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Evaluation of Drug-Drug Interactions Between Hepatitis C Antiviral Agents Ombitasvir, Paritaprevir/Ritonavir, and Dasabuvir and HIV-1 Protease Inhibitors

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Background. Guidelines for the treatment of human immunodeficiency virus (HIV) infection consistently recommend initiation of antiretroviral therapy in patients with hepatitis C virus (HCV)/HIV-1 coinfection. Therefore, potential drug interactions between antiretroviral drugs and HCV direct-acting antiviral agents (DAAs) must be carefully considered. The objective of this investigation was to evaluate the compatibility of a novel combination of DAAs (the 3D regimen) with commonly prescribed HIV-1 protease inhibitors (PIs).

Methods. Five phase 1, multiple-dose, open-label pharmacokinetic studies were performed in 144 healthy volunteers. Participants in each study were randomly assigned 1:1 into cohorts assessing the effects of the steady-state 3D regimen on steady-state HIV-1 PIs or vice versa. The 3D regimen comprised ombitasvir (25 mg once daily), paritaprevir/ritonavir (150/100 mg once daily), and dasabuvir (250 or 400 mg twice daily). The HIV-1 PIs assessed included atazanavir, darunavir, and lopinavir (administered with ritonavir). Safety, tolerability, and pharmacokinetic parameters were assessed to evaluate the compatibility of the drug regimens.

Results. Coadministration of the 3D regimen with the evaluated HIV-1 PIs was generally well tolerated in healthy volunteers. Morning administration of atazanavir (300 mg once daily) and darunavir regimens exhibited no clinically meaningful drug interactions with the 3D regimen. However, owing to higher paritaprevir and/or ritonavir exposures, evening administration of atazanavir (300 mg) plus ritonavir (100 mg) or lopinavir/ritonavir (800/200 mg) with the 3D regimen is not recommended.

Conclusions. The 3D regimen can be coadministered with morning atazanavir and darunavir regimens. However, evening atazanavir plus ritonavir and lopinavir/ritonavir regimens are not recommended in combination with the 3D regimen.

Keywords. pharmacokinetics; hepatitis C; HIV; direct-acting antiviral HCV drugs; HIV protease inhibitors.

Standard therapy for managing human immunodeficiency virus (HIV) infection involves a multidrug regimen, often including a protease inhibitor (PI) [1–4]. The available HIV-1 PIs are metabolized by cytochrome P450 (CYP) enzymes, primarily CYP3A4, and many are capable of inhibiting or inducing CYP enzymes or hepatic transport proteins [5]. These potential sources of drug-drug interactions (DDIs) are particularly salient during hepatitis C virus (HCV) treatment, which typically involves direct-acting antiviral agent (DAA)–based combination therapy.

The 3D regimen, an interferon-free combination of 3 DAAs (ombitasvir, paritaprevir [identified as a lead compound by AbbVie and Enanta Pharmaceuticals and coadministered with ritonavir], and dasabuvir), is a newer option for HCV treatment. The 3D regimen in combination with ribavirin has achieved rates of sustained virologic response at posttreatment week 12 of 91%–100% in HCV genotype-1–infected patients, including those with compensated cirrhosis or HCV/HIV-1 coinfection [6–10].

Before initiation of clinical studies in HCV/HIV-1–coinfected patients, a series of DDI studies were performed in healthy volunteers to evaluate the safety and pharmacokinetics of the 3D regimen coadministered with various label-recommended dosing schemes for the commonly prescribed HIV-1 PIs darunavir, atazanavir, and lopinavir. This article describes the findings of these studies and the implications for clinical use of the 3D regimen with HIV-1 PIs.

MATERIALS AND METHODS

Study Participants

Eligible participants were adult male and female volunteers 18–55 years of age with body mass index ≥18 and <30 kg/m^2 who were in good general health. Individuals who screened positive for hepatitis A virus, hepatitis B virus, HCV, or HIV were ineligible. Volunteers were also excluded from the study if they had used tobacco or nicotine-containing products within 6 months of study initiation. Study participants were prohibited from using known inhibitors or inducers of CYP3A, CYP2C8, or

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organic anion transporting polypeptide 1B1 (OATP1B1) within 1 month before study drug administration or consuming grapefruit juice, star fruit, Seville oranges, or products containing these ingredients within 72 hours before study drug administration. All participants provided written informed consent, as approved by an institutional review board.

Study Design

Data were collected from 5 phase 1, single-center, multiple-dose, open-label studies (Figure 1). Although these studies included both 2-DAA and 3-DAA combinations, only results for the 3D regimen are presented herein. In each of the included treatment arms, participants were randomly assigned at a 1:1 ratio into 2 cohorts. Cohort 1 received the 3D regimen for the first 14 days, followed by addition of the selected HIV-1 PI regimen for another 14 days; cohort 2 received the HIV-1 PI regimen for the first 14 days, followed by addition of the 3D regimen for another 14 days [11].

The HIV-1 PI regimens were as follows: study 1 included darunavir (800 mg; Prezista; Janssen Therapeutics) plus ritonavir (100 mg; (Norvir; AbbVie), administered once daily in the morning, or darunavir (600 mg) plus ritonavir (100 mg), administered twice daily in the morning and evening; study 2, darunavir (800 mg) plus ritonavir (100 mg), administered once daily in the evening; study 3, atazanavir (300 mg; Reyataz; Bristol-Myers Squibb) plus ritonavir (100 mg), administered once daily in the morning or evening; study 4, lopinavir/ritonavir (800/200 mg; Kaletra; AbbVie), administered once daily in the evening; and study 5, lopinavir/ritonavir (400/100 mg), administered twice daily in the morning and evening.

The 3D regimen comprised ombitasvir (25 mg once daily), paritaprevir/ritonavir (150/100 mg once daily), and dasabuvir (400 mg twice daily) in all studies, except for study 2, in which dasabuvir (250 mg twice daily) was administered using optimized (higher-bioavailability) tablets. The 250-mg optimized tablet provides dasabuvir exposures comparable to the 400-mg tablets used in other studies. Because the 3D regimen includes 100-mg ritonavir, additional doses of ritonavir for boosting HIV-1 PIs were not given with morning doses of darunavir or atazanavir during their coadministration with the 3D regimen. The studies were conducted in accordance with the International Conference of Harmonisation guidelines, applicable regulations, and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki.

Assessments

Blood samples were collected on day 13 or 14 for up to 24 hours after dosing and on day 27 or 28 for up to 72 hours after dosing or on subject discontinuation. Blood samples were analyzed using a validated liquid chromatography method with tandem mass spectrometric detection to quantify plasma concentrations of HIV-1 PIs and 3D regimen components. The maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve during a dosing interval (AUC_{τ}), and minimum plasma concentration (C_{trough}) were determined for each drug at steady state. AUC_{τ} was calculated by the linear trapezoidal rule from time 0 to 24 hours (AUC_{24}) for drugs administered once daily and from time 0 to 12 hours for those administered twice daily. The C_{trough} value represented the concentration 24 hours after once-daily regimen dosing and 12 hours after twice-daily regimen dosing. Findings from adverse event (AE) monitoring, electrocardiograms, laboratory assessments, physical examinations, and vital sign measurements were used to evaluate the safety and tolerability of study drugs.

Statistical Analyses

Repeated-measures analyses for log-transformed C_{max}, AUC_{τ}, and C_{trough} values were performed to obtain the geometric mean ratios (GMRs) and 90% confidence intervals (CIs), comparing exposures for the 3D regimen or selected HIV-1 PI regimen alone versus after coadministration. Data from cohort 1 were used to determine the effect of the HIV-1 PI regimen on the 3D regimen, and data from cohort 2 were used to determine the effect of the 3D regimen on the HIV-1 PI regimen. For DAAs, exposures up to 50% lower or 100% higher (GMR, 0.5–2.0) during coadministration with HIV-1 PIs versus DAA administration alone were considered not to be significant. These thresholds were based on the results of phase 2 studies, in which higher and lower DAA doses demonstrated safety and efficacy profiles comparable to those of the approved doses (ombitasvir/paritaprevir/ritonavir, 25/150/100 mg once daily; dasabuvir, 250 mg twice daily) [12, 13]. For HIV-1 PIs, GMRs and 90% CIs in the range of 0.8–1.25 were not considered significant for the comparison of exposures during coadministration with DAAs versus HIV-1 PIs administered alone. The clinical significance of the exposures of HIV-1 PIs outside the range of 0.8–1.25 was based on their dosing recommendations, according to US prescribing information or a summary of product characteristics.

Descriptive statistics were used to evaluate demographic and safety/tolerability data. Statistical analyses were performed using SAS software, version 9.2. Aspects of the data reported herein were presented at the 54th Interscience Conference on Antimicrobial Agents and Chemotherapy [11].

RESULTS

Participant Demographics

A total of 144 healthy volunteers were enrolled in the contributing study cohorts (Table 1). The participants were predominantly male (79%), and their mean age range was 33–38 years. Although distribution of racial groups varied by study, the majority of participants self-identified as either white (54%) or black (42%).

Effect of the 3D Regimen on HIV-1 PI Pharmacokinetics

The 3D regimen resulted in a modest (≤34%) change in the mean C_{max} and AUC_{τ} of darunavir; however, C_{trough} was

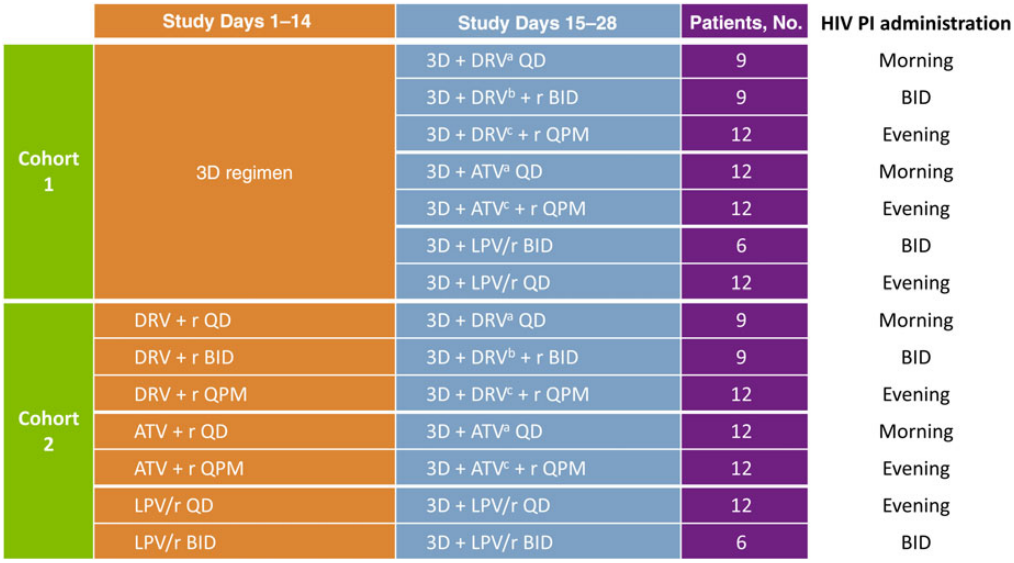

Figure 1. Study design of drug-drug interaction studies. All study drugs were administered under nonfasting conditions. [a]Ritonavir (r; 100 mg) was not coadministered with the indicated protease inhibitor (PI) during coadministration with the 3D regimen, which included ombitasvir (25 mg once daily), paritaprevir and ritonavir (paritaprevir/r; 150/100 mg once daily), and dasabuvir (400 or 250 mg twice daily); [b]Twice-daily dosing with morning and evening administration; the morning dose of ritonavir (100 mg) was omitted after combining the darunavir (DRV) twice-daily regimen with the 3D regimen; [c]Once-daily dosing with evening administration. Abbreviations: 3D, the 3D regimen (ombitasvir, paritaprevir/ritonavir, and dasabuvir); ATV, atazanavir; BID, twice daily, with morning and evening administration; HIV, human immunodeficiency virus; LPV, lopinavir; QD, once daily with morning administration; QPM, once daily with evening administration.

reduced by 43%–48% (Figure 2). The C_{max} and AUC_{τ} values for atazanavir regimens were generally unaffected (≤19% change) by coadministration with the 3D regimen. The atazanavir C_{trough} was increased by 68% with the evening-dosing regimen during coadministration with the 3D regimen but was unchanged with the morning-dosing regimen. The lopinavir C_{max} and AUC_{τ} for the lopinavir/ritonavir once-daily regimen were minimally affected (≤14% change) by coadministration of the 3D regimen, although the lopinavir C_{trough} was increased by 218%. The lopinavir C_{max}, AUC_{τ}, and C_{trough} values for the lopinavir/ritonavir twice-daily dosing regimen were also minimally affected by coadministration of the 3D regimen (≤15% change).

Table 1. Participant Demographics and Baseline Characteristics[a]

Characteristic	Study 1 (3D + DRV[b] or DRV + r[c]) (n = 36)	Study 2 (3D + DRV + r[d]) (n = 24)	Study 3 (3D + ATV[b] or ATV + r[d]) (n = 48)	Study 4 (3D + LPV/r[d]) (n = 24)	Study 5 (3D + LPV/r[c]) (n = 12)
Age, mean (SD), y	36 (10)	33 (8)	35 (8)	36 (7)	38 (9)
Weight, mean (SD), kg	80 (13)	76 (12)	77 (12)	81 (12)	75 (12)
Height, mean (SD), cm	176 (9)	169 (9)	171 (9)	174 (6)	174 (13)
Sex, No. (%)					
Male	34 (94)	17 (71)	32 (67)	22 (92)	9 (75)
Female	2 (6)	7 (29)	16 (33)	2 (8)	3 (25)
Race, No. (%)					
White	19 (53)	10 (42)	27 (56)	15 (63)	6 (50)
Black	16 (44)	11 (46)	19 (40)	8 (33)	6 (50)
Asian	0	2 (8)	2 (4)	0	0
Native Hawaiian	1 (3)	0	0	0	0
Multirace	0	1 (4)	0	1 (4)	0

Abbreviations: 3D, the 3D regimen (ombitasvir, paritaprevir/ritonavir, and dasabuvir); ATV, atazanavir; DRV, darunavir; LPV, lopinavir; r, ritonavir; SD, standard deviation.

[a]Includes all participants enrolled in the relevant treatment arms of the study.

[b] Once-daily dosing with morning administration.

[c] Twice-daily dosing with morning and evening administration.

[d] Once-daily dosing with evening administration.

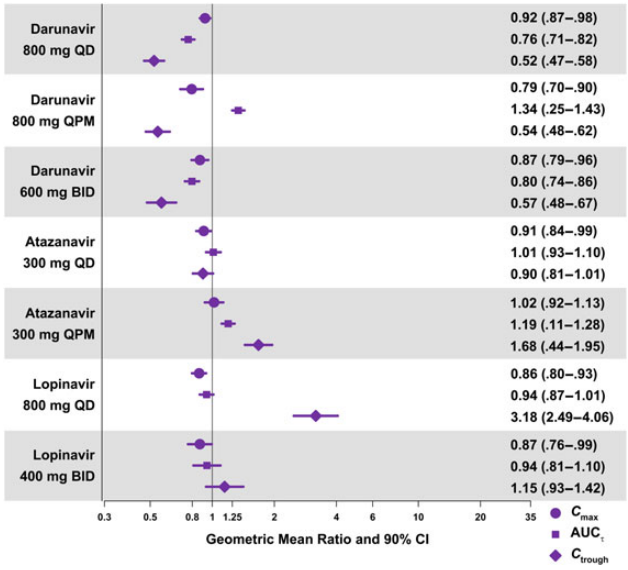

Figure 2. Effect of the 3D regimen on the maximum observed plasma concentration (C_{max}), AUC_{τ}, and minimum observed plasma concentration (C_{trough}) of human immunodeficiency virus protease inhibitors. Abbreviations: AUC_{τ}, area under the plasma concentration-time curve during a dosing interval; BID, twice daily, with morning and evening administration; CI, confidence interval; QD, once daily with morning administration; QPM, once daily with evening administration.

Effect of HIV-1 PIs on 3D Regimen Pharmacokinetics

Ombitasvir and dasabuvir exposures (C_{max}, AUC_{τ}, and C_{trough}) showed up to 27% and 53% change, respectively, when coadministered with HIV-1 PIs (Figure 3). The effects of darunavir once or twice daily on paritaprevir C_{max}, AUC_{τ}, and C_{trough} values were modest (≤59% change; Figure 3). The atazanavir morning-dosing regimen increased the paritaprevir C_{max}, AUC_{τ}, and C_{trough} values by 46%, 94%, and 226%, respectively. Larger increases in paritaprevir exposure (up to 1095%) were observed with the evening-dosing regimen for atazanavir plus ritonavir. Lopinavir/ritonavir once daily had no effect on the paritaprevir C_{max}, but the paritaprevir AUC_{τ} and C_{trough} values increased by 87% and 723%, respectively. Coadministration of lopinavir/ritonavir twice daily with the 3D regimen increased the paritaprevir C_{max}, AUC_{τ}, and C_{trough} values by 104%, 117%, and 136%, respectively.

The darunavir morning-dosing regimen exhibited minimal effects on the C_{max}, AUC_{τ}, and C_{trough} values for ritonavir during coadministration with the 3D regimen (≤16% change; Figure 3). However, evening administration of darunavir plus ritonavir increased the C_{max}, AUC_{τ}, and C_{trough} of ritonavir by 19%, 70%, and 1315%, respectively. Morning administration of once-daily atazanavir minimally affected ritonavir C_{max} and AUC_{τ}, and moderately increased C_{trough} (40%). In contrast, coadministration of atazanavir plus ritonavir in the evening with the 3D regimen notably increased ritonavir C_{max}, AUC_{τ}, and C_{trough} values by 60%, 218%, and >20-fold, respectively, owing to the higher daily ritonavir dose during coadministration. Increases in ritonavir exposure with 3D coadministration were greater with lopinavir/ritonavir once daily than with lopinavir/ritonavir twice daily.

Safety and Tolerability

No deaths or serious AEs were reported in the studies. The majority of AEs were mild in severity and were generally reported in similar proportions for the different study regimens (ie, 3D regimen alone, HIV-1 PI regimen alone, or combination dosing; Table 2). No clinically significant changes in vital signs or laboratory parameters were observed during these studies, except for elevations in total bilirubin levels in the DDI studies with atazanavir. No new safety issues were identified from these studies.

Five discontinuations due to AEs were reported in darunavir DDI studies: 1 participant experienced first-degree atrioventricular block after completing the once-daily treatment phase for darunavir plus ritonavir, and 4 participants experienced maculopapular rash while receiving darunavir plus ritonavir. All events occurred before initiation of the 3D regimen. Elevations in aminotransferase levels (grade 2 alanine aminotransferase [ALT] and grade 1 aspartate aminotransferase [AST]) occurred in 1 participant during coadministration of darunavir (800 mg) and the 3D regimen. This event resolved after study completion.

Two participants discontinued the atazanavir studies owing to AEs. One experienced a first-degree atrioventricular block on day 15 after receiving the initial dose of atazanavir, and the other participant had a maculopapular rash on day 24 (during concomitant treatment with atazanavir and the 3D regimen). Grade 3 elevations in total bilirubin levels occurred in 13 of 24 participants in the atazanavir morning-dosing group and 16 of 24 in the atazanavir evening-dosing group. Bilirubin elevations were predominantly indirect, with no concurrent elevation in aminotransferases, occurred primarily during administration of atazanavir plus ritonavir, and did not worsen during coadministration with the 3D regimen. There were no premature discontinuations due to bilirubin elevations.

No patients discontinued treatment owing to AEs in the lopinavir/ritonavir studies. Five abnormal laboratory findings were observed: 1 asymptomatic elevations (grade 1) in ALT and AST levels during the 3D regimen alone in 1 participant and elevations in total bilirubin levels without elevations in ALT/AST levels in 4 participants (during administration of the 3D regimen alone in 1 and during coadministration of the 3D regimen with lopinavir/ritonavir in 3). None of these findings resulted in AEs or study drug discontinuation, and all were resolved by the end of the study.

DISCUSSION

Data from these DDI studies in healthy volunteers indicate that combining PI regimens with ombitasvir, paritaprevir/ritonavir, and dasabuvir is feasible. Based on phase 2 study data, doses of ombitasvir, dasabuvir, and paritaprevir ranging from 1.5 to

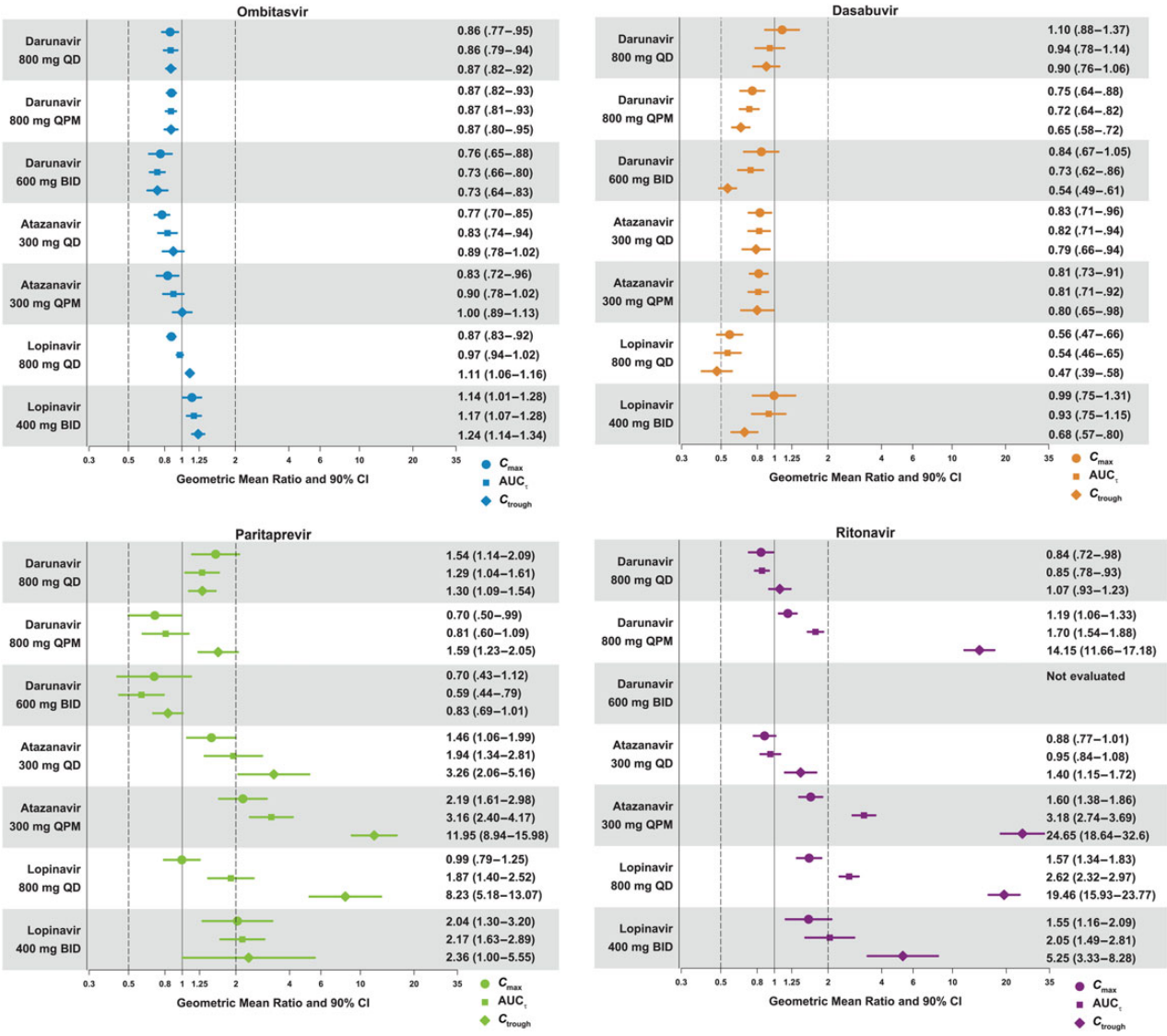

Figure 3. Effect of human immunodeficiency virus protease inhibitors on maximum observed plasma concentration (C_{max}), AUC_{τ}, and minimum observed plasma concentration (C_{trough}) for ombitasvir, dasabuvir, paritaprevir, and ritonavir. Abbreviations: AUC_{τ}, area under the plasma concentration-time curve during a dosing interval; BID, twice daily, with morning and evening administration; CI, confidence interval; QD, once daily with morning administration; QPM, once daily with evening administration.

200 mg daily, 300 to 800 mg twice daily, and 100 to 250 mg daily, respectively, maintain antiviral activity and are well tolerated in the treatment of HCV [14–19]. DDI study data further indicate that increases in exposure of 100% (2-fold) or decreases in exposure of 50% (0.5-fold) for 3D regimen components have no clinically meaningful effects on the efficacy or safety profile of the 3D regimen [12, 13]. Given these thresholds, the modest effects of the darunavir regimens on the C_{max} and AUC_{τ} of 3D regimen components are not expected to affect 3D efficacy or safety. The elevated ritonavir C_{trough} observed with the darunavir evening-dosing regimen was probably due to the increase in total daily ritonavir dose from 100 to 200 mg during coadministration of 3D regimen. The lack of such an increase in the darunavir morning-dosing regimen can be attributed to the omission of the accompanying ritonavir dose because of the presence of ritonavir in the 3D regimen (which was administered in the morning for all dosing scenarios).

A moderate decrease in the darunavir C_{trough} was observed for all darunavir regimens during coadministration with the 3D regimen, although changes in C_{max} or AUC_{τ} were lower. These moderate decreases in C_{trough} are not expected to significantly affect darunavir efficacy. Data from large, phase 3 clinical trials indicate no apparent relationships between the darunavir AUC_{24} and C_{trough} values and the change in $\log_{10}$ HIV viral load or the percentage of patients achieving plasma viral loads <50 or <400 copies/mL [20–22]. In addition, similar virologic failure

Table 2. Adverse Events Reported by >2 Participants in Any Treatment Group

	Participants, No (%)								
	DRV Studies			ATV Studies			LPV/r Studies		
Adverse Event	3D (n = 30)	DRV + r (n = 30)	3D + DRV or 3D + DRV + r (n = 53)	3D (n = 24)	ATV + r (n = 24)	3D + ATV or 3D + ATV + r (n = 48)	3D (n = 18)	LPV/r (n = 18)	3D + LPV/r (n = 36)
Headache	1 (3)	1 (3)	8 (15)	2 (8)	2 (8)	3 (6)	0	0	4 (11)
Diarrhea	1 (3)	3 (10)	3 (6)	1 (4)	0	2 (4)	3 (25)	3 (25)	6 (17)
Nausea	1 (3)	1 (3)	3 (6)	2 (8)	0	2 (4)	0	2 (17)	6 (17)
Dizziness	1 (3)	2 (7)	4 (8)	1 (4)	2 (8)	4 (8)	0	0	1 (3)
Abdominal pain	2 (7)	0	2 (4)	0	0	2 (4)	0	2 (17)	4 (11)
Fatigue	0	1 (3)	2 (4)	0	2 (8)	1 (2)	1 (8)	1 (8)	3 (8)
Contact dermatitis	1 (3)	0	0	1 (4)	1 (4)	5 (10)	0	0	0
Ocular icterus	0	0	0	0	5 (21)	3 (6)	0	0	0
Decreased appetite	0	0	1 (2)	1 (4)	0	0	0	1 (8)	4 (11)
Maculopapular rash	0	5 (17)	0	0	1 (4)	1 (2)	0	0	0
Nasopharyngitis	0	0	0	0	0	3 (6)	3 (25)	0	1 (3)
Abdominal distention	1 (3)	0	1 (2)	0	0	0	0	1 (8)	3 (8)
Dysgeusia	0	0	0	0	0	0	0	1 (8)	5 (14)
Abnormal dreams	3 (10)	0	0	0	0	0	0	0	0

Abbreviations: 3D, the 3D regimen (ombitasvir, paritaprevir/ritonavir, and dasabuvir); ATV, atazanavir; DRV, darunavir; LPV, lopinavir; r, ritonavir.

rates have been reported with darunavir at 600 or 800 mg once daily [23]. Based on these considerations, no dose adjustment is expected to be required for darunavir regimens during coadministration with the 3D regimen in patients without evidence of extensive PI resistance.

Dose adjustments are also not required for the atazanavir morning-dosing regimen when atazanavir is coadministered with the 3D regimen. However, coadministration of the 3D regimen with atazanavir (300 mg) plus ritonavir (100 mg) in the evening is not recommended owing to the observed 216% increase in the paritaprevir AUC_{τ}. These elevations may be partially due to the increased daily dose of ritonavir (200 mg/d for the evening-dosing regimen vs 100 mg/d for the morning-dosing regimen) and the resulting inhibition of paritaprevir metabolism. Moreover, as a substrate of CYP3A, OATP1B1, and OATP1B3 [13], paritaprevir may be subject to the inhibitory effects of both atazanavir and ritonavir on these proteins [24]. Notably, the metabolic enzyme- and transporter protein–based interactions of paritaprevir may also underlie the high degree of variability in paritaprevir pharmacokinetics that has been observed in clinical trials [25–27] and are reflected in the wider CIs for paritaprevir point estimates in the studies reported here.

Increased lopinavir C_{trough} values were observed during coadministration of lopinavir/ritonavir (800/200 mg once daily) with the 3D regimen; however, these elevations were comparable to C_{trough} values observed during administration of lopinavir/ritonavir (400/100 mg twice daily) without the 3D regimen. Coadministration of lopinavir/ritonavir once or twice daily with the 3D regimen had no clinically relevant effect on steady-state exposures of ombitasvir or dasabuvir, yet paritaprevir exposure increased by up to 117%. Elevations in ritonavir exposures were also observed, probably owing to higher daily doses of ritonavir during coadministration with the 3D regimen. These increases in drug exposures did not have an overt effect on tolerability, including no apparent increase in the incidence of gastrointestinal AEs. However, because the increased daily dose of ritonavir (300 mg) may result in a greater incidence of gastrointestinal AEs in HCV/HIV-1–coinfected patients who receive combination therapy for 12–24 weeks to treat chronic HCV infection, coadministration of lopinavir/ritonavir regimens with the 3D regimen is not recommended. If combination therapy is considered, the AE risk should be carefully weighed against the potential benefits of treatment.

Coadministration of the 3D regimen with the evaluated HIV-1 PI regimens was generally well tolerated in healthy volunteers. No new safety findings were observed. Total bilirubin elevations were reported in the DDI study of the 3D regimen with atazanavir; however, the majority of these elevations occurred when atazanavir was administered alone before coadministration of the 3D regimen and did not worsen after coadministration with the 3D regimen. Moreover, none of them met the criteria set forth by Hy's law [28]. Asymptomatic indirect hyperbilirubinemia has been reported with atazanavir administration and is due to inhibition of uridine 5′-diphospho-glucuronosyltransferase [29].

The 3D regimen with ribavirin is currently being evaluated in a phase 2/3 study (TURQUOISE-I) of patients with HCV/HIV-1 coinfection with or without cirrhosis who are receiving a

stable HIV-1 antiretroviral therapy regimen. In parts 1a and 1b of TURQUOISE-I, rates of sustained virologic response at post-treatment week 12 of 91%–100% were reported with the 3D regimen plus ribavirin in patients receiving atazanavir-, raltegravir-, or darunavir-based regimens [10, 30]. Combination treatment with antiretroviral agents and the 3D regimen was generally well tolerated, and no safety signals of concern were identified. Further evaluations of 3D regimen/HIV-1 antiretroviral therapy combinations are currently underway in part 2 of TURQUOISE-I.

As preliminary evaluations leading to trials in the target population (patients with HCV/HIV-1 coinfection), these studies are subject to certain limitations, including enrollment of healthy volunteers and a short duration of treatment (2 weeks per study period). Both of these concerns are addressed by the TURQUOISE-I study. To date, there have been no indications that 12–24 weeks of treatment in patients with HCV/HIV-1 coinfection will result in any difference in the safety or tolerability of concomitant HIV-1 PI/3D regimen therapy [10, 30].

In conclusion, this series of pharmacokinetic studies demonstrates that the 3D regimen was well tolerated in healthy volunteers ,with relatively few clinically significant DDIs or AEs when coadministered with commonly used HIV-1 PIs. Data from these studies indicate that no dosage adjustments should be required for darunavir regimens or morning administration of atazanavir in combination with the 3D regimen, a conclusion supported by available data from the TURQUOISE-I trial. In contrast, the atazanavir plus ritonavir evening-administration regimen is not recommended in combination with the 3D regimen owing to increased paritaprevir exposures. Although short-term coadministration of lopinavir/ritonavir regimens with the 3D regimen posed no interaction or safety concerns, this combination is not recommended because of the possibility of gastrointestinal adverse effects during extended (12–24-week) treatment. Future results from TURQUOISE-I will further elucidate the viability of PI/3D regimen combinations. Until these data are available, clinicians are urged to follow the prescribing information of these drugs when considering concomitant treatment in patients with comorbid HIV-1 and HCV infection.

Notes

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