Pharmacokinetic profile and safety of adjusted doses of darunavir/ritonavir with rifampicin in people living with HIV

Ismaeel Ebrahim¹, Gary Maartens^{1,2}, Lubbe Wiesner ¹, Catherine Orrell³, Wynand Smythe⁴ and Helen McIlleron^{1,2*}

¹Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa; ²Wellcome Centre for Infectious Diseases Research in Africa (CIDRI-Africa), Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa; ³Desmond Tutu HIV Centre, Institute of Infectious Diseases and Molecular Medicine (IDM) and Department of Medicine, University of Cape Town, Cape Town, South Africa; ⁴Clinical Research Centre, University of Cape Town, Cape Town, South Africa

*Corresponding author. E-mail: helen.mcilleron@uct.ac.za

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Background: Darunavir/ritonavir is better tolerated than lopinavir/ritonavir and has a higher genetic barrier to resistance. Co-administration with rifampicin has been contraindicated as a significant reduction in darunavir exposure is expected. This is a barrier to darunavir/ritonavir use where TB is endemic.

Objectives: To evaluate the safety and pharmacokinetic profile of adjusted doses of darunavir/ritonavir with rifampicin.

Methods: Virally suppressed participants on second-line lopinavir/ritonavir-based ART were switched to darunavir/ritonavir 800/100 mg q24h. In sequence: rifampicin was added; the dose of ritonavir was escalated; and darunavir was increased (darunavir/ritonavir 1600/200 mg q24h and 800/100 mg q12h were given in randomized sequence with rifampicin). Darunavir plasma concentrations were measured on the seventh/last day of each treatment period. To prevent viral rebound, dolutegravir (50 mg q12h) was added during rifampicin administration and for 1 week thereafter. Clinical events, ALT and bilirubin were monitored every 2–3 days during rifampicin administration.

Results: A total of 17/28 participants started study treatment. Six (35.3%) were withdrawn for symptomatic hepatitis with severe ALT elevations, developing after 9–11 days of rifampicin and 2–4 days of ritonavir 200 mg. The study was stopped prematurely due to this high rate of hepatotoxicity. Only four participants completed the study. All hepatotoxicity resolved on withdrawal of study treatment. All participants were successfully re-established on their lopinavir/ritonavir-based regimen. After doubling the darunavir/ritonavir doses on rifampicin, darunavir pre-dose concentrations approached those on standard doses without rifampicin for q12h doses, but not for q24h doses.

Conclusions: Adjusted doses of darunavir/ritonavir with rifampicin had unacceptable risk of hepatotoxicity. Darunavir trough concentrations were markedly reduced with the daily adjusted dose.

Introduction

Darunavir/ritonavir is better tolerated than lopinavir/ritonavir and has a higher genetic barrier to resistance.¹ In high-income countries, darunavir is the preferred boosted PI. Co-administration of darunavir/ritonavir with rifampicin, the key component of first-line treatment for TB, is contraindicated as significant reductions in darunavir exposures are expected due to induction of cytochrome P450 (CYP) 3A4 and P-glycoprotein;^{2,3} this has been a barrier to the use of darunavir/ritonavir in resource-limited settings where TB is endemic. Switching rifampicin to rifabutin, which is a weak inducer

of CYP3A4 and does not significantly reduce PI concentrations, is recommended in high-income countries for patients on boosted PIs who develop TB. However, rifabutin is not available in most low- and middle-income countries, is not practical where TB is typically treated with fixed-dose combination tablets and requires dose adjustments when given with boosted PIs.

PIs are substrates of both CYP3A4 and P-glycoprotein and co-administration with rifampicin results in subtherapeutic PI trough concentrations.⁴ Conversely, ritonavir is a potent inhibitor of CYP3A4 and P-glycoprotein and increasing ritonavir doses can counter the inducing effects of rifampicin.^{2,5} Doubling the dose of

lopinavir/ritonavir or adding additional ritonavir can achieve therapeutic lopinavir concentrations when co-administered with rifampicin.^{6,7} However, high rates of symptomatic hepatitis were reported in healthy volunteer studies evaluating adjusted doses of PIs.^{8–10} Severe ALT elevations were reported in 80%–100% of those treated with rifampicin before adding saquinavir/ritonavir, atazanavir/ritonavir or lopinavir/ritonavir (tablet formulation). By contrast, symptomatic hepatitis did not occur in a pharmacokinetic study of double-dose lopinavir/ritonavir with rifampicin in people living with HIV (PLWH) done by our group, but 2/21 had asymptomatic grade 3 or 4 ALT elevation.⁷ A physiologically based pharmacokinetic model predicted that increasing the dose of darunavir/ritonavir to 800/100 mg twice daily or 1600/200 mg once daily would overcome the inducing effects of rifampicin.¹¹ We evaluated the steady-state pharmacokinetics and safety of darunavir in PLWH, without TB, who were given rifampicin with gradual escalation of the PI dose to darunavir/ritonavir 1600/200 mg daily or 800/100 mg every 12 h.

Methods

Ethics

The study (NCT03892161) was approved by the University of Cape Town Human Research Ethics Committee and the South African Health Products Regulatory Authority. Each volunteer was informed of the objectives, nature and potential risks of the study. Written informed consent was obtained from every participant and the study was conducted in accordance with the Declaration of Helsinki and national and institutional standards of Good Clinical Practice.

Study design

The study was an open-label, single-centre, pharmacokinetic study in medically stable PLWH on a second-line ART regimen with a ritonavir-boosted PI

together with dual NRTIs. We planned to enrol 28 participants across three consecutive cohorts. The independent data and safety monitoring committee (IDSMC) proposed stopping the study if two or more of the five participants in cohort 1 (*n* = 5), or more than 20% of the cumulative total of participants thereafter, experienced serious adverse events (SAEs) including grade 3 or 4 events according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Participants in each cohort started treatment on the same day. Enrolment to cohort 2 (*n* = 12) proceeded after the clinical safety of cohort 1 was reviewed by the IDSMC. We planned to include 11 participants in cohort 3.

We recruited participants from an antiretroviral clinic, the Hannan Crusaid Treatment Centre in Gugulethu, Cape Town, South Africa. Participants were ≥18 and ≤60 years of age, with virological suppression (HIV-1 RNA <50 copies/mL), on second-line ART for ≥3 months and weighed ≥38 kg with a BMI >18.5 kg/m² and had a CD4 cell count ≥200 cells/mm³. Women were either postmenopausal, surgically sterile or practising an effective birth control method. Exclusion criteria included active TB, suspicion of TB based on the WHO symptom screen or an elevated C-reactive protein >10 mg/L, impaired hepatic function or documented hepatic cirrhosis, coinfection with HBV or HCV, ALT ≥2.5 times the upper limit of normal, DAIDS grade 3 or 4 haematological abnormality, active (not clinically stabilized >4 weeks) AIDS-defining illness (except for stable cutaneous Kaposi's sarcoma), estimated glomerular filtration rate <50 mL/min (calculated using the modification of diet in renal disease formula), active clinically significant or life-threatening disease that could compromise participant safety or their ability to comply with study procedures, concomitant administration of drugs or over-the-counter medications known or suspected to affect study drug concentrations, active alcohol or recreational-drug abuse or a positive urine screening test for drugs of abuse, pregnancy or breastfeeding, sulphonamide allergy and participation in another clinical trial within 4 weeks prior to screening.

Based on data from a physiologically based pharmacokinetic model,¹¹ we selected two adjusted doses of darunavir/ritonavir (1600/200 mg daily and 800/100 mg every 12 h) with rifampicin for comparison of plasma exposures with darunavir/ritonavir 800/100 mg daily without rifampicin. Using a sequential design (Figure 1), baseline darunavir steady-state pharmacokinetics were determined after 7 days of daily darunavir/ritonavir

Figure 1. Study treatment administration schedule and pharmacokinetic sampling design. Participants were switched from their boosted PI to darunavir/ritonavir for 6 weeks, from Day 1 to Day 42. Throughout, participants remained on their standard-of-care dual NRTIs. Rifampicin (600 mg q24h for participants weighing <70 kg and 750 mg q24h for those 70 kg and above) was given to participants from Day 8, for 28 days. PK sampling, pharmacokinetic sampling on the last day of each 7 day treatment period; IS, sampling pre-dose and at 0.5, 1, 2, 4, 6, 8, 12 and 24 h after the morning dose (intensive pharmacokinetic sampling); SS, morning pre-dose sample only (sparse pharmacokinetic sampling).

800/100 mg. Rifampicin (600 mg daily or 750 mg daily for participants weighing 70 kg or more) was then added for 7 days before the dose of ritonavir was increased to 200 mg. After another 7 days, participants were randomized to doubled doses of darunavir/ritonavir in daily doses or doses every 12 h, with either 1600/200 mg q24h or 800/100 mg q12h. After a further 7 days, participants were crossed over to the alternative doubled darunavir/ritonavir dose. Pharmacokinetics were evaluated after 7 days on each of the adjusted darunavir/ritonavir doses (Days 28 and 35) with rifampicin, which was then discontinued. The adjusted doses of darunavir/ritonavir were given for 7 days after stopping rifampicin. Dual NRTIs were continued throughout with no dose adjustments. Dolutegravir 50 mg every 12 h was added during, and for 7 days beyond, rifampicin administration, to prevent viral rebound during the period of potentially subtherapeutic PI exposures. Treatment adherence was assessed by using a treatment diary and thrice-weekly pill counts.

Darunavir was measured in plasma samples after observed doses at baseline and after each dose adjustment. To measure darunavir pharmacokinetics for the primary analysis (Days 7, 28 and 35 on study treatment), participants were admitted overnight. For participants randomized to the 800/100 mg every 12 h arm, we observed the dose of darunavir/ritonavir taken with the evening meal before pharmacokinetic sampling, ensuring it was 12 h before the pre-dose sample the next morning. Participants ate a light breakfast before the morning dose. Intensive pharmacokinetic sampling was done pre-dose and at 0.5, 1, 2, 4, 6, 8, 12 and 24 h after the morning dose. Darunavir trough concentrations were also measured during sparse pharmacokinetic sampling on Days 14 and 21. On these days, timing of the darunavir dose was self-reported (23–24 h for daily doses and 12–13 h for twice-daily doses). We collected 4 mL blood samples in EDTA tubes for plasma concentration measurement, which were immediately centrifuged to separate the plasma. Plasma was placed in the -80°C freezer within 60 min of blood sampling and stored until the drug concentrations were determined.

Drug assays

A method for the determination of darunavir from 25 μL of human plasma using liquid–liquid extraction and LC–MS/MS analysis was used to assay the pharmacokinetic samples. Darunavir-d9 was used as an internal standard (ISTD). The calibration curves fit quadratic regressions over the range of 30–10 000 ng/mL for darunavir based on the analyte/ISTD peak area ratios. The lower limit of quantification (LLOQ) for darunavir was 30 ng/mL. The mean interday accuracy and precision of the darunavir assay in plasma were observed to range between 101.5% and 103.1%, and 4.4% and 5.2%, respectively.

Safety monitoring

We monitored ALT and total serum bilirubin at baseline and three times per week from the day before rifampicin was started until rifampicin was discontinued (Study days 7, 9, 11, 14, 16, 18, 21, 23, 25, 28, 32 and 35) and at the end of the study period, 6–10 days after stopping rifampicin. Fasting serum glucose, triglycerides and cholesterol were tested at baseline and repeated on Days 21 and 35 after the darunavir/ritonavir dose adjustments. Viral load was tested at baseline and repeated on Day 21. All adverse events were recorded and graded according to the DAIDS grading system.¹² Participants were withdrawn from the study if they developed grade 3 or higher adverse events thought to be related to the study drugs.

Sample size

A sample size of 24 participants provided 90% power to detect a 25%–30% change in darunavir AUC, assuming a coefficient of variance (CV) of approximately 33% and >80% power to detect a 30% change in the minimum concentration of drug in serum, assuming a CV of approximately 40%. These were conservative power estimates as the CVs used were based on

published darunavir measures between participants,¹³ while ours was a within-participant comparison. Allowing for an attrition rate of 15%, we planned to enrol 28 participants.

Statistical analyses

The imputed value of 15 ng/mL (half the LLOQ) was substituted for darunavir concentrations below the limit of quantification. The maximum concentration of drug in plasma (C_{max}), the pre-dose trough concentration (C_0), the trough concentration 12 h after the observed dose (C_{12}), the trough concentration 24 h after the observed dose (C_{24}), the AUC from 0–12 h (AUC_{0-12}) and AUC 0–24 h (AUC_{0-24}) were described for the 12 and 24 h dosing intervals. Non-compartmental analysis was used to calculate the AUC using the trapezoidal rule, with C_{max} , C_0 , C_{12} and C_{24} determined directly from the concentration–time data. The pharmacokinetic measures were summarized as geometric means (95% CIs). The number of morning trough concentrations of darunavir below the EC_{90} (200 ng/mL)¹⁴ was described and box plots were used to illustrate the distribution of the trough concentrations. Geometric mean ratios (90% CIs) were calculated to compare darunavir C_{24} and AUC_{0-24} with the adjusted doses of darunavir/ritonavir (1600/200 mg q24h and 800/100 mg q12h, respectively) with rifampicin, to darunavir/ritonavir 800/100 mg without rifampicin. Stata version 13.1 (Stata Corporation, College Station, TX, USA) was used to determine the pharmacokinetic parameters of darunavir, to compute the summary statistics, to perform the statistical analyses and to generate the graphs.

Results

We enrolled 17 black African participants; their baseline characteristics are given in Table 1. All participants were on lopinavir/ritonavir with two NRTIs, in line with the South African national antiretroviral treatment guidelines for a second-line regimen. Eight participants were given 600 mg and nine participants were given 750 mg of rifampicin. The disposition of the study participants is summarized in Figure 2.

Four of the five participants in cohort 1 completed the study. One participant was withdrawn due to symptomatic hepatitis with grade 4 ALT elevation, which developed on the ninth day of rifampicin, 2 days after doubling the ritonavir dose but before the darunavir dose was doubled (Figure 3). A further three participants in cohort 1 developed modest asymptomatic ALT elevations (<grade 2), after 18–28 days on study treatment. The IDSMC review allowed the study to continue.

Five of the 12 participants in cohort 2 were withdrawn from the study due to symptomatic hepatitis with grade 3 or 4 ALT elevation

Table 1. The baseline characteristics of the enrolled cohort ($n = 17$)

Characteristic	Value
Sex	
men	1
women	16
Age (years)	44 (39–47)
Weight (kg)	73 (67–91)
BMI (kg/m^2)	31 (27–34)
Baseline CD4 count (cells/mm^3)	684 (452–886)
Duration on second-line ART (months)	58 (31–87)

Values are n or median (IQR).

9–11 days after the introduction of rifampicin and 2–4 days after 100 mg ritonavir was added to darunavir/ritonavir 800/100 mg daily (Figure 3). A further three participants in cohort 2 developed asymptomatic grade 1 or 2 ALT elevation, two of whom were

withdrawn before the Day 21 sparse pharmacokinetic sampling. As the study was stopped prematurely by the IDSMC, due to this high frequency of hepatotoxic events, none of the participants in cohort 2 proceeded to doubling the darunavir dose.

All six participants with severe ALT elevations and symptomatic hepatitis developed right upper quadrant pain, one of whom also developed tachycardia and unilateral conjunctivitis. None of the six developed hyperbilirubinaemia. In all participants with grade 3 or 4 ALT elevation, all treatments were stopped immediately and standard-of-care ART (lopinavir/ritonavir with dual NRTIs) was restarted once the ALT returned to <100 IU/L. Three participants who stopped ART following a grade 3 or 4 ALT elevation developed raised viral loads (323, 636 and 12 313 copies/mL); however, after restarting their baseline ART, all achieved viral suppression. Modest changes in serum cholesterol and triglycerides were noted amongst the four participants who completed the study, without consistent trend or measurement higher than DAIDS grade 2. All participants had 100% adherence during the study period, assessed by self-reporting and pill counts.

Darunavir pre-dose concentrations were measured on five occasions in 4 participants; 17 participants had two measurements and 10 participants had three measurements. Intensive pharmacokinetic profiles were available from 17 participants on darunavir/ritonavir 800/100 mg daily before rifampicin was started; however, only 4 participants (2 on the 600 mg dose of rifampicin and 2 on the 750 mg dose) were intensively sampled on doubled doses of darunavir/ritonavir with rifampicin. Seven trough concentrations of darunavir were below the LLOQ (one C₀ and six C₂₄).

The darunavir pharmacokinetic parameters are summarized in Table 2 and Table 3. Morning trough concentrations are shown

Figure 2. The study consort diagram.

Figure 3. Serial ALT levels in the 17 study participants. The vertical dot/dash lines represent the introduction of rifampicin on Day 8 and escalation of the ritonavir dose from 100 to 200 mg on Day 15, respectively. Solid circles represent the ALT levels in six individuals who developed severe ALT elevations during the study. Open circles represent ALT levels in the other participants. Study treatment was stopped after 16–18 days in these six participants and before 21 days in the remaining participants of cohort 2.

Table 2. Steady-state darunavir pharmacokinetic parameters across dosing regimens, expressed as geometric mean (95% CI), and number of participants (*n*) with trough darunavir concentrations below the EC₉₀ (200 ng/mL)

	C ₀ (ng/mL)	<i>n</i> with C ₀ below EC ₉₀	C ₂₄ (ng/mL)	<i>n</i> with C ₂₄ below EC ₉₀	C _{max} (ng/mL)	AUC (ng·h/mL)
DRV/r 800/100 mg q24h (<i>n</i> =17)	2497 (1876–3324)	0/17	2719 (2073–3567)	0/17	6855 (5873–8003)	92 705 (75 226–114 246) ^a
DRV/r 800/100 mg q24h + RIF 7 days (<i>n</i> =17)	38 (26–54)	16/17	—	—	—	—
DRV/r 800/200 mg q24h + RIF 14 days (<i>n</i> =10)	103 (39–272)	8/10	—	—	—	—
DRV/r 1600/200 mg q24h + RIF (<i>n</i> =4)	134 (6–2954)	3/4	209 (31–1412)	2/4	4368 (2109–9048)	36 773 (14 493–93 301) ^a
DRV/r 800/100 mg q12h + RIF (<i>n</i> =4)	642 (23–17 901)	1/4	1176 (339–4082)	0/4	3928 (1632–9455)	25 485 (7704–84 305) ^b

DRV, darunavir; r, ritonavir; RIF, rifampicin.

^aAUC_{0–24}.^bAUC_{0–12}.**Table 3.** Steady-state darunavir geometric mean ratios (GMRs) for adjusted doses of darunavir/ritonavir to darunavir/ritonavir 800/100 mg without rifampicin (referent) (*n* = 4)

	C ₂₄ , GMR (90% CI)	AUC _{0–24} , GMR (90% CI)
DRV/r 1600/200 mg q24h + RIF	0.097 (0.069–0.137)	0.432 (0.281–0.664)
DRV/r 800/100 mg q12h + RIF	0.547 (0.270–1.107)	0.598 (0.302–0.845) ^a

DRV, darunavir; r, ritonavir; RIF, rifampicin.

^aFor q12h dosing, the AUC_{0–24} was imputed by doubling the measured AUC_{0–12}.

in box-and-whisker plots (Figure 4). After a week of daily rifampicin co-administration the darunavir pre-dose concentrations were reduced by more than 98%, with 16 of the 17 participants having concentrations below the EC₉₀. After doubling both the darunavir and ritonavir, the darunavir pre-dose concentrations approached those without rifampicin for the q12h dose but not for the q24h dose.

Discussion

Co-administration of adjusted doses of darunavir/ritonavir with rifampicin was associated with an unacceptably high risk of hepatotoxicity. Our study was stopped prematurely because 6 of 17 (35.3%) enrolled participants developed symptomatic grade 3 or 4 ALT elevations without jaundice. Hepatotoxicity was detected after just over a week on rifampicin, after doubling the dose of ritonavir and before the darunavir dose was increased. As expected, darunavir pre-dose concentrations were markedly reduced, by more than 98%, when rifampicin was co-administered. Darunavir pre-dose concentrations were higher after doubling the dose of ritonavir, although only 2 of these 10 participants achieved EC₉₀ trough concentrations of ≥200 ng/mL. Darunavir C₂₄ trough concentrations exceeded the EC₉₀ in all four participants when

darunavir/ritonavir 800/100 mg was given twice daily with rifampicin, but EC₉₀ was achieved in only two of four participants on once-daily (darunavir/ritonavir 1600/200 mg) doses. These findings suggest that, while in our small cohort the mean darunavir exposures were less than half those without rifampicin, adequate darunavir concentrations may be obtained in the presence of rifampicin when darunavir/ritonavir doses of 800/100 mg are given twice daily.

Similarly high rates of symptomatic hepatotoxicity resulting in premature study discontinuation were observed in several studies of adjusted doses of ritonavir-boosted PIs with rifampicin in healthy volunteers: with lopinavir/ritonavir, atazanavir/ritonavir and saquinavir/ritonavir.^{8–10} The mechanism of this hepatotoxicity is unclear. One hypothesis is that induction of metabolizing enzymes by rifampicin could result in increased hepatic exposure to reactive intermediate metabolites of the PIs. The findings of a recent murine study demonstrating the roles of human pregnane X receptor and CYP3A4 in rifampicin-induced hepatotoxicity with ritonavir supports this hypothesis.¹⁵ Darunavir/ritonavir without rifampicin has also been associated with hepatotoxicity. A post-marketing surveillance study showed symptomatic hepatotoxicity in 15/3063 patients on boosted darunavir, which resulted in a warning by the US FDA.¹⁶ The underlying mechanism is not known, although it has been proposed that it is a hypersensitivity reaction to the structural sulphonamide moiety in darunavir.¹⁷ A recent study in healthy volunteers suggests that dolutegravir may have contributed to the hepatotoxicity seen in our study; weekly rifampentine and isoniazid co-administered with daily dolutegravir resulted in a systemic hypersensitivity reaction with elevated cytokines and ALT levels in two of four participants, which led to premature discontinuation of the study.¹⁸ However, weekly rifampentine and isoniazid co-administered with daily dolutegravir was well tolerated in a study of 61 HIV-infected participants without TB.¹⁹

Our group previously hypothesized that the risk of hepatotoxicity with adjusted doses of rifampicin and lopinavir/ritonavir might be lower in PLWH. We conducted a drug–drug interaction study in PLWH established on lopinavir/ritonavir who were given rifampicin before the dose of lopinavir/ritonavir was doubled in two stages.⁷ Double-dose lopinavir/ritonavir overcame the inducing effect of rifampicin and 2 of 21 participants developed asymptomatic grade

Figure 4. Darunavir pre-dose morning trough concentrations (on a $\log_{10}$ scale) across different adjusted dosing regimens. When full pharmacokinetic profiles were available, the 24 h trough concentration (C_{24}), after the observed dose, was selected (first, fourth and fifth boxes). The dashed line represents the darunavir EC_{90} (200 ng/mL). The 'box' shows the IQR, including the 25th percentile, median and 75th percentile. The whiskers depict the lower and the upper adjacent values $1.5 \times$ IQR from the 25th and 75th percentiles, respectively. Outlier values (circles) are more than $1.5 \times$ IQR from 25th or 75th percentiles. DRV/r, darunavir/ritonavir with doses in milligrams; RIF, rifampicin.

3 or 4 ALT elevation. A retrospective study in TB/HIV coinfecting patients on an ART regimen with doubled doses of lopinavir/ritonavir during TB treatment found that 8 of 18 developed asymptomatic grade 1 or 2 transaminase elevation.²⁰ A similar South African study in coinfecting patients on rifampicin-based TB treatment found a trend towards an increased rate of symptomatic hepatotoxicity amongst those who received superboosted lopinavir (lopinavir/ritonavir 400/400 mg twice daily) compared with those on standard lopinavir/ritonavir doses (lopinavir/ritonavir 400/100 mg twice daily).²¹ This evidence suggests that, while adjusted doses of lopinavir/ritonavir might be safer than darunavir with ritonavir in patients receiving rifampicin-based TB treatment, strategies to increase the ritonavir dose in patients taking rifampicin are associated with hepatotoxicity resulting in a high rate of treatment discontinuation. Cobicistat, an alternative boosting agent to ritonavir, may provide an alternative approach; however, an *in vitro* study suggests that it would be unlikely to adequately support darunavir concentrations in the presence of rifampicin.²

Our study has some limitations. First, we assessed the effect of rifampicin alone on darunavir/ritonavir concentrations in PLWH without TB. TB is treated with combination antituberculosis therapy, including isoniazid, which is a potent inhibitor of CYP3A.²² Both darunavir/ritonavir pharmacokinetics and hepatotoxicity may be different when administered with rifampicin and isoniazid with or without pyrazinamide. There may also be disease effects of TB that could affect toxicity. Sixteen of the 17 participants in our study were women. Their BMIs being, on average, much higher than most patient populations with TB might limit the ability to extrapolate both the pharmacokinetic and safety results. The study was not designed to compare the safety of adjusted doses of darunavir/ritonavir compared with lopinavir/ritonavir with rifampicin. However, the results suggest that darunavir in combination with ritonavir and rifampicin may be more toxic than doubling the dose

of lopinavir/ritonavir, which is current practice for treatment of patients on second-line ART who develop TB. Lastly, only four participants completed both adjusted darunavir/ritonavir dosing regimens; therefore, we are not powered to determine the ideal darunavir/ritonavir dosing regimen needed to achieve the EC_{90} .

In conclusion, we evaluated the steady-state pharmacokinetics of adjusted-dose darunavir/ritonavir and rifampicin in PLWH. We showed that double the dose of darunavir/ritonavir administered twice daily might adequately counteract the inducing effect of rifampicin, but that once-daily administration does not achieve adequate darunavir exposures. However, we lacked power for this conclusion as our study was stopped prematurely owing to the high rates of hepatotoxicity. *In vitro* and animal studies to investigate the underlying mechanism of darunavir/ritonavir-induced hepatotoxicity could inform safer future strategies.

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Transparency declarations

None to declare.

Disclaimer

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