Evaluation of Drug-Drug Interactions Between Direct-Acting Anti-Hepatitis C Virus Combination Regimens and the HIV-1 Antiretroviral Agents Raltegravir, Tenofovir, Emtricitabine, Efavirenz, and Rilpivirine

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Running Head. DDI Assessment of HCV and HIV-1 Drugs

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antiretroviral drug
ABSTRACT

Background. The 3D regimen is a novel combination of direct-acting antiviral agents (DAAs) that has proven effective for the treatment of hepatitis C virus (HCV) infection. Given the potential for coadministration in patients with human immunodeficiency virus infection, possible drug interactions with antiretroviral drugs must be carefully considered.

Methods. Four phase 1, multiple-dose pharmacokinetic studies were conducted in healthy volunteers (N = 66). The 3D regimen of paritaprevir/ritonavir 150/100 mg daily, ombitasvir 25 mg daily, and dasabuvir 400 mg was administered alone or in combination with emtricitabine 200 mg daily and tenofovir disoproxil fumarate (tenofovir DF) 300 mg daily, rilpivirine 25 mg daily, or raltegravir 400 mg twice daily. A 2-DAA regimen of paritaprevir/ritonavir 150/100 mg daily and dasabuvir 400 mg twice daily was also studied in combination with efavirenz/emtricitabine/tenofovir DF 600/200/300 mg daily (Atripla). Pharmacokinetic parameters were determined from plasma drug concentrations.

Results. No clinically significant drug interactions were observed (≤ 32% change in exposure) between the 3D regimen and emtricitabine plus tenofovir DF. Raltegravir exposure was increased up to 134% when coadministered with the 3D regimen. Although coadministration with rilpivirine was well tolerated in healthy volunteers, observed elevations in rilpivirine exposures may increase the potential for adverse drug reactions. Concomitant use of the 2-DAA regimen and Atripla was discontinued owing to poor tolerability and adverse events.
Conclusions. No dose adjustment is required during coadministration of raltegravir, tenofovir DF, or emtricitabine with the 3D regimen. Rilpivirine is not recommended and efavirenz is contraindicated for coadministration with the 3D regimen.
Coinfection with the hepatitis C virus (HCV) is common among patients diagnosed with the human immunodeficiency virus (HIV). Approximately 25% of HIV-infected individuals in the United States are also infected with HCV (1). Although advances in antiretroviral (ARV) therapy have had positive effects on the disease course and life expectancy of HIV-infected individuals, coinfection with HCV substantially increases the risk for liver disease and its associated morbidity and mortality (2, 3).

Treatment of HCV is complicated by the risk for drug-drug interactions (DDIs) with ARV therapy in patients with comorbid HIV. Treatment regimens for both conditions often involve the coadministration of multiple drugs, which may have overlapping metabolic enzyme, transporter, and/or elimination pathways. In clinical practice, use of medications with DDI potential are commonplace among patients with HCV/HIV coinfection who are initiating treatment with a first-generation direct-acting antiviral agent (DAA)—a drug class that has emerged as a mainstay of HCV treatment (4). For certain DAAs, caution or avoidance of use in combination with several ARV regimens, such as tenofovir disoproxil fumarate (tenofovir DF)–based treatments, is advised owing to alterations in drug exposures (5).

One of the newest additions to the HCV treatment armamentarium is the all-oral, interferon-free 3D regimen. This combination therapy consists of paritaprevir (coadministered with ritonavir to enhance drug exposure [designated as paritaprevir/r]),
ombitasvir, and dasabuvir. The 3D regimen with or without ribavirin has proven to be efficacious and well tolerated in phase 3 clinical trials, with sustained virologic response rates 12 weeks after treatment (SVR12) of 92% to 100% in patients with genotype 1 HCV infection (6-9). Ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin were approved in the United States and the European Union for the treatment of patients with chronic genotype 1 HCV infection, including those with compensated cirrhosis and those with HCV/HIV-1 coinfection.

Based on in vitro data, paritaprevir and ritonavir are primarily metabolized by cytochrome P450 (CYP) 3A, dasabuvir is primarily metabolized by CYP2C8, and ombitasvir is predominantly metabolized by amide hydrolysis followed by oxidative metabolism (10). The DAAs and ritonavir are in vitro substrates of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and paritaprevir is also a substrate of organic anion transporting polypeptide (OATP) 1B1/1B3 (10,11). In addition, the DAAs are inhibitors of UDP-glucuronosyltransferase (UGT) 1A1, and ritonavir is an inhibitor of CYP3A4 (12). At clinically relevant concentrations, paritaprevir is an inhibitor of OATP 1B1/1B3 and paritaprevir, ritonavir, and dasabuvir are potential inhibitors of P-gp and BCRP (10,11).

Among the HIV antiretroviral agents, tenofovir DF and emtricitabine are primarily renally eliminated as unchanged drugs by a combination of glomerular filtration and active tubular secretion; tenofovir DF is a substrate of OAT1 (13-15). These data suggest that tenofovir DF and emtricitabine are the least likely to have a potential for
pharmacokinetic interaction with the 3D regimen. On the other hand, raltegravir is 
eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway, 
rilpivirine is primarily metabolized by CYP3A, and efavirenz is a CYP3A inducer (16-19); 
hence, these drugs have the potential to have a pharmacokinetic interaction with the 3D 
regimen.

This series of DDI studies evaluated the pharmacokinetic effects and tolerability of 
coadministering the 3D regimen (or a modified version thereof) with commonly 
prescribed ARVs representing different agent classes. These studies were designed to 
test the feasibility of treating HCV infection with the 3D regimen in HCV/HIV-1 
coinfected patients receiving ARV therapy.
MATERIALS AND METHODS

Study participants. Healthy adult male and female participants aged 18 to 55 years with a body mass index (BMI) ≥18 and <30 kg/m² were eligible to participate in these studies. Volunteers with positive test results for hepatitis A, hepatitis B, HCV, or HIV—or those who regularly used prescription or over-the-counter medications, vitamins, or supplements—were excluded. Participants were prohibited from receiving any drug by injection within 30 days prior to study drug administration; ingesting a known inhibitor or inducer of cytochrome P450 (CYP) 3A, CYP2C8, or organic anion transporting polypeptide 1B1 within 1 month prior to study drug administration; using tobacco or nicotine-containing products within 6 months of study initiation; or consuming grapefruit juice, star fruit, Seville oranges, or products containing these ingredients within 72 h prior to study drug administration. All study participants provided written informed consent as approved by an institutional review board.

Study design. Data were extracted from four phase 1, single-center, multiple-dose, open-label studies (Fig. 1). Three of the four studies involved two participant cohorts: cohort 1 received a DAA regimen for the first 14 days before addition of the selected ARV regimen for another 7 to 14 days; cohort 2 received the ARV regimen for 7 to 14 days before addition of the DAA regimen for another 14 days. In the fourth study, all participants received the ARV regimen for 3 days followed by the addition of the DAA regimen for another 14 days.
Dosing of ARV drugs was based on label-recommended doses. In study 1, the 3D regimen (paritaprevir/r 150/100 mg once daily [QD], ombitasvir 25 mg QD, and dasabuvir 400 mg twice daily [BID]) was combined with emtricitabine 200 mg QD (Emtriva®; Gilead Sciences, Inc., Foster City, CA, USA) and tenofovir DF 300 mg QD (Viread®; Gilead Sciences, Inc., Foster City, CA, USA). In study 2, the 3D regimen was combined with rilpivirine 25 mg (Edurant®; Tibotec, Inc., Raritan, NJ, USA) administered QD in the morning. When combined with efavirenz/emtricitabine/tenofovir DF 600/200/300 mg daily (Atripla®; Bristol-Myers Squibb, Princeton, NJ, USA) in study 3, a 2-DAA regimen, which was one of the initial DAA combination regimens evaluated in clinical studies and consisted of paritaprevir/r 150/100 mg QD and dasabuvir 400 mg BID, was used. In study 4, the 3D regimen was combined with raltegravir 400 mg BID (Isentress®; Merck & Co., Inc., Whitehouse Station, NJ, USA). The 400-mg dose of dasabuvir used in these studies provides equivalent exposures to that of the 250-mg marketed dose of dasabuvir.

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.

**Pharmacokinetic and safety assessments.** Pharmacokinetic assessments were performed at steady state. Blood samples were collected prior to dosing and at regular intervals after dosing for up to 96 h to quantify plasma concentrations of paritaprevir, ombitasvir, ritonavir, dasabuvir, and ARV drugs. Intensive blood sampling for the
determination of maximum observed plasma concentration ($C_{\text{max}}$) and area under the plasma concentration-time curve during a dosing interval ($\text{AUC}_1$; $\text{AUC}_{24}$ for drugs administered QD and $\text{AUC}_{12}$ for drugs administered BID) were performed in the last dosing interval of each treatment phase. Blood draws for the measurement of trough drug levels ($C_{\text{trough}}$) were performed periodically during the treatment phase in each study. The $C_{\text{trough}}$ levels were measured at 24 h postdose ($C_{24}$) for drugs administered QD and at 12 h after the morning dose ($C_{12}$) for drugs administered BID. Plasma concentrations of paritaprevir, ritonavir, ombitasvir, and dasabuvir were determined using a validated protein precipitation and online solid-phase extraction method with liquid chromatography and tandem mass spectrometric detection (LC-MS/MS) (20). Plasma concentrations of emtricitabine/tenofovir, rilpivirine, efavirenz/emtricitabine/tenofovir, and raltegravir were determined by validated LC-MS/MS methods at a commercial laboratory (PPD, Middleton, WI). The lower limits of quantitation were 20.0/5.00 ng/mL, 0.500 ng/mL, 100/20.0/5.00 ng/mL, and 10.0 ng/mL, respectively. Safety and tolerability were evaluated based on adverse event (AE) monitoring, vital sign measurements, physical examinations, electrocardiography, and laboratory assessments. All AEs were recorded, severity assessed, and relationship to study drug evaluated.
Pharmacokinetic and statistical analyses. Pharmacokinetic analyses, performed via noncompartmental methods, and statistical analysis were performed using SAS, Version 9.2 (Cary, NC, USA). Geometric mean ratios (GMRs) and 90% confidence intervals (CIs) comparing exposures (C_{max}, AUC_{τ}, and C_{trough}) of DAA or ARV regimens alone with that of DAA/ARV coadministration were calculated through repeated-measures analysis. With the exception of the raltegravir DDI study, data from cohort 1 of each study were used to assess the effect of the ARV drugs on the pharmacokinetics of DAAs and ritonavir. Data from cohort 2 were used to determine the effect of the 3D regimen on ARV drug exposure. The effects of raltegravir on the pharmacokinetics of DAAs and ritonavir were evaluated by cross-study comparison of the 3D regimen plus raltegravir study data with historical data for the 3D regimen administered alone (data on file, AbbVie USA). Raltegravir has minimal potential for a pharmacokinetic interaction with metabolizing enzymes or drug transporters that affect the disposition of DAAs and, hence, was not anticipated to alter the pharmacokinetics of DAAs. For DAAs, exposures up to 50% lower or 100% higher (GMR, 0.5–2.0) during coadministration with ARV drugs versus DAA administration alone was considered not to be significant. For ARV drugs, GMR and 90% CIs in the range of 0.8 to 1.25 for the comparison of exposures during coadministration with DAAs versus ARV drugs administered alone was not considered to be significant. The clinical significance of the exposures of ARV drugs outside the range of 0.8 to 1.25 was based on their dosing recommendations as per US prescribing information or summary of product characteristics.
Demographic and safety/tolerability data were evaluated using descriptive statistics.
RESULTS

Participants. A total of 66 healthy volunteers were enrolled in the study cohorts that contributed to this analysis (Table 1). All participants in studies 1 and 4 completed their respective studies as planned. Two (10%) participants prematurely discontinued from study 2 (3D regimen with rilpivirine): one at the discretion of the investigator and one because of an AE. The DDI study of the 2-DAA regimen with efavirenz/emtricitabine/tenofovir DF (study 3) was terminated early owing to the occurrence of AEs that led 9 of 16 participants to discontinue from the study.

Pharmacokinetic analysis for this combination was, therefore, not performed.

Effect of the 3D regimen on HIV-1 antiretroviral pharmacokinetics. Emtricitabine exposure was not affected by coadministration of the 3D regimen; $C_{\text{max}}$, $AUC_{\tau}$, and $C_{\text{trough}}$ GMRs indicated an increase of <10% during coadministration of emtricitabine and tenofovir DF with the 3D regimen (Fig. 2). Tenofovir $C_{\text{max}}$ and $AUC_{\tau}$ were not affected, with approximately 7%, and 13% increases, respectively, but tenofovir $C_{\text{trough}}$ was 24% higher, during coadministration of emtricitabine and tenofovir DF with the 3D regimen. These minor changes were within the prespecified GMR range of 0.8 to 1.25 for $C_{\text{max}}$ and $AUC_{\tau}$ and are, therefore, not expected to be clinically meaningful.

Raltegravir and rilpivirine exposures were notably elevated when administered with the 3D regimen. The $C_{\text{max}}$, $AUC_{\tau}$, and $C_{\text{trough}}$ values for raltegravir increased by 100% to 134%. GMRs for the pharmacokinetic parameters of rilpivirine were in the range of 2.55
to 3.62 for the comparison of rilpivirine plus the 3D regimen versus rilpivirine alone, indicating a 155% to 262% increase in rilpivirine exposure.

**Effect of HIV-1 Antiretroviral Drugs on 3D Regimen Pharmacokinetics.** Paritaprevir AUC and C\textsubscript{trough} were minimally affected, whereas C\textsubscript{max} GMR decreased by 32% when the 3D regimen was coadministered with emtricitabine plus tenofovir DF (Fig. 3). When coadministered with rilpivirine, changes in paritaprevir exposures ranged from a 5% decrease to a 30% increase. Pharmacokinetic parameters for ritonavir, ombitasvir, and dasabuvir were not affected (≤20% change) when the 3D regimen was coadministered with emtricitabine plus tenofovir DF or rilpivirine (Fig. 3).

Cross-study comparisons of geometric mean AUC values indicated that exposures for paritaprevir, ritonavir, ombitasvir, and dasabuvir during coadministration of the 3D regimen with raltegravir were within the range of AUC values for the 3D regimen alone in historical phase 1 studies.

**Safety and Tolerability.** The most common treatment-emergent AEs (TEAEs) that occurred in the emtricitabine plus tenofovir DF study were headache and abdominal pain (n=2 each). All TEAEs in this study were mild in severity. No clinically significant changes in vital signs or laboratory measurements were observed.

Adverse events reported during the rilpivirine study were generally mild in severity and considered to be unrelated to study drug administration. The most common TEAEs
were headache and constipation. One (5%) participant discontinued from the rilpivirine study owing to a TEAE of increased blood creatinine phosphokinase and Grade 3 aspartate aminotransferase [AST] elevation. The event was deemed unrelated to study treatment and resolved during follow-up on study day 38. Two other participants experienced isolated elevations in aminotransferases (Grade 2 AST [n=1] or alanine aminotransferase [ALT; n=1]) that were not accompanied by a concurrent elevation in bilirubin and resolved with continued combination dosing. No clinically significant changes in vital signs or other laboratory measurements were observed.

Three participants experienced a single TEAE with concomitant administration of the 3D regimen and raltegravir. These events were mild and included dyspepsia, bilirubin (indirect) increase, and ALT increase (Grade 1). All TEAEs resolved during the course of the study. No serious TEAEs occurred, and no clinically significant changes in vital signs or other laboratory measurements were reported.

Of the 16 participants enrolled in the efavirenz/emtricitabine/tenofovir DF study, nine prematurely discontinued owing to TEAEs (included dizziness, headache, nausea, vomiting, and aminotransferase elevations) that occurred in the second study period (on or after Study Day 15). Discontinuations were more frequent in cohort 2, wherein efavirenz/emtricitabine/tenofovir DF was administered prior to initiation of paritaprevir/r and dasabuvir. The determination was made to terminate the study on Study Day 17, 3 days after initiation of the coadministration of the 2-DAA regimen with efavirenz/emtricitabine/tenofovir DF, based on the AE profile. No serious TEAEs were
reported; however, one participant experienced a severe TEAE (severe nausea, vomiting, and feeling abnormal) and three participants experienced Grade 3 or 4 aminotransferase elevations. All reported events resolved without sequelae, after discontinuation of study medication.
This series of DDI studies indicate that HCV therapy with the 3D regimen is compatible with several commonly prescribed ARV agents. Based on drug exposure data, combining the 3D regimen with emtricitabine plus tenofovir DF or with raltegravir BID dosing should not require dose adjustment. The 3D regimen had minimal to no effect on the pharmacokinetic profile of emtricitabine or tenofovir, and exposures to 3D regimen components were not affected or only minimally influenced by emtricitabine plus tenofovir DF or raltegravir. The greatest change in 3D component exposure in the presence of emtricitabine and tenofovir DF occurred with paritaprevir, for which C_max decreased by 32%. Paritaprevir, dasabuvir, and ombitasvir at doses of 100 to 250 mg administered QD, 300 to 800 mg administered BID, and 1.5 to 200 mg administered QD, respectively, provided comparable efficacy and were well tolerated in phase 2 studies (21-26). These DAA doses used in Phase 2 studies, which produce exposures up to 55% lower and up to 250% higher than those used as part of the 3D regimen, along with the exposure-response relationship, suggest that exposure increases of 100% (2×) or decreases of 50% (0.5×) do not necessitate dose adjustment (11,27).

Although raltegravir exposure increased by 100% to 134% during 3D regimen coadministration, this elevation is not expected to be clinically important owing to the wide safety margin of raltegravir. In the US Food and Drug Administration summary review of raltegravir’s New Drug Application, an increase by as much as two-fold in raltegravir AUC and a decrease of 60% in C_\text{trough} were not considered clinically relevant.
Based on the results of phase 2 and 3 clinical trials (28). Moreover, data from a DDI study of raltegravir with gastric pH–altering agents demonstrated greater increases in raltegravir exposure (e.g., 315% and 212% in C_{max} and AUC, respectively) than observed during 3D regimen treatment, yet coadministration of gastric pH–altering agents in phase 3 studies of raltegravir revealed no unique safety signals (29). Because the increase in raltegravir exposure during its coadministration with the 3D regimen is within the safety margin for raltegravir established in phase 2 and 3 clinical trials, no dose adjustment for raltegravir is anticipated to be necessary during coadministration with the 3D regimen.

The influence of raltegravir on DAA pharmacokinetics was not evaluated directly, as raltegravir does not inhibit or induce metabolic enzymes or drug transporters known to affect the disposition of paritaprevir, ritonavir, ombitasvir, or dasabuvir. Cross-study comparisons with previous phase 1 study data affirmed that DAA pharmacokinetics were within the expected range during coadministration of raltegravir with the 3D regimen.

Coadministration of the 3D regimen with rilpivirine is not recommended. Addition of the 3D regimen to steady-state rilpivirine resulted in a more than two-fold increase in rilpivirine exposure. Alternate dosing regimens of rilpivirine with the 3D regimen, including administration of rilpivirine in the evening after an evening snack or at night approximately 4 h after dinner, have also been tested with comparable results. Results from previous studies of rilpivirine suggest that increases in rilpivirine exposure could
result in QTc prolongation; therefore, coadministration of any drugs that appreciably increase the exposure of rilpivirine are not recommended (17).

Coadministration of the 3D regimen with efavirenz-containing ARV regimens is contraindicated. When the 2-DAA regimen of paritaprevir/r and dasabuvir was coadministered with efavirenz/emtricitabine/tenofovir DF 600/200/300 mg QD, 9 of 16 patients discontinued from the study owing to AEs. These safety findings were attributed to efavirenz, a CYP3A inducer, as coadministration of the 3D regimen with emtricitabine and tenofovir DF was well tolerated in healthy volunteers. Similar safety findings have been observed when the CYP3A inducers rifampin or efavirenz were coadministered with ritonavir-boosted protease inhibitors such as lopinavir and saquinavir in healthy volunteers (30-32). Patients treated with these therapy combinations reported AEs consistent with our observations, including abdominal symptoms and transaminase elevations.

Coadministration of the 3D regimen with emtricitabine plus tenofovir DF, raltegravir, or rilpivirine for 7 to 14 days was generally well tolerated in these phase 1 DDI studies. Multiple-dose administration did not reveal new safety findings of concern in any study.

Additional studies have evaluated and are exploring potential DDIs between the 3D regimen and other commonly prescribed HIV-1 medications, including atazanavir, darunavir, lopinavir/ritonavir, dolutegravir, and abacavir/ lamivudine. Moreover, coadministration of the 3D regimen plus ribavirin with the ARV drugs tenofovir DF,
emtricitabine, atazanavir, or raltegravir is being investigated in a phase 2/3 study (TURQUOISE-I) that enrolled patients with genotype 1 chronic HCV and HIV-1 coinfection. After 12 weeks of treatment with 3D plus ribavirin in part 1a of TURQUOISE-I, 94% (29/31; 95% CI, 79%–98%) of patients achieved SVR12, no serious TEAEs were reported, and no patients prematurely discontinued study treatment owing to an AE (33). Patients on stable darunavir-containing ARV regimens are being evaluated in the ongoing part 1b of the study.

Despite the robust study designs used herein, one possible limitation was the enrollment of healthy volunteers. Greater variability is seen in the real world or clinical trial setting than in pharmacokinetic studies with healthy volunteers owing to the effects of sex, ethnicity, age, medication adherence, body weight/BMI, genetic background, comorbidities, and concomitant medications. Patients who are coinfected with HIV and HCV represent the target population for 3D/ARV combination therapy; however, the evaluation of DDIs in this patient population is not only challenging due to the unpredictable relationship between population dose-response and individual concentration-response, but also because a clinically significant DDI could put these patients at risk for treatment failure or AEs. Nonetheless, results from the TURQUOISE-I study do not indicate differences in treatment response or a notable elevation in the risk for adverse drug reactions with combination 3D/ARV therapy in the target population (33). Other factors that may affect real-world applicability of our results include the small number of subjects, limited duration of the studies, and restrictions on concomitant medications. With regard to the latter, phase 3 studies in which patients.
were allowed wider lenience in terms of concomitant medications have not yielded any interactions of concern (Menon R, Badri P, Khatri A, Wang T, Bow D, Polepally A, Podsadecki T, Awni W, Dutta S, presented at the 15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, Washington, DC, 19 to 21 May 2014).

In conclusion, the interferon-free 3D regimen may be appropriate for a broad range of patients with HCV infection, including those with HIV. The low risk for clinically significant DDIs when the 3D regimen is coadministered with the ARV agents emtricitabine, tenofovir DF, or raltegravir makes it a potentially viable treatment option for patients who are coinfected with HCV and HIV.
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AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options.
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### TABLE 1 Study participant demographics and baseline characteristics

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<td>(3D + FTC + TDF)</td>
<td>18</td>
<td>32.7 ± 9.5</td>
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<td>179 ± 7.3</td>
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<td>42.1 ± 11.5</td>
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Includes all participants enrolled in the relevant treatment arms of the study.

2-DAA, paritaprevir/ritonavir and dasabuvir; 3D, paritaprevir/ritonavir, ombitasvir, and dasabuvir; EFV, efavirenz; FTC, emtricitabine; RAL, raltegravir; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate.
FIGURE LEGENDS

FIG 1 Study design of drug-drug interaction studies. All study drugs were administered under nonfasting conditions. Paritaprevir/ritonavir and ombitasvir once-daily doses were administered in the morning and dasabuvir was administered in the morning and evening. aThe drug-drug interaction study of efavirenz (EFV)/tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) (ie, Atripla®) with direct-acting antiviral (DAA) agents was conducted with the 2-DAA regimen of paritaprevir/ritonavir and dasabuvir.

3D, paritaprevir/ritonavir, ombitasvir, and dasabuvir; ARV, antiretroviral; RAL, raltegravir.

FIG 2 Effect of the 3D regimen on the Cmax, AUCτ, and Ctrough of HIV-1 antiretroviral drugs. AUCτ, area under the plasma concentration-time curve during a dosing interval; CI, confidence interval; Cmax, maximum observed plasma concentration; Ctrough, minimum observed plasma concentration; GMR, geometric mean ratio.

FIG 3 Effect of HIV-1 antiretroviral drugs on the Cmax, AUCτ, and Ctrough of paritaprevir, ritonavir, ombitasvir, and dasabuvir. AUCτ, area under the plasma concentration-time curve during a dosing interval; CI, confidence interval; Cmax, maximum observed plasma concentration; Ctrough, minimum observed plasma concentration.
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</tbody>
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<th>Cohort 1</th>
<th>Day 14</th>
<th>Day 28</th>
<th>HIV-1 ARV Administration</th>
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<tbody>
<tr>
<td>2-DAA regimen</td>
<td>2-DAA + EFV/TDF/FTC</td>
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<tr>
<td>Cohort 2</td>
<td>EFV/TDF/FTC</td>
<td>2-DAA + EFV/TDF/FTC</td>
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<th>Day 17</th>
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<th>N</th>
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<tbody>
<tr>
<td>RAL</td>
<td>3D + RAL</td>
<td></td>
<td>Twice daily</td>
<td>12</td>
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