Received: 20 October 2023 | Revised: 14 November 2023 | Accepted: 18 November 2023

DOI: 10.1111/bcp.15975

ORIGINAL ARTICLE

Population pharmacokinetic analysis of doravirine in real-world people with HIV

Paul Thoueille[1] | Luc Delarive[1] | Matthias Cavassini[2] | Thierry Buclin[1] | Laurent A. Decosterd[1] | Catia Marzolini[1,3,4] | François R. Girardin[1] | Monia Guidi[1,5,6] | on behalf of The Swiss HIV Cohort Study

[1]Service and Laboratory of Clinical Pharmacology, Department of Laboratory Medicine and Pathology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

[2]Service of Infectious Diseases, Department of Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

[3]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, University of Basel, Basel, Switzerland

[4]Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK

[5]Center for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

[6]Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, University of Lausanne, Geneva, Switzerland

Correspondence
Monia Guidi, Service and Laboratory of Clinical Pharmacology, Department of Laboratory Medicine and Pathology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; and Center for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland.
Email: monia.guidi@chuv.ch

Funding information
Swiss National Science Foundation, Grant/Award Number: 324730_192449

Aims: The pharmacokinetics of doravirine has been studied in clinical trials but not in real-world settings. Our study aims to characterize and identify factors influencing doravirine (a CYP3A4 substrate) pharmacokinetics in real-world people with HIV (PWH).

Methods: A total of 174 doravirine concentrations measured in 146 PWH followed up in the therapeutic drug monitoring (TDM) program at the University Hospital of Lausanne (Switzerland) between 2019 and 2023 were included in the analysis. Demographic data, clinical information and comedications were recorded during the routine SHCS visits (every 3–6 months). Population pharmacokinetic analysis and Monte Carlo simulations to investigate the clinical significance of the covariates retained in the final model were performed using NONMEM.

Results: A one-compartment model with first-order absorption and linear elimination best described doravirine pharmacokinetics. Potent CYP3A4 inhibitors and, to a lesser extent age, were the only tested covariates to significantly impact doravirine clearance (CL). Potent CYP3A4 inhibitors reduced CL by 50%, and a 30% decrease in CL was observed in an 80-year-old compared with a 55-year-old PWH. The effect of potent CYP3A4 inhibitors was prominent, explaining 59% of between-subject variability in CL. Model-based simulations predicted 2.8-fold and 1.6-fold increases in median steady-state trough and maximum doravirine concentrations, respectively, when a potent CYP3A4 inhibitor was co-administered.

Conclusions: Our findings show that potent CYP3A4 inhibitors and age influence doravirine pharmacokinetics. However, given the good tolerability of doravirine, dosing adjustment of doravirine is probably not mandatory in those situations. TDM remains useful essentially in specific clinical situations, such as hepatic impairment, suspected nonadherence or pregnancy.

François R. Girardin and Monia Guidi are co-senior authors.

Monia Guidi is the principal investigator of this study.

KEYWORDS
pharmacometrics, therapeutic drug monitoring, clinical pharmacology, population analysis, modelling and simulation, HIV/AIDS, doravirine

1 | INTRODUCTION

Doravirine is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) used to treat human immunodeficiency virus (HIV) infection. This drug is indicated in treatment-naive patients or as a replacement therapy in virologically suppressed patients with no history of previous treatment failure and no known resistance to doravirine.[1] Doravirine is prescribed in combination with other antiretrovirals, usually as a single triple-drug-therapy oral pill with lamivudine and tenofovir disoproxil fumarate. Studies showed that doravirine is non-inferior to other HIV treatments and has a favourable safety and lipid profile.[2,3] Doravirine is also characterized by a unique and robust resistance profile compared to other NNRTIs.[4–6]

In biochemical assays, doravirine was found to display a 95% inhibitory concentration of 8 ng/mL.[7] However, a higher clinical minimum trough concentration (C_{trough}) (ie, 230 ng/mL) has been suggested based on efficacy and safety trials.[8] This value corresponded to the 10th percentile of doravirine C_{trough} reported in phase III trials and was set as a conservative lower bound for efficacy for a daily dose of doravirine of 100 mg. However, it should be noted that phase 2 and 3 data have shown that the exposure-response relationship for virologic response was flat for doravirine exposures achieved over the 25-200 mg once-daily range.[8] With regard to safety and tolerability, single doses of up to 1200 mg and multiple doses of up to 750 mg daily for 10 days were usually well tolerated.[7,9] In addition, there is no evidence of exposure- or dose-related toxicity associated with the maximum plasma concentration (C_{max}) of doravirine. Data from phase II/III studies suggest that increases in doravirine exposure of up to three-fold, relative to the mean exposure observed with the recommended 100-mg daily dose, are not considered to be clinically relevant.[10]

Studies conducted in healthy volunteers or clinical trials participants showed that patient age and gender,[11] body weight, body mass index (BMI), race or ethnicity,[8] moderate hepatic impairment[12] and severe renal impairment[8,13] did not influence doravirine pharmacokinetics to a significant extent. However, because doravirine is primarily metabolized by cytochrome P450 3A4 (CYP3A4),[14] potent CYP3A4 inducers are contraindicated with doravirine, while dosage adjustment is recommended with moderate CYP3A4 inducers.[1,10]

To date, population pharmacokinetic (popPK) analyses have been conducted using data from clinical trials participants.[8,15] Although doravirine's excellent efficacy and safety profile limits the relevance of therapeutic drug monitoring (TDM), the characterization of its concentration-time relationship and associated variability, and the identification of the factors affecting its circulating exposure have not yet been performed in real-world people with HIV (PWH). The popPK model developed will enable the establishment of real-world reference percentile curves that can be used to support the interpretation of doravirine measurements performed within a clinical TDM programme for the care of PWH.

What is already known about this subject

- Doravirine is a safe and effective second-generation non-nucleoside reverse transcriptase inhibitor.
- Doravirine is subject to drug-drug interactions with CYP3A4 inhibitors and inducers.
- The pharmacokinetics of doravirine has only been studied in clinical trial settings.

What this study adds

- Potent CYP3A4 inhibitors and patient age influence doravirine pharmacokinetics, but to an extent that does not warrant dose adjustment, in line with the label recommendation.
- Our study provides real-world reference percentile curves for doravirine to be used to interpret concentration measurements for therapeutic drug monitoring.

2 | METHODS

2.1 | Study population

The Scientific Board of the Swiss HIV Cohort Study (SHCS), a nationwide, multicentre, longitudinal study for the follow-up of PWH in Switzerland,[16] formally approved this study. Participants enrolled in SHCS provided their informed consent. Data were also collected from PWH not included in the SHCS as part of their medical care. Their results were subsequently anonymized and pooled with the study data in accordance with Swiss legislation. Doravirine plasma concentrations were collected as part of the TDM programme performed at Lausanne University Hospital (Switzerland) between December 2019 and January 2023. Missing information on time of administration or last drug intake, as well as unreliable information due to suspected nonadherence led to data exclusion. Demographic data, clinical information and comedications (moderate to potent CYP3A4 inhibitors or inducers) were recorded during the routine SHCS visits (every 3-6 months).

2.2 | Analytical method

Doravirine plasma concentrations were quantified at the Laboratory of Clinical Pharmacology in Lausanne (Switzerland) using a previously published liquid chromatography coupled to tandem mass-spectrometry method.[17] The lowest limit of quantification was 30 ng/mL.

2.3 | Population pharmacokinetics analysis

The popPK analysis was performed with the nonlinear mixed effects modelling software NONMEM® (v7.5.1; ICON Development Solutions), assisted by PsN v5.3.1[18] and Pirana v2.9.3.[19] Pre-exploratory analyses, graphical exploration and statistical analyses were performed with R (v4.1.1; R Development Core Team, http://www.r-project.org/). Steady state was assumed for all individuals because doravirine reaches steady state in 2 days,[1] and all included PWH received doravirine for at least 6 days prior to sampling.

2.4 | Base and covariate models

The well-established stepwise procedure for population analyses allowed the model that best fitted the concentrations of doravirine to be identified. One- and two-compartment models with first- or zero-order or sequential combined absorption processes and linear elimination were compared. A one-compartment model with first-order absorption was eventually retained. However, because TDM is usually performed during the post-absorption phase of drugs, only a limited number of samples collected right after drug oral intake was available. Therefore, based on preliminary model development and literature information on doravirine half-life and time to peak concentration,[1] the first-order absorption rate (k_a) of doravirine was fixed at 1.9 h^{-1}. Parametrization was additionally performed in terms of apparent clearance (CL) and apparent volume of distribution (V), which were assumed to follow a log-normal distribution. Between-subject variability (BSV) was sequentially tested on these parameters, while additive, proportional and mixed error models were compared to evaluate the residual unexplained variability (RUV).

The following covariates were initially tested one by one for significance on the base model parameters with associated BSV using linear or allometric functions as appropriate: sex, ethnicity, age, bodyweight, height, BMI (recorded on the nearest date to the sampling) and comedications (ie, moderate and potent CYP3A4 inhibitors or inducers recorded at sampling date). The latter were tested by assigning a separate effect to moderate and potent CYP3A4 inhibitors or inducers and then regrouped according to fixed-effect estimates. The same approach was used for ethnicity, using the following groupings in the second step: African and Hispano-American in one group, and Caucasian, Asian and missing information in another group. The identified significant covariate-parameter relationships were then combined and a backward deletion step was subsequently conducted to build the final model. Missing information was imputed using the median of the study population or as a separate category for continuous and qualitative covariates, respectively.

2.5 | Model selection and evaluation

During base model building and forward covariate insertion steps, hierarchically nested models were statistically discriminated using the variation of the NONMEM® objective function value (ΔOFV) at a significance level of 0.05 (ΔOFV < −3.84 for one additional parameter). Moreover, a significance level of 0.01 (ΔOFV > 6.63 for the removal of one parameter) was used during backward deletion. On the other hand, Akaike's information criterion was used for non-nested models. The accuracy of the pharmacokinetic parameters, the BSVs and the covariates effects estimates was quantified by the relative standard error (RSE). Lastly, standard goodness-of-fit diagnostic plots also helped in model selection.

Prediction- and variability-corrected visual predictive checks (pvcVPCs) were performed to evaluate the final model predictive performances comparing fifth, 50th and 95th observed and prediction percentiles.[18,20,21] In addition, the final model reliability was assessed through the nonparametric bootstrap method (n = 2000),[18] which allowed comparison of the original model parameter estimates with the corresponding bootstrap median values and their 95% confidence intervals.

2.6 | Model-based Monte Carlo simulations

Model-based simulations of the final model were performed at steady state using the standard 100-mg once-daily treatment to investigate the clinical relevance of the retained covariates. One thousand individuals per group were simulated for the categorical covariates, while continuous covariates were discretized into clinically relevant groups, assuming a uniform distribution to generate individual values (n = 1000). Simulations were thus performed in the presence/absence of potent CYP3A4 inhibitors, with and without the age effect, using a cut-off of 65 years (25-65 *vs* 65-80 years), in line with the demographic data available in our study. This allowed the comparison of concentration-time profiles as a function of the differences in covariate values. In addition, doravirine C_{max}, C_{trough} and the area under the curve ($AUC_{0\text{-}24}$) were calculated from 1000 simulated individuals per group and compared.

2.7 | Nomenclature of targets and ligands

Key ligands and targets in this article are hyperlinked to corresponding entries in www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/2022.[22]

3 | RESULTS

Overall, 174 doravirine concentrations collected from 146 PWH were studied. Most patients provided only one sample (range 1-3). Table 1 summarizes the characteristics of the study population. It should be noted that due to a high proportion of missing values, we do not report HIV RNA (93% missing) and CD4 (79% missing) measurements.

3.1 | Structural, statistical and covariate models

A one-compartment model with first-order absorption and linear elimination best described doravirine concentrations. Parameter estimates of the base popPK model with BSV (CV%) were k_a of 1.9 h^{-1} (fixed), V of 75.2 L and CL of 3.48 L/h (44.4%). The assignment of BSV on V did not significantly improve data description ($\Delta OFV = 0$, $P > 0.05$), neither did the use of alternative absorption models ($\Delta OFV > 1$, $P > 0.05$). A two-compartment model with zero-order absorption process siginificantly decreased the OFV ($\Delta OFV = -8$, $P < 0.05$), but was not retained because of the poor precision of the parameter estimates (ie, RSE ~50%). A proportional error model best captured doravirine RUV.

The univariate analysis revealed significant effects of potent CYP3A4 inhibitors ($\Delta OFV = -69$, $P < 0.001$), age ($\Delta OFV = -20$, $P < 0.001$), ethnicity ($\Delta OFV = -5$, $P < 0.05$) and sex ($\Delta OFV = -4$, $P < 0.05$) on CL. Forward insertion and backward deletion steps allowed retention of only the effects of potent CYP3A4 inhibitors and age on doravirine CL in the final model, as follows:

$$CL_i = TVCL \times (1 + \theta_{\text{Strong CYP3A4 inhibitors}}) \times \left(1 + \theta_{\text{Age}} \times \frac{(\text{Age} - \text{Age}_M)}{\text{Age}_M}\right) \times e^{\eta_i}$$

where θ is the estimated parameter for the covariate effect, Age_M is the median value in the study population (55 years), TVCL is the typical CL in our population, CL_i is the individual value of CL in the ith subject and η_i is the corresponding ith component of the BSV. Table 2 shows the final doravirine popPK model.

The final model shows that potent CYP3A4 inhibitors decrease doravirine clearance by 50%. Similarly, an 80-year-old would have a CL of 2.77 L/h, which is 30% lower than the CL of 3.98 L/h of a middle-aged person (ie, median = 55 year-old). Finally, the covariates included in the final popPK model explained 59% of the BSV on CL, all resulting from the inclusion of

TABLE 1 Characteristics of the PWH included in the analysis.

Last recorded value	Number (%) or median (range)	Missing data (number, %)
Sex		6 (4%)
Male	93 (64%)	
Female	47 (32%)	
Ethnicity		55 (38%)
Caucasian	61 (42%)	
African	26 (18%)	
Asian	2 (1%)	
Hispano-American	2 (1%)	
Age (year)	55 (25-78)	1 (<1%)
Body weight (kg)	76 (39-125)	30 (21%)
Height (cm)	170 (145-198)	26 (18%)
BMI (kg/m^2)	26 (15-46)	32 (22%)
Comedications reported[a]		25 (14%)
Potent CYP3A4 inhibitors[b]	34 (20%)	
Moderate CYP3A4 inhibitors[c]	3 (2%)	
Potent CYP3A4 inducers	1 (<1%)	
Moderate CYP3A4 inducers[d]	5 (3%)	

Abbreviations: BMI, body mass index; CYP3A4, Cytochrome P450.
[a]Number of comedications based on the number of samples considered for analysis.
[b]Includes atazanavir, cobicistat, darunavir and ritonavir.
[c]Includes amiodarone and diltiazem.
[d]Includes dexamethasone and etravirine.

TABLE 2 Final population PK parameter estimates of doravirine with their bootstrap evaluations

Parameters	Final model Estimate (RSE, %)	Bootstrap (n = 2000) Median ($CI_{95\%}$)
k_a (h^{-1})	1.9 FIX	1.9 FIX
V (L)	82.2 (13)	83.7 (66.4-111.6)
TVCL (L/h)	3.98 (4)	3.95 (3.67-4.27)
ω_{CL} (CV%)	27 (18)	27 (13-35)
$\theta_{\text{Strong CYP3A4 inhibitors}}$	−0.502 (6)	−0.498 (−0.555 to −0.425)
θ_{Age}	−0.670 (21)	−0.672 (−0.939 to −0.409)
σ_{prop} (CV%)	26 (16)	26 (18-35)

Abbreviations: $CI_{95\%}$, 95% confidence interval; RSE, relative standard error.
Note: Final model:

$$TVCL_i = TVCL \times (1 + \theta_{\text{Strong CYP3A4 inhibitors}}) \times \left(1 + \theta_{\text{Age}} \times \frac{(\text{Age} - \text{Age}_M)}{\text{Age}_M}\right)$$

k_a, first-order absorption rate constant; V, apparent volume of distribution; TVCL, typical apparent clearance; $TVCL_i$, typical value of CL in the ith subject; $\theta_{\text{Strong CYP3A4 inhibitors}}$, effect of potent CYP3A4 inhibitors on CL; θ_{Age}, age effect on CL with $\text{Age}_M = 55$ years old, which is the median age value in the study population; ω_{CL}, between-subject variability (BSV) on CL; σ_{prop}, proportionnal residual error.
[a]Coefficient of variation (CV, %) for BSV calculated as follows: $\sqrt{(e^{\omega^2} - 1)}$.

potent CYP3A4 inhibitors alone. No additional drop in BSV was observed when adding age in the model.

3.2 | Model evaluation

The diagnostic plots of the final model (Supporting Information Figure S1), together with the pvcVPC and the bootstrap results, shown in Figure 1 and Table 2, respectively, demonstrate the reliability of the final model.

3.3 | Model-based Monte Carlo simulations

Figure 2 shows the simulated pharmacokinetic profiles in individuals receiving doravirine alone and in combination with potent CYP3A4 inhibitors under the standard 100-mg once-daily treatment. The median C_{trough} at steady state after oral administration of doravirine was 571 (95% prediction interval [$PI_{95\%}$] 229-1258 ng/mL). Our model predicted that 2.5% of PWH would have a doravirine C_{trough} below the minimum recommended concentration for efficacy (ie, 230 ng/mL).[8] On the other hand, when CYP3A4 inhibitors were co-administered, the doravirine C_{trough} was 1578 (707-3022) ng/mL, resulting in a 2.8-fold increase compared to doravirine alone. Potent CYP3A4 inhibitors were also found to increase the C_{max} of doravirine by 1.6-fold, with median C_{max} predicted to be 1624 (1253-2327) ng/mL and 2650 (1765-4101) ng/mL in individuals receiving doravirine alone or in combination with potent CYP3A4 inhibitors, respectively. Figure 3 compares the effect of age on the C_{max} and C_{trough} of doravirine administered with and without potent CYP3A4 inhibitors. Importantly, model-based simulations highlighted that younger individuals (ie, 25-65 years) receiving doravirine alone would have a lower C_{trough} than older subjects, with approximately 10% below the threshold of 230 ng/mL recommended for clinical efficacy. Finally, the effect of age on doravirine exposure (ie, $AUC_{0\text{-}24}$) was similar between individuals receiving doravirine alone and those receiving potent CYP3A4 inhibitors (Supporting Information Table S1). Doravirine $AUC_{0\text{-}24}$ was found to be 1.4-fold higher in older individuals compared to younger individuals, whereas potent CYP3A4 inhibitors increased $AUC_{0\text{-}24}$ by two-fold, regardless of age.

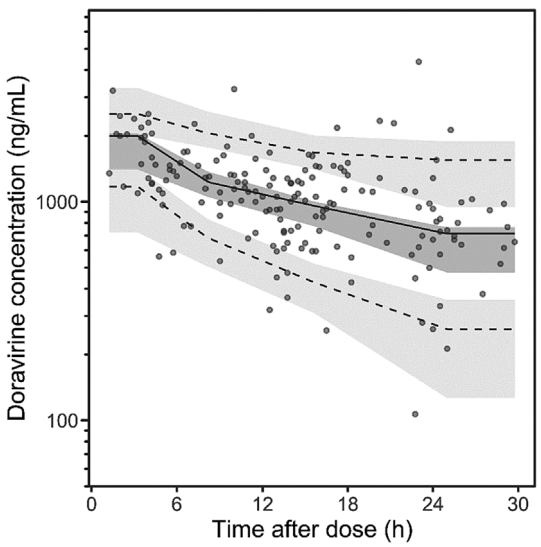

FIGURE 1 Prediction-variability-corrected visual predictive check of the final model for doravirine. Circles represent the observed plasma concentrations. Solid and dashed lines represent the median and 90% prediction intervals ($PI_{90\%}$) of the observed data, respectively. The dark and light shaded areas represent the model-predicted 90% confidence intervals of the simulated median and $PI_{90\%}$, respectively.

4 | DISCUSSION

This study describes a popPK model of doravirine based on real-world PWH and characterizes the effect of potent CYP3A4 inhibitors and age on doravirine exposure. Our one-compartment model is consistent with previously reported popPK modelling based on phase I and IIb/III trials.[8] During model development, a two-compartment model with zero-order absorption denoted a statistically better data description. However, it was judged not to be stable enough for further development (in fact, the peripheral compartment could only be accurately described when a zero-order absorption was included, but with RSE attaining 50% for parameter estimate). The decision to retain notwithstanding the one-compartment model with a fixed k_a relied primarily on the assessment of the RSE and the evaluation of the diagnostic plots (Supporting Information Figure S1), which were found to be satisfactory for the final retained base model. In addition, since doravirine is administered orally, k_a tends to be more appropriate to fit the data after drug intake. The base model allowed the estimations of both a time to peak concentration of 2 h and a terminal half-life of 15 h, identical to the values reported in the drug monograph.[1]

Model-based simulations predicted that doravirine co-administered with potent CYP3A4 inhibitors resulted in 1.6-, 2.8- and two-fold increases in doravirine C_{max}, C_{trough} and $AUC_{0\text{-}24}$, respectively, compared to individuals receiving 100 mg of doravirine alone. Regarding the additional effect of age on doravirine CL, our model-based simulations showed that the increase in doravirine exposure was similar between individuals receiving doravirine alone or in combination with potent CYP3A4 inhibitors. This observation is explained by the fact that aging impacts the exposure of the victim and perpetrator drugs to a similar extent and therefore the magnitude of the drug interaction remains unchanged in elderly compared to young individuals.[23] Overall, the increases in doravirine exposure presented in our model-based simulations were not considered clinically relevant. Indeed, none of the model-predicted increase in doravirine exposure exceeded the three-fold increase limit previously reported.[10] On the other hand, our results suggest that younger PWH receiving doravirine alone may be at higher risk for suboptimal exposure, with almost 10% having doravirine C_{trough} below the minimal efficacy target of 230 ng/mL. While the predicted median C_{trough} is in line with

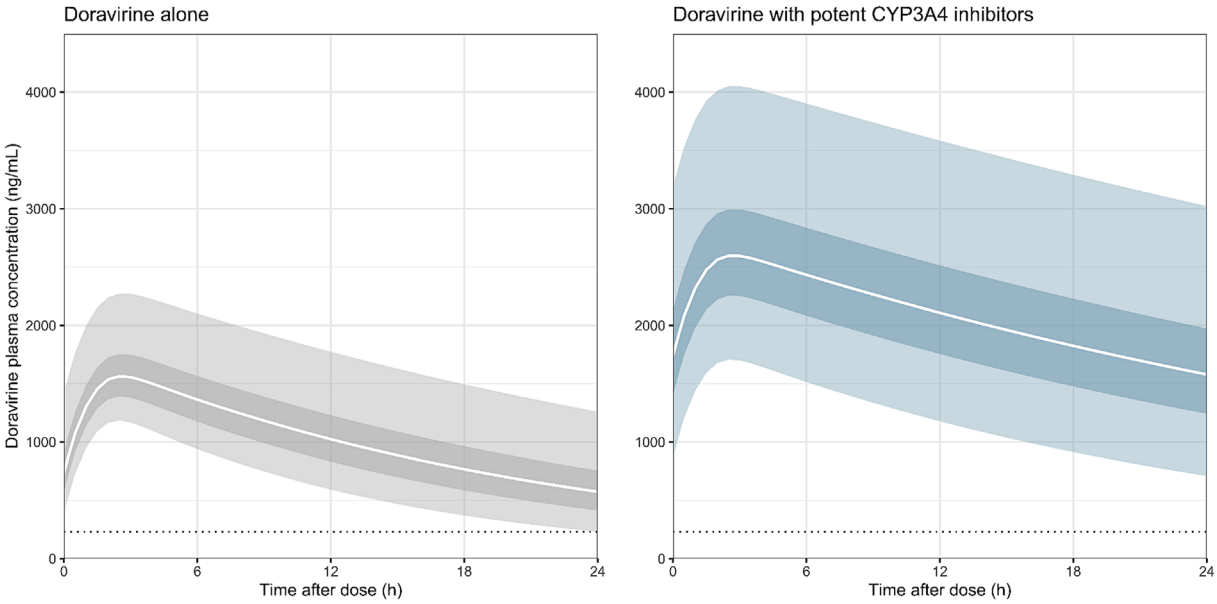

FIGURE 2 Simulated percentiles of doravirine concentrations at steady-state under the standard 100 mg once-daily regimen without (left panel) and in combination with (right panel) potent CYP3A4 inhibitors, irrespective of the effect of age. The solid white lines represent the median (50% percentile), while the dark shaded areas are the 50% prediction intervals and the light shaded areas are the 95% prediction intervals. The dotted line shows the minimum concentration recommended for efficacy (230 ng/mL).[8]

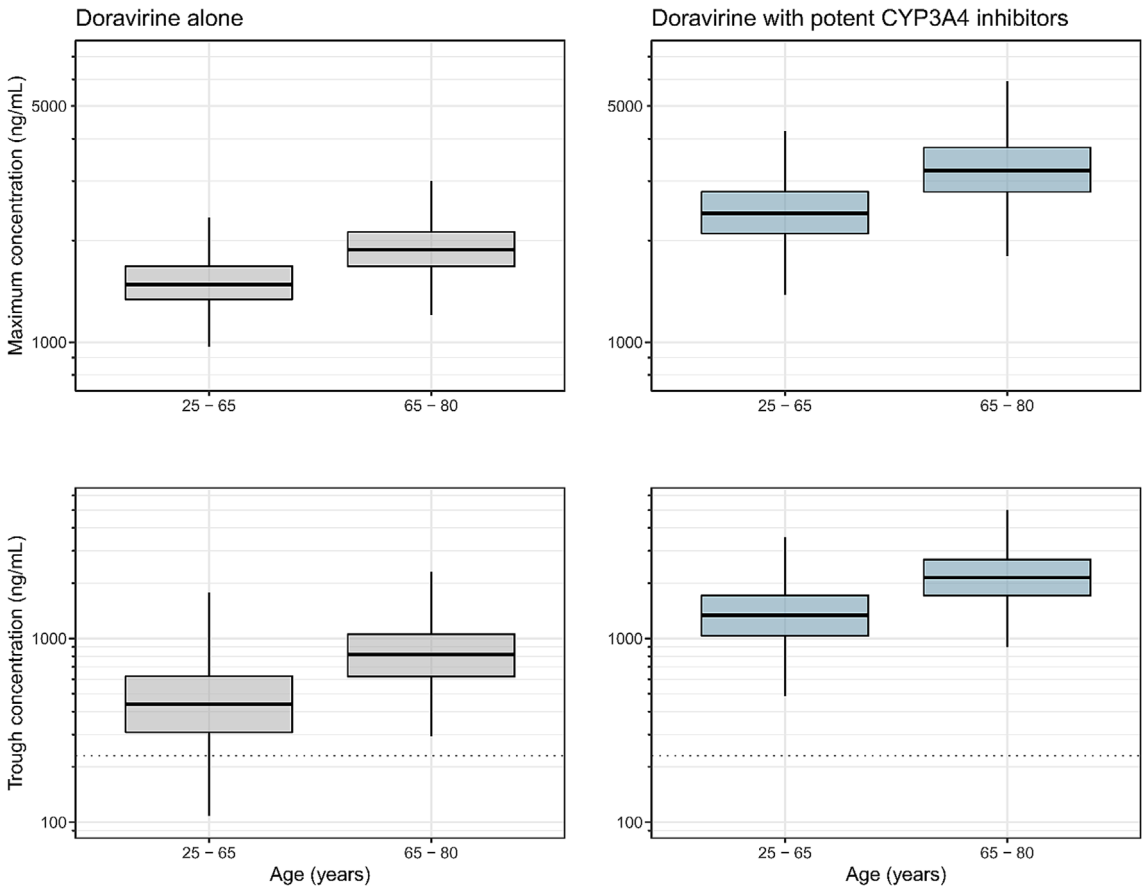

FIGURE 3 Simulated maximum and trough concentrations of doravirine in individuals of different ages receiving doravirine alone or in combination with potent CYP3A4 inhibitors. The dotted line shows the minimum concentration recommended for efficacy (230 ng/mL).[8] The boxplots encompass the 25-75% prediction percentiles, with the midlines representing the median. The whiskers delineate the 5-95% prediction percentiles.

the one reported in the product label,[1] and no dose adjustment is required in clinical practice, our findings emphasize the importance of conducting real-world studies to confirm that this applies to actual patient care.

The limitations of the present work should be acknowledged. Insufficient data were available in the absorption phase, thus limiting the adequate description of k_a and its associated variability. In addition, as most PWH contributed to one sample and no detailed pharmacokinetic sampling was available, discrimination between BSV and RUV variabilities was limited. It should also be noted that data were collected from a moderately diverse population with a relatively important proportion of missing values, thus possibly preventing the identification of further factors influencing doravirine disposition (eg, evaluation of the hepatic or renal function). Unfortunately, external and/or data-splitting validations could not be performed, thus limiting the generalisability of our analyses to a wider population. Finally, because viral load and CD4 count were not available for a sufficient number of PWH included in the analysis, we did not perform pharmacokinetic-pharmacodynamic analyses, which could have been particularly relevant in PWH with low doravirine concentrations. However, data from phase II/III trials have shown that the exposure-response relationship was fairly flat over the range of exposure achieved with the 100-mg daily doravirine dose. It has been suggested that a decrease in response in individuals with doravirine levels below the 10th percentile most probably results from suboptimal adherence.

In conclusion, this study confirmed similar results in doravirine exposure between real-world PWH and clinical trial participants. Age and potent CYP3A4 inhibitors were found to significantly influence doravirine pharmacokinetics. However, due to the reported good tolerability of doravirine, dosage adjustment is probably not mandatory in the case of increased doravirine exposure. Doravirine TDM is certainly not to recommend routinely in PWH. However, despite limited clinical validation, it may be of particular relevance during pregnancy[24] or in patients receiving haemodialysis[25] or developing hepatic impairment. Furthermore, TDM can be useful to detect individuals with poor adherence who are exposed to a low level, thereby increasing the risk of developing viral resistance. Finally, the percentile curves derived from our analysis can be used to interpret doravirine measurements as part of TDM to address clinical questions related, for example, to treatment adherence, drug exposure in pregnancy or hepatic impairment.

AUTHOR CONTRIBUTIONS

Paul Thoueille, Luc Delarive and Monia Guidi performed the population pharmacokinetic analysis. Paul Thoueille and Laurent A. Decosterd were responsible for drug level measurements. Monia Guidi, Thierry Buclin, François R. Girardin and Laurent A. Decosterd were responsible for project administration, acquisition of funding and resources. Paul Thoueille was responsible for data management and data visualization, and drafted the manuscript. All authors critically reviewed and approved the final manuscript, and had full access to the data in the study.

ACKNOWLEDGMENTS

Members of the Swiss HIV Cohort Study: Abela I, Aebi-Popp K, Anagnostopoulos A, Battegay M, Bernasconi E, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H, Fux CA, Günthard HF (President of the SHCS), Hachfeld A, Haerry D (deputy of 'Positive Council'), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Huber M, Jackson-Perry D (patient representatives), Kahlert CR (Chairman of the Mother & Child Substudy), Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Kusejko K (Head of Data Centre), Labhardt N, Leuzinger K, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nemeth J, Nicca D, Notter J, Paioni P, Pantaleo G, Perreau M, Rauch A (Chairman of the Scientific Board), Salazar-Vizcaya L, Schmid P, Speck R, Stöckle M (Chairman of the Clinical and Laboratory Committee), Tarr P, Trkola A, Wandeler G, Weisser M, Yerly S. This work was supported by the Swiss National Science Foundation, grant number No 324730_192449 (to L.A.D.).

CONFLICT OF INTEREST STATEMENT

M.C. reports grants and payment for expert testimony from Gilead, MSD and ViiV, and support for attending meetings from Gilead, paid to his institution outside of the submitted work. C.M. has received speaker honoraria from ViiV, MSD and Gilead unrelated to this work. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

A request for data sharing can be sent to the Scientific Board of the Swiss HIV Cohort Study (https://www.shcs.ch/). A detailed explanation of the purpose for the request as well as a study protocol, if applicable, should be presented. The final decision about data release will be taken by the Scientific Board of the SHCS.

ORCID

Paul Thoueille https://orcid.org/0000-0002-2305-4277
François R. Girardin https://orcid.org/0000-0002-0842-927X
Monia Guidi https://orcid.org/0000-0002-6419-9317

REFERENCES

1. European Medicines Agency. Pifeltro: EPAR—Product Information. Published January 10, 2019. Updated October 11, 2022. Accessed October 31, 2022. https://www.ema.europa.eu/en/documents/product-information/pifeltro-epar-product-information_en.pdf
2. Orkin C, Squires KE, Molina JM, et al. Doravirine/lamivudine/tenofovir disoproxil fumarate (TDF) versus efavirenz/emtricitabine/TDF in treatment-naive adults with human immunodeficiency virus type 1 infection: week 96 results of the randomized, double-blind, phase 3 DRIVE-AHEAD noninferiority trial. *Clin Infect Dis*. 2021;73(1):33-42. doi:10.1093/cid/ciaa822
3. Molina J-M, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial. *Lancet HIV*. 2020;7(1):e16-e26. doi:10.1016/S2352-3018(19)30336-4
4. Brenner BG, Oliveira M, Ibanescu RI, Routy JP, Thomas R. Cell culture selections reveal favourable drug resistance profiles for doravirine and islatravir. *J Antimicrob Chemother*. 2021;76(8):2137-2142. doi:10.1093/jac/dkab126

5. Martin EA, Lai MT, Ngo W, et al. Review of doravirine resistance patterns identified in participants during clinical development. *J Acquir Immune Defic Syndr*. 2020;85(5):635-642. doi:10.1097/QAI.0000000000002496
6. Lai M-T, Feng M, Falgueyret JP, et al. In vitro characterization of MK-1439, a novel HIV-1 nonnucleoside reverse transcriptase inhibitor. *Antimicrob Agents Chemother*. 2014;58(3):1652-1663. doi:10.1128/AAC.02403-13
7. Anderson MS, Gilmartin J, Cilissen C, et al. Safety, tolerability and pharmacokinetics of doravirine, a novel HIV non-nucleoside reverse transcriptase inhibitor, after single and multiple doses in healthy subjects. *Antivir Ther*. 2015;20(4):397-405. doi:10.3851/IMP2920
8. Yee KL, Ouerdani A, Claussen A, de Greef R, Wenning L. Population pharmacokinetics of Doravirine and exposure-response analysis in individuals with HIV-1. *Antimicrob Agents Chemother*. 2019;63(4):e02502-18. doi:10.1128/AAC.02502-18
9. Khalilieh SG, Yee KL, Fan L, et al. A randomized trial to assess the effect of doravirine on the QTc interval using a single supratherapeutic dose in healthy adult volunteers. *Clin Drug Investig*. 2017;37(10):975-984. doi:10.1007/s40261-017-0552-x
10. Khalilieh S, Yee KL, Sanchez R, Stoch SA, Wenning L, Iwamoto M. Clinical pharmacokinetics of the novel HIV-1 non-nucleoside reverse transcriptase inhibitor doravirine: an assessment of the effect of patient characteristics and drug-drug interactions. *Clin Drug Investig*. 2020;40(10):927-946. doi:10.1007/s40261-020-00934-2
11. Behm MO, Yee KL, Fan L, Fackler P. Effect of gender and age on the relative bioavailability of doravirine: results of a phase I trial in healthy subjects. *Antivir Ther*. 2017;22(4):337-344. doi:10.3851/IMP3142
12. Khalilieh S, Yee KL, Liu R, et al. Moderate hepatic impairment does not affect doravirine pharmacokinetics. *J Clin Pharmacol*. 2017;57(6):777-783. doi:10.1002/jcph.857
13. Ankrom W, Yee KL, Sanchez RI, et al. Severe renal impairment has minimal impact on doravirine pharmacokinetics. *Antimicrob Agents Chemother*. 2018;62(8):e00326. doi:10.1128/AAC.00326-18
14. Sanchez RI, Fillgrove KL, Yee KL, et al. Characterisation of the absorption, distribution, metabolism, excretion and mass balance of doravirine, a non-nucleoside reverse transcriptase inhibitor in humans. *Xenobiotica*. 2019;49(4):422-432. doi:10.1080/00498254.2018.1451667
15. Vaddady P, Kandala B, Yee KL. Population pharmacokinetic and pharmacodynamic analysis to evaluate a switch to doravirine/lamivudine/-tenofovir disoproxil fumarate in people living with HIV-1. *Antimicrob Agents Chemother*. 2020;64(11):e00590-20. doi:10.1128/AAC.00590-20
16. Scherrer AU, Traytel A, Braun DL, et al. Cohort profile update: the Swiss HIV cohort study (SHCS). *Int J Epidemiol*. 2022;51(1):33-4j. doi:10.1093/ije/dyab141
17. Courlet P, Alves Saldanha S, Cavassini M, et al. Development and validation of a multiplex UHPLC-MS/MS assay with stable isotopic internal standards for the monitoring of the plasma concentrations of the antiretroviral drugs bictegravir, cabotegravir, doravirine, and rilpivirine in people living with HIV. *J Mass Spectr: JMS*. 2020;55(6):e4506. doi:10.1002/jms.4506
18. 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(3):241-257. doi:10.1016/j.cmpb.2005.04.005
19. Keizer RJ, van Benten M, Beijnen JH, Schellens JH, Huitema AD. Piraña and PCluster: a modeling environment and cluster infrastructure for NONMEM. *Comput Methods Programs Biomed*. 2011;101(1):72-79. doi:10.1016/j.cmpb.2010.04.018
20. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS j*. 2011;13(2):143-151. doi:10.1208/s12248-011-9255-z
21. Jonsson EN, Karlsson MO. Xpose--an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. *Comput Methods Programs Biomed*. 1999;58(1):51-64. doi:10.1016/S0169-2607(98)00067-4
22. Alexander SPH, Cidlowski JA, Kelly E, et al. The concise guide to pharmacology 2021/22: introduction and other protein targets. *Br J Pharmacol*. 2021;178 Suppl 1(S1):S246-S263. doi:10.1111/bph.15540
23. Stader F, Decosterd L, Stoeckle M, et al. Aging does not impact drug-drug interaction magnitudes with antiretrovirals. *Aids*. 2020;34(6):949-952. doi:10.1097/QAD.0000000000002489
24. Bukkems VE, van Hove H, Roelofsen D, et al. Prediction of maternal and fetal doravirine exposure by integrating physiologically based pharmacokinetic modeling and human placenta perfusion experiments. *Clin Pharmacokinet*. 2022;61(8):1129-1141. doi:10.1007/s40262-022-01127-0
25. Kushida H, Watanabe D, Yagura H, et al. Evaluation of plasma doravirine concentrations in patients with HIV-1 undergoing hemodialysis. *J Infect Chemother*. 2023;29(5):558-561. doi:10.1016/j.jiac.2023.02.003

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Thoueille P, Delarive L, Cavassini M, et al. Population pharmacokinetic analysis of doravirine in real-world people with HIV. *Br J Clin Pharmacol*. 2024;1-8. doi:10.1111/bcp.15975