**Simulation of the Impact of Rifampicin on Once Daily Darunavir/Ritonavir Pharmacokinetics and Dose Adjustment Strategies: A Population Pharmacokinetic Approach**

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**Synopsis**

**Objectives:** Treatment of HIV/TB co-infection is challenging due to potent drug-drug interactions between antiretrovirals and rifampicin. The effect of rifampicin on darunavir/ritonavir has not been studied. Population pharmacokinetic modelling was applied to investigate the interaction and generate alternative doses to inform clinical trial design.

**Patients and Methods:** Darunavir/ritonavir concentrations were modelled simultaneously including data from 3 studies in HIV patients (n=51, 7 female). The darunavir/ritonavir-rifampicin interaction was assumed to mimic that previously observed with lopinavir/ritonavir. Daily darunavir/ritonavir 800/100 mg was simulated as a reference (n=1000; -rifampicin). Simulations with apparent oral clearance increased by 71% and 36% and relative bioavailability decreased by 20% and 45% for darunavir and ritonavir, respectivelywere performedfor +rifampicin, 600 mg once daily (n=1000). Darunavir/ritonavir 1200/200 mg, 1600/200 mg once daily, 800/100 mg and 1200/150 mg twice daily +rifampicin were simulated. Darunavir parameters for each dose +rifampicin were compared to -rifampicin by geometric mean ratio (90% CI).

**Results:** A maximum effect model, with ritonavir inhibiting darunavir clearance, best described the relationship between the drugs. Compared to -rifampicin, simulated darunavir AUC0-24 was 57%, 30%, 1% and 16% lower for 800/100 mg, 1200/200 mg*,* 1600/200 mg once daily and 800/100 mg twice daily + rifampicin, respectively; but 39% higher with 1200/150 mg twice daily + rifampicin.

**Conclusions:** Darunavir/ritonavir 1600/200 mg once daily, 800/100 mg and 1200/150 mg twice daily could potentially overcome reduced darunavir concentrations with rifampicin. In the absence of clinical data, modelling and simulation may be useful to predict drug-drug interactions and aid optimal dose selection.

**Introduction**

Approximately 12% of TB patients are co-infected with HIV globally and TB remains the leading cause of mortality amongst individuals living with HIV.1 Treatment of HIV/TB co-infection is challenging due to the high propensity for drug-drug interactions between antiretrovirals and rifampicin.2 Use of ritonavir or cobicistat-boosted protease inhibitors (PI) in combination with rifampicin is contraindicated, due to well-documented induction of CYP3A4 and efflux transporters by rifampicin,3-5 reducing PI concentrations and risking therapy failure.

Once daily darunavir/ritonavir (800/100 mg) is approved for use in treatment-naïve and experienced patients6, 7 and can be used as a second-line alternative to lopinavir/ritonavir or atazanavir/ ritonavir in resource-limited settings.8 Although neither currently recommended nor previously studied, co-administration of darunavir/ritonavir with TB medications, such as rifampicin may be necessary for co-infected patients with few other treatment options.

Population pharmacokinetic modelling may play a role in assessing the potential impact of rifampicin on darunavir/ritonavir pharmacokinetics. The aim of this analysis was to simulate the change in darunavir/ritonavir exposure co-administered with rifampicin and generate alternative dosing strategies to mitigate the interaction.

**Patients and Methods**

***Study population and Pharmacokinetic Sampling***

Data were combined from 3 published clinical pharmacokinetic studies conducted at Imperial College Healthcare Trust at St. Mary’s Hospital (London, UK; n=1) and St. Stephen’s Centre, Chelsea & Westminster Foundation Trust (London, UK; n=2) that enrolled HIV-1-infected adults.9-11

Details of study designs have been described previously.9-11 Pregnant or lactating females, patients suffering from active opportunistic infections or significant comorbidities, dependent on alcohol or illicit substance use or receiving therapies known to affect drug metabolism were not permitted to participate. Studies received approval from local ethics committees and written informed consent was obtained.9-11

Sampling was performed at steady-state following a standardised breakfast after 10-14 days of darunavir/ritonavir intake. Blood was collected pre-dose (0 hour) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 hours post-dose9, 10 or 1, 2, 4, 6, 8, 12, 24 hours post-dose.11 Darunavir/ritonavir plasma concentrations were quantified by a validated high-performance tandem mass spectrometry (HPLC-MS/MS) method.12

***Pharmacokinetic Modelling***

A previously developed darunavir/ritonavir model was used to investigate the potential impact of rifampicin on darunavir/ritonavir pharmacokinetics.13 Non-linear mixed effects modelling was applied to darunavir/ritonavir concentration-time data simultaneously using the SAEM algorithm of Monolix (v. 4.1.2, Lixoft, Paris, France14) to estimate pharmacokinetic parameters and the influence of ritonavir on darunavir apparent oral clearance (CL/F). Model fit was assessed by standard modelling procedures including statistical and graphical methods. For the purposes of this analysis, assessment of covariates was limited to inclusion of bodyweight on darunavir and ritonavir clearance and volume of distribution to allow more generalisable simulations.

To evaluate the model, 1000 concentration-time curves were simulated and 90% prediction intervals (P5-P95) generated for darunavir and ritonavir. At least 90% of observed concentrations within a prediction interval was representative of a satisfactory model.

***Simulation of Rifampicin Interaction***

An initial assumption was made that the darunavir/ritonavir-rifampicin interaction would mimic that observed for twice daily lopinavir/ritonavir administered to HIV-infected, TB negative patients (n=21).15 In the presence of rifampicin (600 mg once daily), lopinavir and ritonavir CL/F increased by 71% and 36%, respectively whilst relative bioavailability (F) decreased by 20% (lopinavir) and 45% (ritonavir).15

Simulations of darunavir/ritonavir 800/100 mg once daily (n=1000; NONMEM v. 7.2, ICON Development Solutions, Ellicott City, MD, USA16) were performed to establish darunavir/ritonavir pharmacokinetic profiles in the absence of rifampicin (-rifampicin). Typical values of darunavir and ritonavir CL/F and F were altered by the magnitudes reported for lopinavir/ritonavir (see above). Simulations under these conditions (n=1000) represented profiles in the presence of rifampicin (+rifampicin).

***Simulated Dose Adjustments in the Presence of Rifampicin***

Alternative darunavir/ritonavir doses were based on increments of combination tablets of 400/50 mg or 600/100 mg. Dose adjustments of darunavir/ritonavir 1200/200 mg and 1600/200 mg once daily and 800/100 mg and 1200/150 mg twice daily +rifampicin were simulated (n=1000). Changes in darunavir trough (Ctrough; 12 hour or 24 hour post-dose for a twice and once daily regimen, respectively) and area under the curve 0-24 hours (AUC0-24) were determined by geometric mean ratio (GMR) and 90% CI, using darunavir/ritonavir 800/100 mg once daily -rifampicin as a reference.

**Results**

***Study population and Pharmacokinetic Sampling***

To develop the model, 51 HIV-1 patients (n=7 female; n=32 Caucasian, n=12 African, n=4 Asian, n=4 other) were included with a median (range) age, weight and baseline CD4 cell count of 39 years (21-63), 74 kg (57-105) and 500 cells/mm3 (227-1129), respectively; 49/51 were virologically suppressed at sampling. Patients were stable on darunavir/ritonavir 800/100 mg (n=32)9, 11 or 900/100 mg once daily (n=1910) and 1 pharmacokinetic profile per patient was included, totalling 506 and 505 darunavir and ritonavir concentrations, respectively.

***Pharmacokinetic Modelling***

A two-compartment model parameterised by CL/F [estimate (relative standard error, RSE%): 14.8 L/h (7.4%)], apparent volume of the central compartment [Vc/F; 128 L (7.0%)], intercompartmental clearance [Q/F; 21.9 L/h (11.9%)], apparent volume of the peripheral compartment [Vp/F; 420 L (16.9)], absorption rate constant [ka; 1.01 h-1 (0.02%)] and lag-time [0.53 h (14.3%)] best described darunavir pharmacokinetics and a one-compartment model was fitted to ritonavir data with final parameters CL/F, V/F, ka and lag-time: 23.0 L/h (4.3%), 200 L (5.0%), 1.37 h-1 (0.4%) and 2.16 h (8.3%), respectively. F was fixed to 1.00 for both drugs in the absence of rifampicin. Interindividual variability was included on darunavir and ritonavir CL/F, Vc/F (or V/F) and lag-time: 45.6% (12.3%) and 30.2% (10.6%), 35.5% (15.5%) and 30.9% (12.6%), 77.3% (15.5%) and 56.3% (10.7%), respectively. Residual variability was 25.2% (3.8%) and 28.2% (3.9%) for darunavir and ritonavir, respectively (proportional error model). Inhibition of darunavir CL/F by ritonavir followed a maximum effect function (Figure 1). Ritonavir concentration of 0.82 mg/L (0.3%) was associated with 50% maximum inhibition (IC50) of darunavir CL/F [maximum inhibitory effect (Emax)=1]. Weight was included on all clearance and volume of distribution parameters using allometric scaling.

Ninety-three percent of measured darunavir and ritonavir concentrations were within the 90% prediction intervals.

***Simulation of Rifampicin Interaction and Dose Adjustments***

Darunavir and ritonavir population CL/F estimates were increased to 25.3 L/h and 31.3 L/h (71% and 36% for darunavir and ritonavir, respectively) and F decreased by 20% and 45% to 0.80 and 0.55, respectively to perform the simulations +rifampicin [using darunavir CL/F as an example the following parameterisation was applied: TVCL/FDRV = θ1 \* (θRIF\*\*RIF); where θ1 is the typicalvalue of darunavir CL/F (TVCL/FDRV, 14.8 L/h), θRIF is relative change in CL/F associated with the addition of rifampicin (1.71), RIF is an indicator variable taking on the value of 0 without rifampicin and 1 in the presence of rifampicin]. Geometric mean darunavir Ctrough was decreased by 70% from 1.64 mg/L to 0.49 mg/L whereas AUC0-24 was reduced by 57% from 69.4 mg.h/L to 29.7 mg.h/L compared to –rifampicin (Table 1).

Geometric mean (90% CI) darunavir Ctrough and AUC0-24 following dose adjustments are presented (Table 1). Ctrough and AUC0-24 were 46% and 26%, 28% and 1%, 20% and 16% lower for 1200/200 mg once daily, 1600/200 mg once daily and 800/100 mg twice daily, respectively. Darunavir exposure was increased by 39% for 1200/150 mg twice daily (Table 1).

**Discussion**

Due to dramatic decreases in HIV PI concentrations studied in combination with rifampicin,17, 18 co-administration is contraindicated; however, under certain circumstances combined use may be unavoidable. Modelling can play a role in determining the potential pharmacokinetic impact of drug-drug interactions and identify prospective dosing regimens for clinical investigation. Given that darunavir/ritonavir in combination with rifampicin has not been evaluated, a modelling approach was undertaken to address this. Based on simulations, darunavir/ritonavir 800/100 mg and 1200/150 mg twice daily and 1600/200 mg once dailycould potentially overcome the interaction.

Limitations of the analysis were the assumptions that the interaction was of a similar magnitude to that observed with twice daily lopinavir/ritonavir and variability in parameters remained unchanged. Darunavir and lopinavir are substrates for CYP3A4 and transporters ABCB1, SLCO1B1, 1B3 and 1A2.19 Although darunavir and lopinavir have been identified as weak inhibitors and inducers of CYP3A4, ABCB1 and SLCO1B1, their induction and inhibition potentials are not equal (e.g. *in vitro*, using a Chinese hamster ovary cell system, SLCO1B1 was more potently inhibited by lopinavir, Ki=0.5 µM *vs.* darunavir, Ki=3.1 µM20), and may result in differential impact on pharmacokinetics.21, 22 The combined effect of ritonavir and rifampicin may alter the effect of darunavir and lopinavir on gene expression and protein inactivation, defining a complex scenario which has not been fully elucidated. However, the simulations are in agreement with a physiologically-based pharmacokinetic model, which incorporated *in vitro* data to allow more mechanistic predictions in a virtual population of individuals.23 Darunavir AUC0-24 and Ctrough were estimated to decrease by 58% and 80%, respectively with rifampicin23 compared to 57% and 70%, respectively for the present analysis. Darunavir/ritonavir 800/100 mg twice daily and 1600/200 mg once daily were also suggested as favourable dose adjustments.23 The dose adjustments proposed would require a higher pill burden and potentially a greater risk of ritonavir-related adverse events, which could impact adherence. Moreover, the effect on virological outcome would require investigation. Of note, the interaction did not consider the potential effect of other TB drugs used in combination with rifampicin.

Optimal treatment of HIV/TB co-infected patients requires clinicians to manage drug-drug interactions safely. Clinical trials are not always ethically justifiable (e.g. rifampicin + PIs in HIV-negative individuals) therefore, in the absence of specific clinical data, modelling and simulation may be particularly useful to predict drug-drug interactions but also inform trial design and aid optimal dose selection. Real-life data are now necessary to further validate suggested dose adjustments to overcome the darunavir/ritonavir-rifampicin interaction.

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**Figure Legends**

**Figure 1** Diagram illustrating the simultaneous darunavir/ritonavir model and potential interaction with rifampicin

**Table 1** Model simulated darunavir geometric mean Ctrough and AUC0-24 for each dosing regimen without and with rifampicin. The changes in parameters are presented as GMR (90% CI) with darunavir/ritonavir 800/100 mg once daily without rifampicin as reference.

|  |  |  |
| --- | --- | --- |
| **Regimen** | **Geometric mean (90% CI)** | **GMR (90% CI)\*** |
| ***DRV Ctrough (mg/L)b*** |  |  |
| 800/100 mg once daily(-RIF)***a*** | 1.64 (1.59-1.70) | - |
| 800/100 mg once daily (+RIF) | 0.49 (0.47-0.51) | 0.296 (0.293-0.299) |
| 1200/200 mg once daily (+RIF) | 0.88 (0.85-0.92) | 0.538 (0.533-0.542) |
| 1600/200 mg once daily (+RIF) | 1.18 (1.13-1.23) | 0.717 (0.711-0.723) |
| 800/100 mg twice daily (+RIF) | 1.31 (1.27-1.36) | 0.798 (0.761-0.837) |
| 1200/150 mg twice daily (+RIF) | 2.27 (2.20-2.35) | 1.383 (1.319-1.449) |
| ***DRV AUC0-24 (mg.h/L)***c |  |  |
| 800/100 mg once daily (-RIF)***a*** | 69.4 (68.0-70.8) | - |
| 800/100 mg once daily (+RIF) | 29.7 (29.0-30.4) | 0.428 (0.426-0.430) |
| 1200/200 mg once daily (+RIF) | 51.4 (50.3-52.6) | 0.741 (0.738-0.743) |
| 1600/200 mg once daily(+RIF) | 68.5 (67.0-70.1) | 0.987 (0.984-0.991) |
| 800/100 mg twice daily (+RIF) | 58.7 (57.6-59.8) | 0.845 (0.823-0.869) |
| 1200/150 mg twice daily (+RIF) | 96.7 (95.0-98.6) | 1.394 (1.357-1.432) |

\* Geometric mean ratio of change in parameter relative to DRV/RTV 800/100 mg once daily *without* rifampicin

Ctrough: trough concentration; AUC0-24: area under the curve over the 24 hour dosing interval; DRV: darunavir; RIF: rifampicin; GMR: geometric mean ratio; CI: confidence interval

a Reference regimen; b concentration 12 hours or 24 hours post-dose for twice daily or once daily regimen, respectively; c AUC0-12 x2 for twice daily regimens

**Figure 1**



DRV: darunavir; RTV: ritonavir; RIF: rifampicin; kaDRV: DRV absorption rate constant; kaRTV: RTV absorption rate constant; LagDRV: DRV absorption lag-time; LagRTV: RTV absorption lag-time; FDRV: DRV bioavailability; FRTV: RTV bioavailability; Vc/F: apparent volume of the central compartment for DRV; Q/F: intercompartmental clearance; Vp/F: apparent volume of the peripheral compartment for DRV; V/F: RTV apparent volume of distribution; k23: transfer rate constant between DRV central & peripheral compartments; k32: transfer rate constant between DRV peripheral & central compartments; CL/FDRV: DRV apparent oral clearance; CL/FRTV: RTV apparent oral clearance

CL/F0: DRV apparent oral clearance in the absence of RTV; Emax: maximum inhibitory effect of RTV; EC50: RTV concentration producing 50% of maximum inhibition; CRTV: RTV concentration