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Confirming model-predicted pharmacokinetic interactions between bedaquiline and lopinavir/ritonavir or nevirapine in patients with HIV and drug-resistant tuberculosis

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ABSTRACT

Bedaquiline and its metabolite M2 are metabolised by CYP3A4. The antiretrovirals ritonavir-boosted lopinavir (LPV/r) and nevirapine inhibit and induce CYP3A4, respectively. Here we aimed to quantify nevirapine and LPV/r drug–drug interaction effects on bedaquiline and M2 in patients co-infected with HIV and multidrug-resistant tuberculosis (MDR-TB) using population pharmacokinetic (PK) analysis and compare these with model-based predictions from single-dose studies in subjects without TB. An observational PK study was performed in three groups of MDR-TB patients during bedaquiline maintenance dosing: HIV-seronegative patients ($n = 17$); and HIV-infected patients using antiretroviral therapy including nevirapine ($n = 17$) or LPV/r ($n = 14$). Bedaquiline and M2 samples were collected over 48 h post-dose. A previously developed PK model of MDR-TB patients was used as prior information to inform parameter estimation using NONMEM. The model was able to describe bedaquiline and M2 concentrations well, with estimates close to their priors and earlier model-based interaction effects from single-dose studies. Nevirapine changed bedaquiline clearance to 82% (95% CI 67–99%) and M2 clearance to 119% (92–156%) of their original values, indicating no clinically significant interaction. LPV/r substantially reduced bedaquiline clearance to 25% (17–35%) and M2 clearance to 59% (44–69%) of original values. This work confirms earlier model-based predictions of nevirapine and LPV/r interaction effects on bedaquiline and M2 clearance from subjects without TB in single-dose studies, in MDR-TB/HIV co-infected patients studied here. To normalise bedaquiline exposure in patients with concomitant LPV/r therapy, an adjusted bedaquiline dosing regimen is proposed for further study.

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1. Introduction

Bedaquiline is a diarylquinoline recently approved for the treatment of multidrug-resistant tuberculosis (MDR-TB). Bedaquiline is predominantly metabolised by cytochrome P450 3A4 (CYP3A4) into the *N*-monodesmethyl metabolite M2, and both compounds have a long terminal half-life of >5 months [1]. Clearance of M2 is also thought to be mediated by CYP3A4 [2,3]. For these reasons, co-administration of drugs that induce or inhibit CYP3A4 may affect the pharmacokinetics of bedaquiline and M2. This may pose problems for TB patients co-infected with human immunodeficiency virus (HIV) (in 2014, there were 1.2 million new cases of TB amongst people living with HIV [4]), since commonly used antiretroviral therapy (ART) includes several drugs that affect CYP3A4.

Nevirapine (NVP) and ritonavir-boosted lopinavir (LPV/r) are important antiretroviral drugs [5] that influence CYP3A4 activity. NVP is a moderate inducer of CYP3A4 activity [6]. However, a population pharmacokinetic (PK) analysis of the NVP interaction with bedaquiline in HIV-infected patients without TB did not predict any clinically relevant effects of NVP on bedaquiline and M2 exposure during long-term co-administration [7]. Ritonavir is a strong inhibitor of CYP3A4 [8]. A population PK analysis of the LPV/r interaction with single doses of bedaquiline in healthy volunteers predicted a close to three-fold increase in bedaquiline and a two-fold increase in M2 exposure at steady-state during long-term co-administration [7]. These drug–drug interaction studies in HIV-infected individuals without TB were performed following a single dose of bedaquiline, whilst in clinical practice patients receive bedaquiline treatment for 24 weeks. Furthermore, the impact of NVP or LPV/r therapy on bedaquiline and M2 exposure might be different in MDR-TB patients co-infected with HIV compared with individuals without TB. Therefore, an interaction study was conducted in MDR-TB patients receiving bedaquiline, without or with

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HIV co-infection and concomitant ART including either NVP or LPV/r [9]. Results from a non-compartmental analysis (NCA) of this study indicated that the magnitude of the earlier model-based predictions was correct, but the difference in time on bedaquiline treatment between groups could not be handled in this NCA [9]. Therefore, in the present work, we aimed to quantify NVP and LPV/r drug interaction effects in HIV/MDR-TB co-infected patients using population PK analysis and to compare these results with the previously predicted drug interaction effects from single-dose studies in individuals without TB.

2. Methods

2.1. Study design and data

An observational PK study was performed in HIV-infected and HIV-seronegative adult patients (age ≥ 18 years) with MDR-TB in the Bedaquiline Clinical Access Program of South Africa. Patient inclusion and exclusion criteria have been reported elsewhere [9]. The study was approved by the Human Research Ethics Committee of the University of Cape Town (Cape Town, South Africa). All patients provided written informed consent.

Participants were enrolled in three groups: HIV-seronegative patients without ART (control group); and HIV-infected patients on ART including either NVP (NVP group) or LPV/r (LPV/r group). To ensure maximal CYP3A4 induction, patients in the NVP group had to have been on NVP therapy for ≥ 2 weeks and had their NVP dose increased to 200 mg twice daily prior to PK sampling. For the LPV/r group, patients had to be on LPV/r for ≥ 3 days prior to PK sampling.

Bedaquiline dosing followed the standard recommended regimen (400 mg daily for 2 weeks, followed by a 22-week maintenance period of 200 mg bedaquiline three times weekly). During the maintenance dosing period (between treatment Weeks 3–24) when further bedaquiline and M2 accumulation is slow, all patients underwent an intense PK sampling scheme (just before and 1, 3, 4, 5, 6, 8, 24 and 48 h after dosing) and 28 patients also underwent a sparse PK sampling scheme (at 24 h and 48 h post-dose) at separate occasions. The time point for PK sampling varied widely between all patients (Supplementary Table S1). Sample handling and analysis have been described previously [9]. In brief, total concentrations of bedaquiline and M2 were determined using a liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay validated according to US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines. The lower limit of quantification (LLOQ) was 9.77 ng/mL and 3.31 ng/mL for bedaquiline and M2, respectively. Body weight data were collected at the start of treatment and at the time of PK sampling.

2.2. Population pharmacokinetic modelling

The modelling and simulation were performed in NONMEM 7.3 with the first-order conditional estimation method, including eta-epsilon interaction [10]. Perl-speaks-NONMEM functionalities aided the development work [11], and Xpose 4 was used for graphical evaluation [12]. Piraña was utilised as a link between the aforementioned software and the computation cluster and for creation of documentation [13]. R 3.2.1 was used for graphical evaluation and estimation of degrees of freedom of the priors for random effects [14].

The population pharmacokinetics of bedaquiline and M2 in MDR-TB patients was described using a previously developed model based on data from 325 MDR-TB patients [15]. Briefly, this model consisted of three disposition compartments for bedaquiline, one for M2 and an oral absorption model including a delay by two transit compartments. A schematic representation of this model is

provided in Supplementary Fig. S2. In addition, this model described time-varying albumin concentrations and body weights and their effects on disposition parameters. The impact of NVP and LPV/r on bedaquiline and M2 clearances was defined by separate factors (including interindividual variability in the case of LPV/r) as described in the models for the drug–drug interaction based on data from studies in subjects without TB [7]. The parameter values of these models were used as priors to inform the pharmacokinetics of bedaquiline and M2, and the drug–drug interaction effects in this study and are shown in Supplementary Table S3. For this purpose, the NONMEM PRIOR subroutine was used. This method, in which the prior parameter estimates and their uncertainty are considered, may stabilise parameter estimation with the new data by imposing a penalty function on the objective function value (OFV) [16]. The penalty of the prior information was derived from a normal-inverse Wishart distribution (NWPRI option in NONMEM 7.3). For the fixed effects, the information from the prior was quantified by the theta covariance matrix estimated in the previously developed PK models. For the random-effect parameters (omegas and epsilons), this was quantified by the assigned degrees of freedom, with a higher number increasing the penalty [16]. The degrees of freedom were estimated using maximum likelihood based on the probability density function of the inverse Wishart distribution (R packages *mle* and *diwish*). Since no albumin concentrations were available for the current patient study, the albumin model parameters and albumin–body weight correlations were fixed to the prior values.

Three models were evaluated: (i) a model with fixed prior values, which consisted of the prior values for all parameters without performing any estimation; (ii) a ‘Full-Prior model’ using the previously estimated parameter values as priors on all parameters except the residual errors for bedaquiline and M2 concentrations; and (iii) a ‘Reduced-Prior model’ using the previously estimated parameter values as priors on the parameters of the PK model and no priors on the drug–drug interaction effects or the residual errors for bedaquiline and M2 concentrations. When using the PRIOR subroutine, it is not possible to apply the log-likelihood ratio test to compare models directly when changes are made in the prior information. Therefore, to test whether the NVP and LPV/r interaction effect parameters were significantly different from its priors in the Full-Prior model, a parameter without prior was added to each interaction effect in a univariate procedure. A drop in OFV of more than 3.84 points ($P < 0.05$) was considered statistically significant.

The performance of the tested models was assessed by evaluating the parameter estimates and performing simulation-based posterior predictive checks using NCA metrics (ncappc). For the ncappc evaluation, bedaquiline and M2 profiles of each patient were simulated 1000 times and the area under the concentration–time curve of 0–48 h (AUC_{0-48h}) was computed. The model is deemed to capture AUC_{0-48h} well if the median of the observed AUC_{0-48h} falls within the 95% non-parametric prediction interval of the simulated median AUC_{0-48h} . Furthermore, prediction and variability corrected visual predictive checks (pvcVPCs, 1000 replicated simulations) were performed [17,18]. Precision in parameter estimates was obtained with the SIR procedure [19].

To interpret the NVP and LPV/r effects on bedaquiline and M2 clearance on the exposure of both compounds at selected times during bedaquiline treatment, the typical AUC_{0-48h} values at the end of Weeks 10 and 24 of treatment with and without interaction effects were simulated and compared. Lastly, bedaquiline weekly trough concentrations (1 h before the first dose of the week) for different drug–drug interaction scenarios were simulated, also applying an earlier proposed alternative bedaquiline dosing regimen for LPV/r co-administration (300 mg once daily for Weeks 1 and 2, followed by 100 mg thrice weekly) [7].

3. Results

A total of 488 bedaquiline and 486 M2 samples were available for analysis. The control and NVP groups consisted of 17 patients each, and the LPV/r group consisted of 14 patients. Two patients participated both in the NVP and LPV/r groups as they switched ART from NVP to LPV/r. None of the measured plasma concentrations were below the LLOQ. In addition, 120 weight observations from 46 patients were available. Patient characteristics can be found in [Supplementary Table S1](#).

The previously developed population PK model for bedaquiline and M2 concentrations was able to describe the data from the control group well without estimation ([Supplementary Fig. S4](#), top panels). The population PK parameter estimates in the Full- and Reduced-Prior models were very close to the prior values for both bedaquiline and M2 PK parameters and also for NVP and LPV/r typical interaction effects ([Table 1](#); [Supplementary Table S3](#)). The univariate addition of parameters without prior information to each interaction effect showed no significant improvement in OFV for any of the parameters ($P > 0.05$), indicating a lack of substantial differences between the priors and the new data. However, the large interindividual variability for the LPV/r effect estimated with the Full-Prior model ([Table 1](#)) is implausible since it may suggest an inducing effect of LPV/r for some (extreme) individuals. For this reason and the fact that the parameter estimates are solely based on patient data, the results of the Reduced-Prior model are presented below.

The parameter estimates indicate that NVP co-administration reduced bedaquiline clearance to 82% [95% confidence interval (CI) 67–99%] and increased M2 clearance to 119% (92–156%) in comparison with bedaquiline and M2 clearance values without interacting medication ([Table 1](#)). LPV/r co-administration reduced bedaquiline clearance to 25% (17–35%) and M2 clearance to 59% (44–69%) in comparison with its clearance without interacting medication ([Table 1](#)). At Week 10 of bedaquiline treatment, these estimated NVP and LPV/r interaction effects would result in a 14% and 120% increase in the typical predicted bedaquiline AUC_{0-48h} in comparison with the control group, respectively. At Week 24, this would be 17% and 187%, respectively.

[Fig. 1](#) shows the distribution of the population median of AUC_{0-48h} for each group and compound, calculated from the observed and 1000 model-simulated data sets. As the observed median AUC_{0-48h} values fall within the 95% non-parametric prediction interval, this indicates that the model is able to capture the median AUC_{0-48h} well for each subgroup. Finally, this figure illustrates the substantial increase in bedaquiline AUC_{0-48h} for the LPV/r group. Also, the

variability in bedaquiline AUC_{0-48h} was well captured by the model ([Supplementary Fig. S5](#)). For time–concentration profiles of the Reduced-Prior model and data, see the pvcVPCs presented in [Supplementary Fig. S6](#).

[Fig. 2](#) shows the simulated typical bedaquiline and M2 weekly trough concentrations when the standard bedaquiline dosing regimen is administered without concomitant interacting ART, with concomitant NVP treatment and with concomitant LPV/r treatment, and with an adjusted bedaquiline dosing regimen with LPV/r treatment. The rapid decline in concentration after Week 2 can be explained by bedaquiline distribution over the peripheral compartments in addition to its metabolism to M2. After 24 weeks of treatment, the bedaquiline decline mainly represents the distribution of bedaquiline from the peripheral compartments back to the central compartment.

The dose simulations show that LPV/r substantially increases bedaquiline concentrations, which continue to rise over time on treatment, whereas M2 concentrations are affected to a lesser extent. The suggested adjusted bedaquiline dosing regimen should bring bedaquiline exposure closer to normal when LPV/r is co-administered.

4. Discussion

We found that drug interaction effect estimates for the Reduced-Prior model were close to their prior values: an 11% and 13% deviation for the effect of NVP on bedaquiline and M2 clearances, and 28% and 1% for the effects of LPV/r ([Table 1](#)). In addition, we found that the separately developed population PK model of bedaquiline and M2 fitted the data from the control group well without re-estimation of parameter values, thus providing an external validation of this bedaquiline and M2 population PK model ([Supplementary Fig. S4](#), top panels).

The reduction in uncertainty for the parameters of the Full-Prior model in comparison with the prior parameter values indicates that the current study was able to add new information ([Table 1](#); [Supplementary Table S3](#)). Also, the uncertainty of the interaction parameters of the Reduced-Prior model is still reasonably low (relative standard errors between 10 and 30%; [Supplementary Table S3](#)), despite lacking prior information. The large estimate for interindividual variability for the LPV/r effect on clearance in the Full-Prior model is likely to stem from the strength of the prior values for the fixed effects of LPV/r effect on bedaquiline and M2 clearance, favouring a misfit of the variability instead ([Table 1](#)).

Table 1
Parameter values for drug–drug interaction effects in the evaluated models, including 95% confidence intervals.

	Model with fixed prior values [7] [value (95% CI)]	Full-Prior model [estimate (95% CI)]	Reduced-Prior model [estimate (95% CI)]
Nevirapine (NVP) drug interaction effect parameters			
Fixed effects			
Factor change BDQ CL	0.915 (0.81–1.02)	0.904 (0.80–1.00)	0.816 (0.67–0.99) ^a
Factor change M2 CL	1.05 (0.84–1.26)	1.08 (0.92–1.26)	1.19 (0.92–1.56) ^a
Ritonavir-boosted lopinavir (LPV/r) drug interaction effect parameters			
Fixed effects			
Factor change BDQ CL	0.347 (0.28–0.41)	0.332 (0.27–0.40)	0.250 (0.17–0.35) ^a
Factor change M2 CL	0.578 (0.48–0.68)	0.563 (0.48–0.65)	0.585 (0.44–0.69) ^a
Random effects			
BSV effect BDQ CL (CV %)	34.6 (19.7–44.7)	174.7 (130–199)	95.9 (84.5–125) ^a
Scaling BSV for M2 effect ^b	0.335 (–0.22 to 0.89)	0.491 (0.23–0.72)	0.484 (0.16–0.80) ^a

CI, confidence interval; BDQ, bedaquiline; CL, clearance; BSV, between-subject variability; CV, coefficient of variation calculated with $\sqrt{\exp(\text{OMEGA}) - 1}$ where OMEGA is the estimated variance.

See Reference [15] for the parameterisation of covariate effects in the model.

^a These parameters were not supported by prior information.

^b The correlation between BSV in LPV/r interaction effects on BDQ and M2 clearances was 100%; BSV in the effect on M2 was scaled from BSV in the effect on BDQ with an estimated factor.

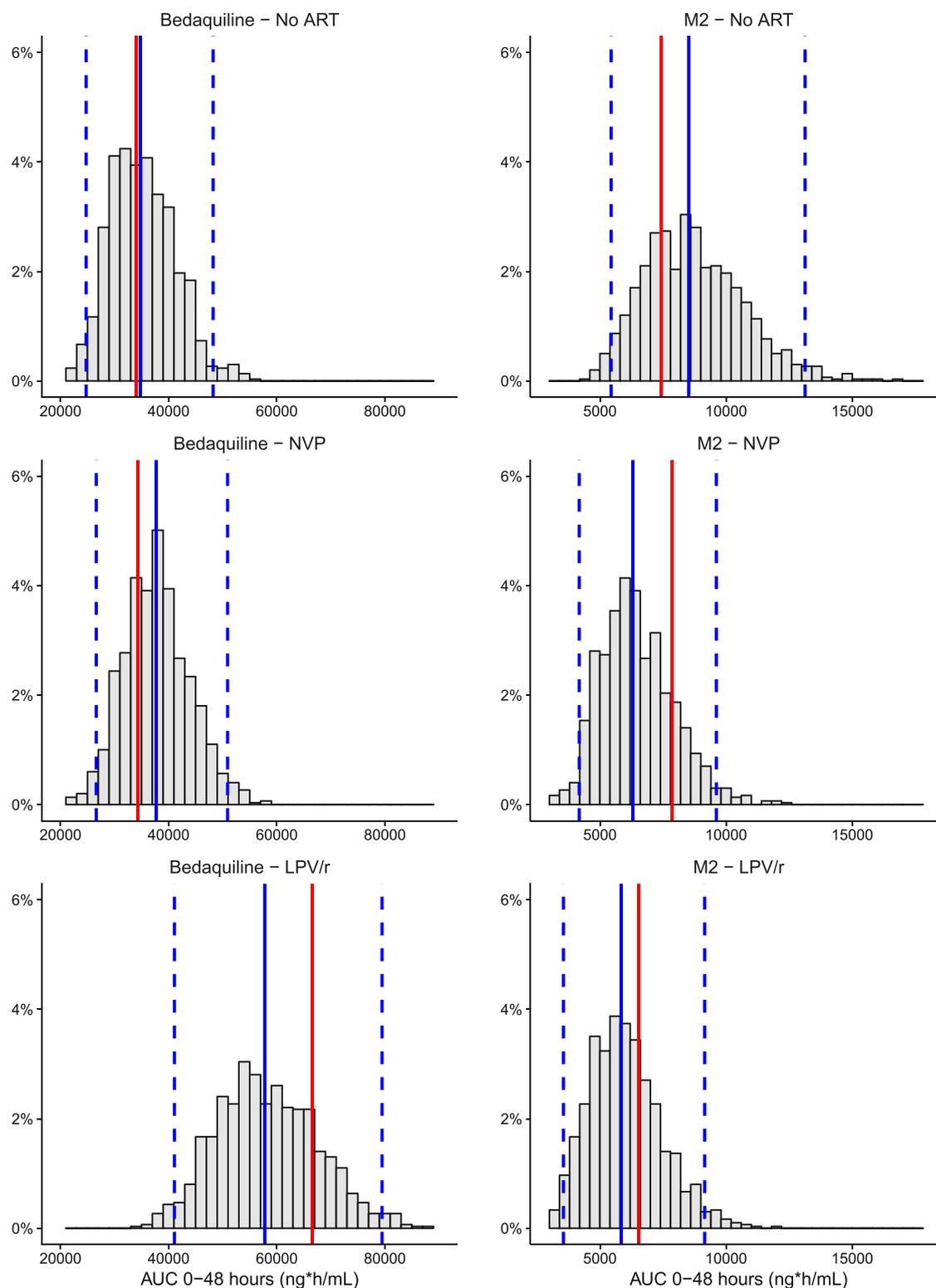


Fig. 1. Histograms of the population median AUC_{0-48h} values from 1000 simulated data sets using the Reduced-Prior model. The red and blue solid vertical lines represent the median of the observed data and the median of the model-simulated population median AUC_{0-48h} values. The blue dashed vertical lines represent the spread or 95% non-parametric prediction interval boundaries for the population median of AUC_{0-48h} values obtained from the simulated data. AUC_{0-48h} , area under the concentration-time curve of 0–48 h; ART, antiretroviral therapy; NVP, nevirapine; LPV/r, ritonavir-boosted lopinavir. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The estimated NVP drug effect on bedaquiline clearance may suggest a minor inhibitory effect, despite the fact that it has been considered as a CYP3A4 inducer [6]. However, the 95% CIs of these parameter estimates include 1, indicating that a mean NVP effect

of ‘no inhibition or induction effect’ (as represented by a value of 1) cannot be excluded based on these data. Rather, our results indicate that a clinically significant effect of NVP on bedaquiline and M2 clearance in HIV/TB co-infected patients is unlikely. This result

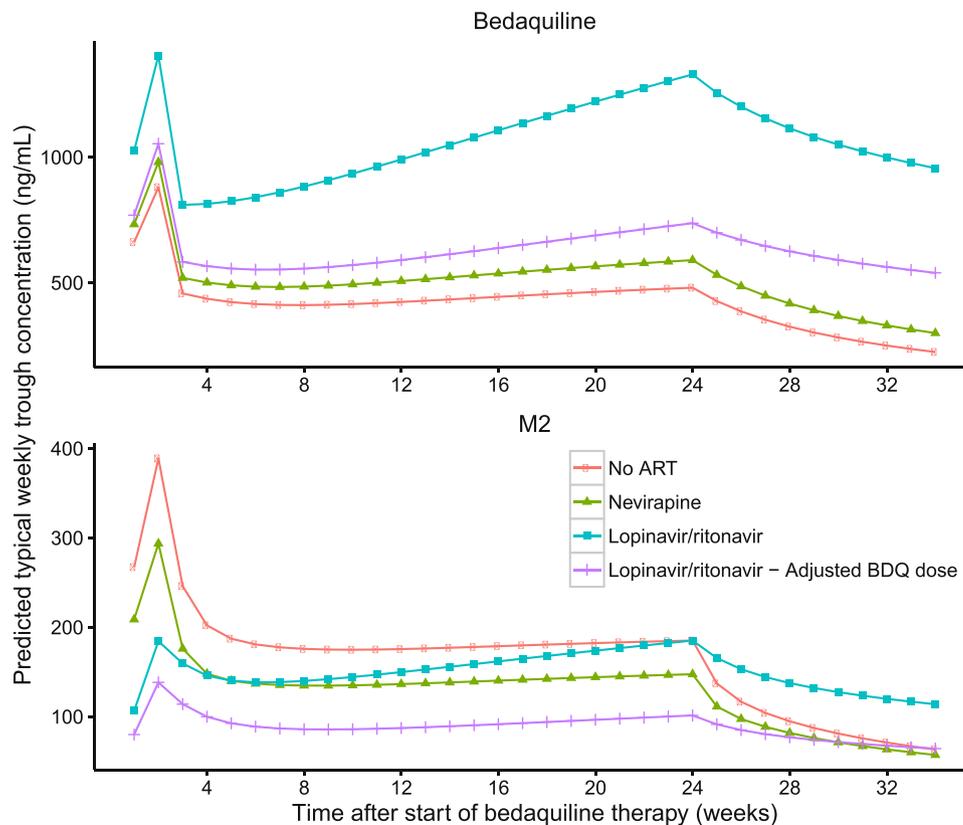


Fig. 2. Predicted typical bedaquiline and M2 trough concentrations simulated using the Reduced-Prior model for a Black (41/46 patients were Black) MDR-TB patient of 35 years (median age of patients in the study) on standard bedaquiline dosing (400 mg daily for 2 weeks, thereafter 200 mg three times weekly until Week 24) without interacting co-administration (red dots), with concomitant nevirapine (green triangles), with concomitant ritonavir-boosted lopinavir (LPV/r) (blue squares) and for the adjusted bedaquiline dosing (300 mg daily for 2 weeks, thereafter 100 mg three times weekly until Week 24) with LPV/r co-administration (purple pluses). ART, antiretroviral therapy; BDQ, bedaquiline. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

is in line with the uncertainty around CYP3A4-inducing abilities of NVP and that NVP has also been suggested to be an inducer of CYP2B6 [20–23]. Whilst some *in vitro* studies support evidence for an inhibitory effect of NVP on CYP3A4 activity [24,25], no CYP3A4 induction or inhibition was found at 14 days and 28 days of NVP treatment in a study of 15 patients [26].

The close resemblance between the interaction effects we found in HIV/MDR-TB co-infected patients on long-term treatment and those found in the model-based analysis of the single-dose studies in subjects without TB is reassuring since PK drug–drug interactions are often assessed in phase 1 studies with single or few doses and are subsequently extrapolated to the clinical situation [7]. In contrast to the model-based analysis, an NCA of the single-dose bedaquiline study in patients on LPV/r found only a 22% increase in bedaquiline AUC and a 41% decrease for the M2 metabolite [27]. This misleading result is a direct consequence of the extremely long half-life of both compounds; the NCA uses partial AUCs in the comparison and therefore underpredicts the impact of the LPV/r interaction effect [28]. The NCA of the current study in MDR-TB patients confirmed the model-based predictions, as the data were collected closer to steady-state of both bedaquiline and M2 [9]. However, the difference in the time on treatment between the groups, leading to different degrees of accumulation of both bedaquiline and M2, makes the NCA results more difficult to interpret than the direct comparison provided by the present population PK model analysis.

The clinical relevance of increased bedaquiline and M2 exposure caused by LPV/r co-medication is uncertain given that the

exposure range for effective and safe bedaquiline treatment is not well established. However, recently Svensson et al were able to relate bedaquiline exposure to outcome as measured by time to sputum culture conversion in 206 MDR-TB patients and found that higher bedaquiline concentrations early during treatment led to faster response and higher sputum conversion rates after the end of the treatment [29]. This suggests that the higher bedaquiline exposure for the LPV/r group found in the current study may actually be beneficial to these patients as it may result in faster and more likely sputum culture conversion. Thus, an adjusted dosing regimen to mimic bedaquiline concentrations of patients without concomitant LPV/r may not be needed. Yet bedaquiline treatment, and particularly M2 exposure, has also been associated with QTcF (Fridericia-corrected QT interval) prolongation [3]. So, from a safety perspective, it may be preferable to limit an increase of bedaquiline and especially M2 concentrations by applying an adjusted bedaquiline dosing regimen for patients on concomitant LPV/r therapy until more cardiotoxicity data are available. However, the simulations indicate that M2 concentrations in the LPV/r group stay below M2 concentrations in the control group until the very last week of treatment (Fig. 2).

In conclusion, this work confirms earlier model-based prediction of NVP and LPV/r interaction effects on bedaquiline and M2 from phase 1 studies for MDR-TB/HIV co-infected patients. To normalise bedaquiline exposure in patients with concomitant LPV/r therapy, an adjusted bedaquiline dosing regimen is proposed; however, future exposure–response and safety studies should guide appropriate bedaquiline dosing for patient receiving concomitant LPV/r treatment.

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Competing interests: GM has served on the Data Safety and Monitoring Board for Janssen Pharmaceuticals for the TMC207 (bedaquiline) C208 and C207 phase 2 trials in patients with MDR-TB (2007–2012); MOK has received research grants from Janssen Pharmaceuticals. All other authors declare no competing interests.

Ethical approval: The study was approved by the Human Research Ethics Committee of the University of Cape Town (Cape Town, South Africa) [reference no. 444/2013].

Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2016.10.020.

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