in a
269 virally suppressed patient.

270

271 **Study Highlights**

272 **What is the current knowledge of the topic?**

273 Co-infection with latent tuberculosis in persons living with Human Immunodeficiency Virus-1 (HIV-1) is
274 common. Rifapentine is an anti-tuberculosis antibiotic available as once-weekly treatment for latent
275 tuberculosis and is a potent inducer of cytochrome (CYP) 3A metabolic enzyme. There are limited
276 studies that evaluate rifapentine in the presence with antiretrovirals, including doravirine, a novel non-
277 nucleoside reverse transcriptase inhibitor metabolized by CYP3A.

278 **What question did this study address?**

279 This study evaluated the pharmacokinetics of twice-daily doravirine when co-administered with once-
280 weekly rifapentine and isoniazid.

281 **What does this study add to our knowledge?**

282 Following rifapentine-mediated CYP3A induction, doravirine steady-state trough concentrations
283 declined in a time-dependent manner. Steady-state clearance of doravirine increased with a >50%

284 reduction in plasma half-life following co-administration with rifapentine and isoniazid. Despite this
285 reduction, doravirine exposure is in a range that is likely to maintain viral suppression.

286 **How might this change clinical pharmacology or translational science?**

287 Doravirine 100 mg given twice-daily can mitigate the interactive effects of once-weekly rifapentine. Co-
288 administration was generally well tolerated with a modest decrease in doravirine exposure unlikely to
289 be clinically relevant. This dosing regimen may offer an alternative to virally suppressed patients on
290 antiretroviral therapy co-infected with latent tuberculosis and considering a rifapentine based regimen.

291

292 **Acknowledgements**

293 We thank the volunteers, nurses, and staff of the Clinical Research Unit at Thomas Jefferson University
294 for their contributions to this research.

295

296 **Author Contributions**

297 E.L. designed the wrote the manuscript, research, and analyzed the data; J.S. and T.Z. contributed to
298 analytical tools and analyzed the data; R.Z. and W.K.K. performed the research.

299

300 **References**

- 301 1. Molina, J.M., *et al.* Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults
302 with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-
303 inferiority trial. *Lancet HIV*. **5**, e211-e220 (2018).
- 304 2. Orkin, C., *et al.* Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to
305 Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-naive Adults With Human
306 Immunodeficiency Virus-1 Infection: Week 48 Results of the DRIVE-AHEAD Trial. *Clin Infect Dis*.
307 **68**, 535-544 (2019).
- 308 3. Sanchez, R.I., *et al.* Characterisation of the absorption, distribution, metabolism, excretion and
309 mass balance of doravirine, a non-nucleoside reverse transcriptase inhibitor in humans.
310 *Xenobiotica*. **49**, 422-432 (2019).
- 311 4. Sterling, T.R., *et al.* Three months of rifapentine and isoniazid for latent tuberculosis infection. *N*
312 *Engl J Med*. **365**, 2155-2166 (2011).
- 313 5. Yee, K.L., *et al.* The Effect of Single and Multiple Doses of Rifampin on the Pharmacokinetics of
314 Doravirine in Healthy Subjects. *Clin Drug Investig*. **37**, 659-667 (2017).
- 315 6. Khalilieh, S.G., *et al.* Multiple Doses of Rifabutin Reduce Exposure of Doravirine in Healthy
316 Subjects. *J Clin Pharmacol*. (2018).
- 317 7. Sterling, T.R., *et al.* Three months of weekly rifapentine and isoniazid for treatment of
318 Mycobacterium tuberculosis infection in HIV-coinfected persons. *AIDS*. **30**, 1607-1615 (2016).
- 319 8. Højsgaard, S., Halekoh, U. & Yan, J. The R Package geepack for Generalized Estimating Equations.
320 *2005*. **15**, 11 (2005).
- 321 9. Schurmann, D., *et al.* A randomized, double-blind, placebo-controlled, short-term monotherapy
322 study of doravirine in treatment-naive HIV-infected individuals. *AIDS*. **30**, 57-63 (2016).
- 323 10. Anderson, M.S., *et al.* Safety, tolerability and pharmacokinetics of doravirine, a novel HIV non-
324 nucleoside reverse transcriptase inhibitor, after single and multiple doses in healthy subjects.
325 *Antivir Ther*. **20**, 397-405 (2015).
- 326 11. Burman, W.J., Gallicano, K. & Peloquin, C. Comparative pharmacokinetics and
327 pharmacodynamics of the rifamycin antibacterials. *Clin Pharmacokinet*. **40**, 327-341 (2001).
- 328 12. Regazzi, M., Carvalho, A.C., Villani, P. & Matteelli, A. Treatment optimization in patients co-
329 infected with HIV and Mycobacterium tuberculosis infections: focus on drug-drug interactions
330 with rifamycins. *Clin Pharmacokinet*. **53**, 489-507 (2014).
- 331 13. Keung, A., *et al.* Enzyme induction observed in healthy volunteers after repeated administration
332 of rifapentine and its lack of effect on steady-state rifapentine pharmacokinetics: part I. *Int J*
333 *Tuberc Lung Dis*. **3**, 426-436 (1999).
- 334 14. Brooks, K.M., *et al.* Cytokine-Mediated Systemic Adverse Drug Reactions in a Drug-Drug
335 Interaction Study of Dolutegravir With Once-Weekly Isoniazid and Rifapentine. *Clin Infect Dis*.
336 **67**, 193-201 (2018).
- 337 15. Xu, Y., *et al.* Characterizing Class-Specific Exposure-Viral Load Suppression Response of HIV
338 Antiretrovirals Using A Model-Based Meta-Analysis. *Clin Transl Sci*. **9**, 192-200 (2016).
- 339 16. Lai, M.T., *et al.* In vitro characterization of MK-1439, a novel HIV-1 nonnucleoside reverse
340 transcriptase inhibitor. *Antimicrob Agents Chemother*. **58**, 1652-1663 (2014).
- 341 17. Yee, K.L., Ouerdani, A., Claussen, A., de Greef, R. & Wenning, L. Population Pharmacokinetics of
342 Doravirine and Exposure-Response Analysis in Individuals with HIV-1. *Antimicrob Agents*
343 *Chemother*. **63**, (2019).

- 344 18. Sterling, T.R., *et al.* Flu-like and Other Systemic Drug Reactions Among Persons Receiving Weekly
345 Rifapentine Plus Isoniazid or Daily Isoniazid for Treatment of Latent Tuberculosis Infection in the
346 PREVENT Tuberculosis Study. *Clin Infect Dis.* **61**, 527-535 (2015).
- 347 19. Sanchez, R.I., *et al.* Characterisation of the absorption, distribution, metabolism, excretion and
348 mass balance of doravirine, a non-nucleoside reverse transcriptase inhibitor in humans.
349 *Xenobiotica.* 1-11 (2018).

350

351

352 **Figure and Table Legends**

353 **Table 1.** Steady-state doravirine pharmacokinetic parameters^a and summary statistics following twice-
 354 daily doses of doravirine 100 mg alone or twice-daily doravirine 100 mg co-administered with once-
 355 weekly rifapentine and isoniazid.

	Doravirine + rifapentine	Doravirine	Doravirine + rifapentine / Doravirine
Parameter	Geometric mean (95% CI)		Geometric mean ratio (90% CI)
AUC ₀₋₁₂ (hr x ug/mL)	12.3 (10.4-14.3)	17.3 (14.9-20.0)	0.71 (0.60-0.85)
C ₁₂ (ug/mL)	0.9 (0.7-1.0)	1.2 (1.0-1.4)	0.69 (0.54-0.89)
C _{avg} (ug/mL) ^b	1.0 (0.8-1.2)	1.4 (1.2-1.7)	0.71 (0.60-0.85)
C _{max} (ug/mL)	1.3 (1.1-1.5)	1.7 (1.5-2.0)	0.75 (0.63-0.88)
t _{1/2} (hr) ^c	6.4 (17.0)	15.2 (19.4)	
CL/F (L/hr) ^c	8.4 (26.1)	5.9 (24.0)	
Accumulation ratio	1.2-1.6	1.8-3.2	

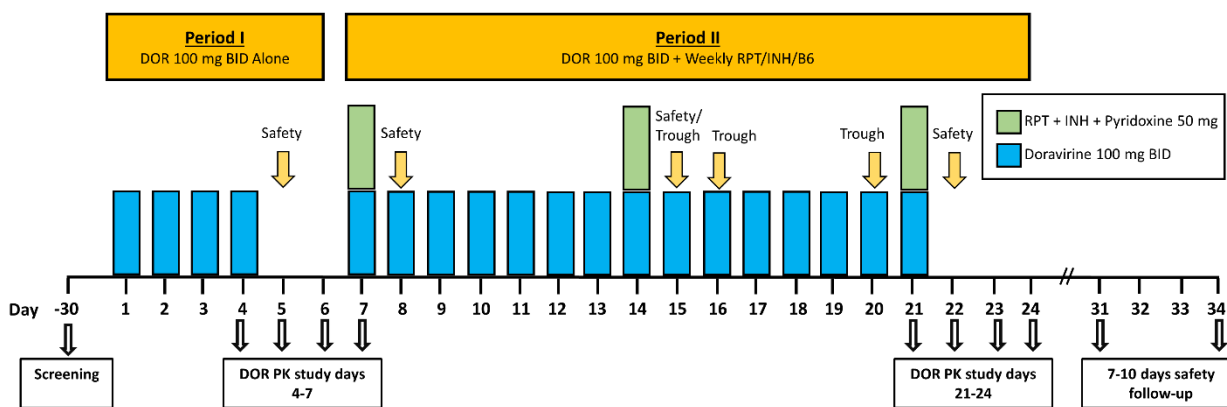
356 ^a. Parameters with exposures are expressed as ug/mL.

357 ^b. The average steady-state plasma concentration during multiple-dose administration was computed as
 358 AUC₀₋₁₂/dosing interval.

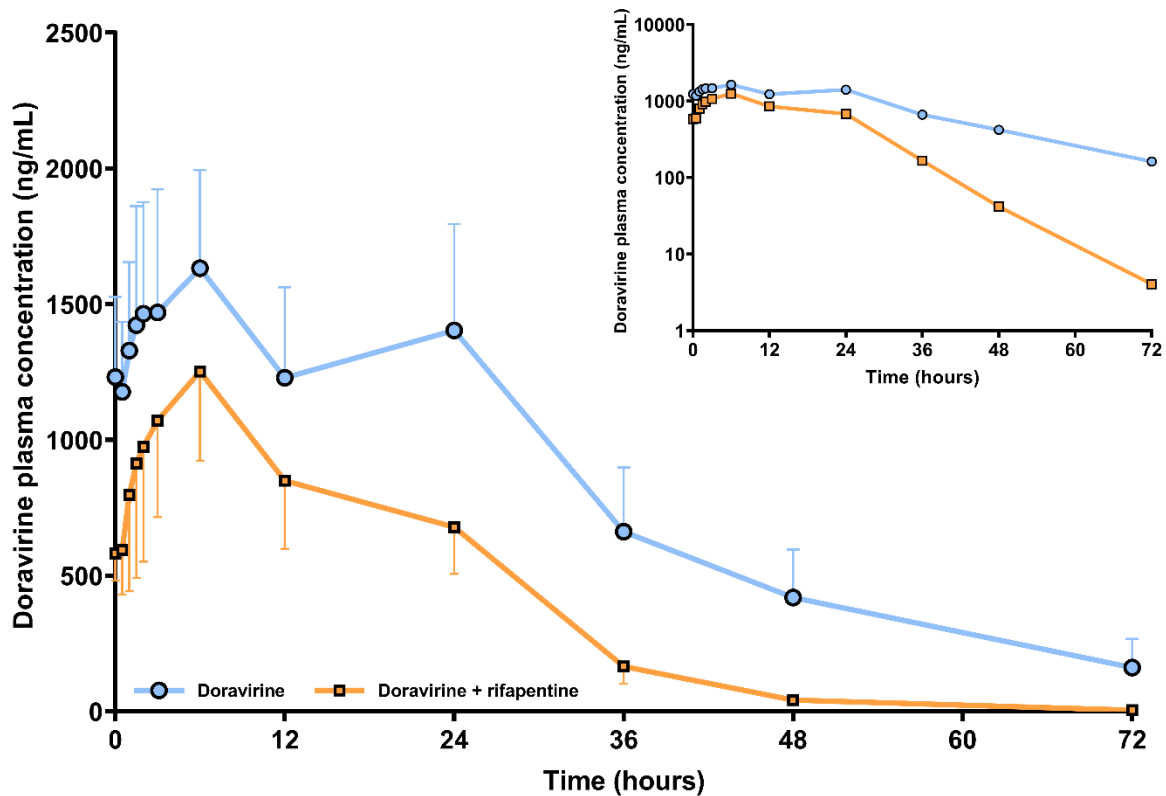
359 ^c. Values for t_{1/2} and CL/F are expressed as the geometric mean (%CV).

360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385

Figure 1. Study schematic. B₆ = vitamin B₆ (pyridoxine), BID = Twice-daily, DOR = doravirine, INH = isoniazid, PK = pharmacokinetics, RPT = rifapentine. Arrows indicate blood for PK or safety laboratory.

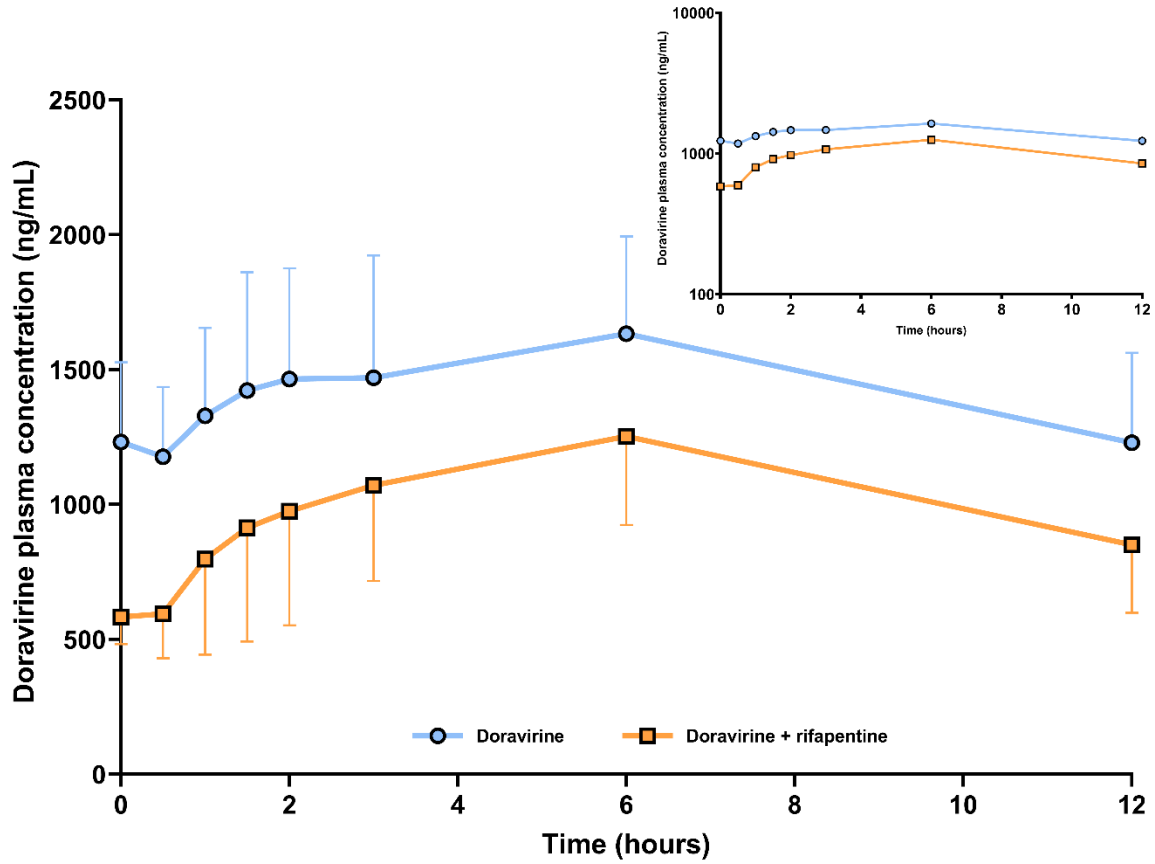


386 **Figure 2.** Mean (\pm SD) doravirine plasma concentration-time profiles following twice-daily doses of
387 doravirine 100 mg alone or together with once-weekly rifapentine and isoniazid. The inset represents
388 the concentration-time profile plotted on a log-linear scale.



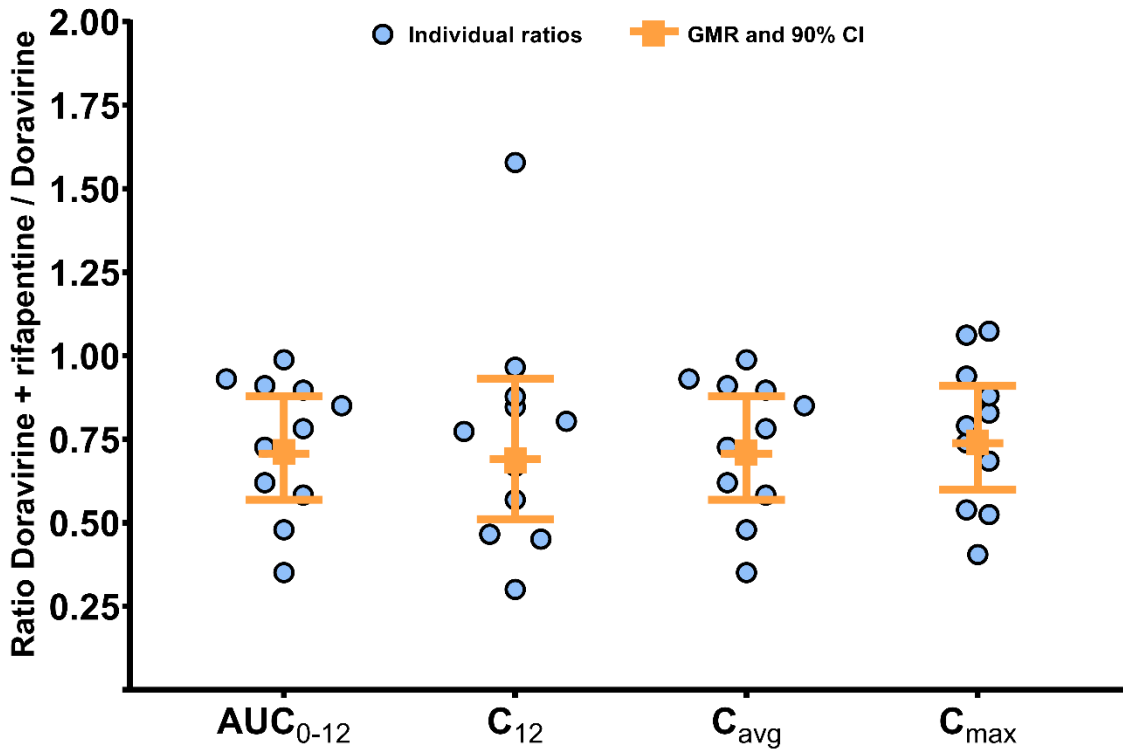
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409

410 **Figure 3.** Mean (\pm SD) doravirine plasma concentration-time profiles during the 12 hour dosing interval
411 following twice-daily doses of doravirine 100 mg alone or together with once-weekly rifapentine and
412 isoniazid. Sampling at time 0 and 12 hours were taken prior to the second dose of doravirine. The inset
413 represents the concentration-time profile plotted on a log-linear scale.



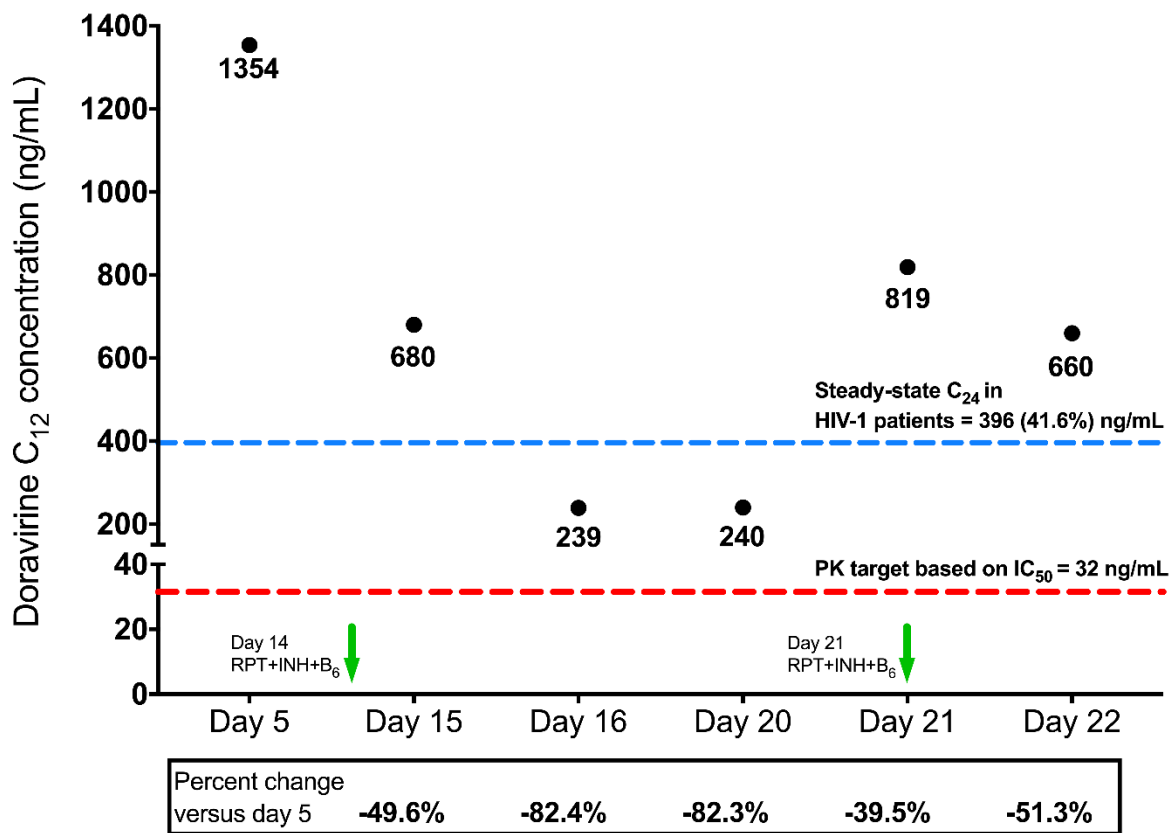
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431

432 **Figure 4.** Individual ratios (Doravirine/doravirine + rifapentine), geometric mean ratios, and
 433 corresponding 90% confidence intervals for doravirine exposure parameters. AUC_{0-12} = Area under the
 434 concentration time during the 12 hour dosing interval, C_{12} = plasma concentration at the end of the
 435 dosing interval prior to the second dose, C_{avg} = average steady-state plasma concentration during the
 436 dosing interval, C_{max} = maximum steady-state concentration



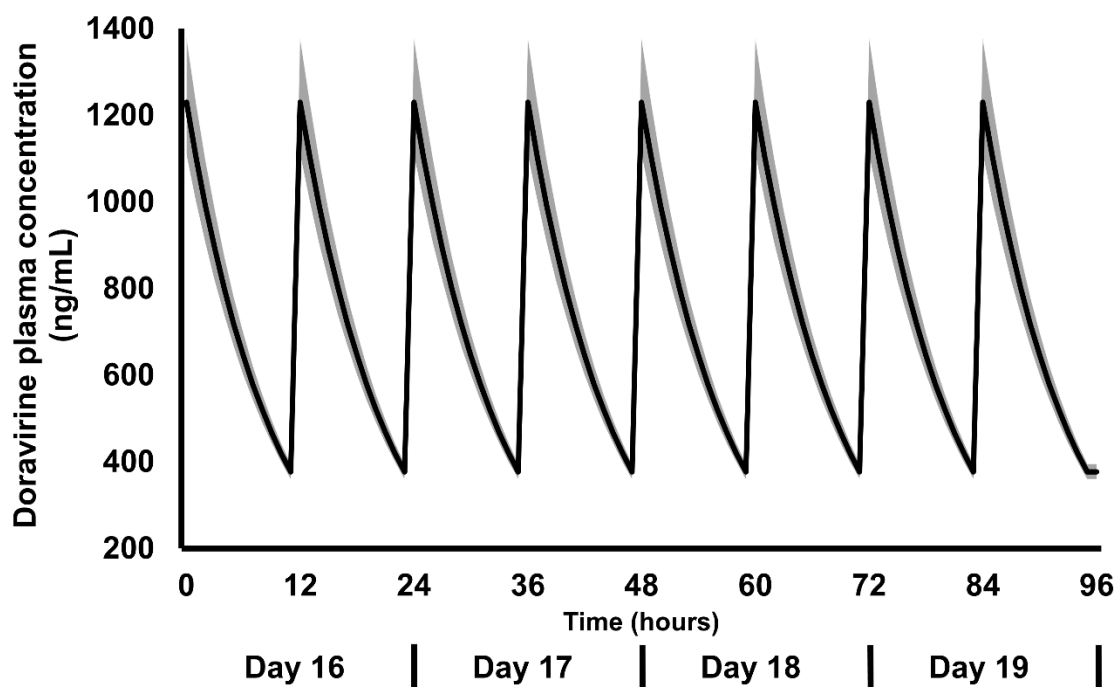
437
 438
 439
 440
 441
 442
 443
 444
 445
 446
 447
 448
 449
 450
 451
 452
 453
 454
 455
 456
 457
 458

459 **Figure 5.** Trend of doravirine C_{12} concentrations throughout the study study days across the two study
 460 periods. The values represent the geometric mean C_{12} concentration reported for that study day. Day 5
 461 was used as a reference to calculate the percent change in C_{12} concentrations for subsequent days. The
 462 green down arrows indicate rifapentine, isoniaizd, and pyridoxine co-administered with the morning
 463 dose of doravirine 100 mg. The horizontal red line indicates the steady-state pharmacokinetic target 6-
 464 fold above the IC_{50} associated with 99% viral reduction. The horizoantal blue line represents the steady-
 465 state C_{24} (% coefficient of variance) values observed in pivotal studies following once-daily doses of
 466 doravirine 100 mg. B6 = pyridoxine, C_{12} = observed trough concentration prior to the second dose for a
 467 twice-daily regimen, C_{24} = observed trough concentration prior to the second dose for a once-daily
 468 regimen, INH = Isoniazid, PK = pharmacokinetic, RPT = rifapentine.
 469



470
 471
 472
 473
 474
 475
 476
 477
 478
 479
 480
 481
 482

483 **Figure 6.** Predicted mean doravirine plasma concentrations at study days 16-19. The gray shaded regions
484 represent the standard error of the mean. Predictions were based on doravirine pharmacokinetic
485 parameters estimated following co-administration of rifapentine on day 21.
486



487