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Effects of Etravirine Alone and with Ritonavir-Boosted Protease Inhibitors on the Pharmacokinetics of Dolutegravir[▽]

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Dolutegravir (DTG) is an unboosted, once-daily integrase inhibitor currently in phase 3 trials. Two studies evaluated the effects of etravirine (ETR) alone and in combination with ritonavir (RTV)-boosted protease inhibitors (PIs) on DTG pharmacokinetics (PK) in healthy subjects. DTG 50 mg every 24 h (q24h) was administered alone for 5 days in period 1, followed by combination with ETR at 200 mg q12h for 14 days in period 2 (study 1) or with ETR/lopinavir (LPV)/RTV at 200/400/100 mg q12h or ETR/darunavir (DRV)/RTV at 200/600/100 mg q12h for 14 days in period 2 (study 2). PK samples were collected on day 5 in period 1 and day 14 in period 2. All of the treatments were well tolerated. ETR significantly decreased exposures of DTG, with geometric mean ratios of 0.294 (90% confidence intervals, 0.257 to 0.337) for the area under the curve from time zero until the end of the dosage interval ($AUC_{0-\tau}$), 0.484 (0.433 to 0.542) for the observed maximum plasma concentration (C_{max}), and 0.121 (0.093 to 0.157) for the plasma concentration at the end of the dosage interval (C_{τ}). ETR combined with an RTV-boosted PI affected the exposure of DTG to a lesser degree: ETR/LPV/RTV treatment had no effect on the DTG plasma $AUC_{0-\tau}$ and C_{max}, whereas the C_{τ} increased by 28%. ETR/DRV/RTV modestly decreased the plasma DTG $AUC_{0-\tau}$, C_{max}, and C_{τ} by 25, 12, and 37%, respectively. Such effects of ETR/LPV/RTV and ETR/DRV/RTV are not considered clinically relevant. The combination of DTG and ETR alone should be avoided; however, DTG may be coadministered with ETR without a dosage adjustment if LPV/RTV or DRV/RTV is concurrently administered.

The HIV integrase inhibitors (INIs) are a promising new class of antiretrovirals that offer excellent potency with a favorable safety profile (12). Dolutegravir (DTG) is a next-generation INI with pharmacokinetics (PK) that support once-daily dosing without the need for ritonavir (RTV) boosting. It has demonstrated potent efficacy at 16 weeks in treatment-naive subjects in combination with two nucleoside reverse transcriptase inhibitors (3). DTG also possesses a distinct resistance profile and has demonstrated activity against raltegravir-resistant strains (5, 18).

DTG is primarily metabolized via UDP-glucuronosyltransferase (UGT) 1A1 with a minor component of cytochrome P450 (CYP) 3A4. It does not inhibit CYP or UGT isozymes *in vitro* and demonstrated no significant effect on midazolam in healthy subjects (9). Clinical studies in healthy subjects have shown that no dosage adjustments are necessary for DTG when combined with atazanavir, atazanavir/RTV, darunavir (DRV)/RTV, lopinavir (LPV)/RTV, tenofovir, multivitamins, and omeprazole, although separation of dosing is required for antacids (11, 13, 14, 16, 17).

The second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine (ETR) is commonly used in treatment-experienced patients. ETR has a number of drug interactions given its induction potential of CYP isozymes (6). As DTG progresses in phase 3 studies, the combination of these drugs will likely be used in treatment-experienced subjects. Thus, an evaluation of potential drug interactions was warranted to provide dosing recommendations for phase 3 studies. Since ETR is commonly coadministered with RTV-boosted protease inhibitors (PIs) in treatment-experienced subjects, the effect of both ETR alone and in combination with PIs on DTG exposure was evaluated.

(These data were presented in part at the 11th International Workshop on the Clinical Pharmacology of HIV Therapy, Sorrento, Italy, April 2010.)

MATERIALS AND METHODS

Two studies evaluated the effects of ETR alone (study 1) and in combination with RTV-boosted PIs (study 2) on DTG PK in healthy subjects. Both studies were conducted at the same clinical site with different subjects who were confined to the clinical site for the duration of the study. Written informed consent was obtained from all subjects, and the protocols were approved by the institutional review board of the study site, IntegReview, Inc., Austin, TX.

The study designs are shown in Table 1. Study 1 was an open-label, two-period, crossover study in 16 healthy adult subjects. DTG administered at 50 mg every 24 h (q24h) was administered alone for 5 days in period 1, followed by DTG at 50 mg q24h and ETR at 200 mg q12h for 14 days in period 2. All doses were given with a moderate-fat meal, and there was no washout between periods.

Study 2 was a randomized, open-label, crossover study in 17 healthy adult subjects. Subjects received DTG at 50 mg q24h administered alone for 5 days in period 1 and coadministered with ETR/LPV/RTV at 200/400/100 mg q12h or ETR/DRV/RTV at 200/600/100 mg q12h for 14 days in period 2. All doses were given with a moderate-fat meal, and there was no washout between periods.

DTG is unlikely to affect ETR, LPV, DRV, or RTV exposures given that these drugs are predominantly metabolized by CYP3A, and a previous study demonstrated no effect of DTG on the PK of the CYP3A substrate midazolam (9). Therefore, the studies were designed to only evaluate the one-way

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TABLE 1. Study designs

Study and cohort	Sample size	Drug[a] (dosage)	
		Period 1, days 1 to 5	Period 2, days 1 to 14
Study 1			
Cohort 1	16	DTG (50 mg, q24h)	DTG (50 mg, q24h) + ETR (200 mg, BID)
Study 2			
Cohort 1	8	DTG (50 mg, q24h)	DTG (50 mg, q24h) + ETR (200 mg, BID) + LPV/RTV (400/100 mg, BID)
Cohort 2	9	DTG (50 mg, q24h)	DTG (50 mg, q24h) + ETR (200 mg, BID) + DRV/RTV (600/100 mg, BID)

[a] DTG, dolutegravir; ETR, etravirine; LPV, lopinavir; RTV, ritonavir; DRV, darunavir; BID, twice daily.

drug interaction effect of ETR, ETR/LPV/RTV, and ETR/DRV/RTV on DTG PK.

Subjects were judged to be healthy by physical exam, medical history, and laboratory testing. Adult males or females of non-child-bearing potential were enrolled. Exclusion criteria included a positive HIV or hepatitis C antibody result; a positive hepatitis B surface antigen result; a positive illicit drug or alcohol screen; and the use of any prescription or nonprescription drugs, including vitamins or herbal products, within 7 days prior to the first dose and throughout the study. Subjects had a screening visit within 30 days prior to the first dose of the study drug(s), two treatment periods, and a follow-up visit 7 to 14 days after the last dose of the study drug(s).

For both studies, serial PK samples were collected on day 5 of period 1 and day 14 of period 2. Safety evaluations, including adverse-event (AE) assessments, vital signs, laboratory testing, and electrocardiograms (ECGs), were performed at regular intervals throughout the studies.

Bioanalytical methods. Following extraction from plasma by protein precipitation, DTG concentrations were determined by validated, high-performance liquid chromatography–tandem mass spectrometry methods (MDS Sciex Analyst, version 1.4.2; Applied Biosystems, Foster City, CA; SMS2000, version 2.1; GlaxoSmithKline, Research Triangle Park, NC) using TurboIonSpray and multiple reaction monitoring at GlaxoSmithKline. For analysis of DTG, [2H7,15N]DTG was used as an internal standard. The validated linear concentration range was 5 to 5,000 ng/ml, and three concentrations of quality control (QC) samples were included in each run at 20, 400, and 4,000 ng/ml. Based on the results of the analysis of these QC samples, the bias ranged from −3.5 to 3.7%, and the within-run precision and the between-run precision were less than or equal to 8.9 and 1.6%, respectively.

Pharmacokinetic analysis. A noncompartmental PK analysis of the concentration-time data was performed with WinNonlin (version 5.2; Pharsight Corp., Mountain View, CA). Plasma PK parameters for DTG were calculated by using the actual recorded times for each treatment. Parameters that were determined include the area under the curve from time zero until the end of the dosage interval ($AUC_{0-\tau}$), the observed maximum plasma concentration (C_{max}), the time to observed maximum plasma concentration (t_{max}), the plasma concentration at the end of the dosage interval (C_{τ}), the observed minimum plasma concentration over the dosage interval (C_{min}), the apparent oral clearance (CL/F), and the apparent terminal half-life ($t_{1/2}$). The $AUC_{0-\tau}$ was calculated by trapezoidal rule using the linear-up/log-down method.

Statistical analysis. Statistical analysis was performed on the log-transformed PK parameters $AUC_{0-\tau}$, C_{τ}, and C_{max}. Analysis of variance was performed using the SAS mixed-linear-models procedure to assess the effect of ETR, ETR/LPV/RTV, or ETR/DRV/RTV on the PK of DTG. Subject was fitted as a random effect, and treatment was fitted as a fixed effect in the model. The ratio of geometric-least-squares (GLS) means and associated 90% confidence interval (CI) was estimated for the PK parameters of interest. DTG given alone was considered to be the reference treatment, and DTG coadministered with ETR, ETR/LPV/RTV, or ETR/DRV/RTV was considered to be the test treatment.

RESULTS

Demographics. In study 1, 16 subjects were enrolled, and 15 subjects completed the study. All subjects were male, with a median age of 41.5 years (range, 19 to 64 years) and a median weight of 84.8 kg (range, 68.9 to 110.7). Seven of the subjects were African-American, and nine were Caucasian. In study 2, 17 subjects (8 on ETR/LPV/RTV and 9 on ETR/DRV/RTV) were enrolled, and all subjects completed the study. All subjects were male, with a median age of 41.0 years (range, 20 to 61 years) and a median weight of 83.0 kg (range, 76.2 to 99.8 kg). Eight of the subjects were African-American, and nine were Caucasian.

Safety. DTG was well tolerated. No deaths, serious AEs, or withdrawals due to AEs were reported in either study. In addition, no clinically significant changes in clinical laboratory values, vital signs, or ECGs were observed.

In study 1, one subject was withdrawn at the investigator's discretion for a personal matter unrelated to the study. The most commonly reported drug-related AE was headache (four subjects). Abdominal pain, reported by one subject, was the only other AE considered to be drug related. All AEs were reported as grade 1 or mild.

No subjects withdrew in study 2. Seventeen subjects enrolled and completed the study. The most frequently reported drug-related AE was constipation (two subjects). All other drug-related AEs were reported in one subject each. In period 1, one subject each reported abnormal dreams and epistaxis. In period 2, one subject each reported abdominal pain, diarrhea, flatulence, and contact dermatitis (LPV/RTV cohort) and headache and rash (DRV/RTV cohort). All AEs were mild in intensity.

Pharmacokinetics. Figure 1 shows steady-state mean concentration-time profiles of DTG with or without concomitant ETR. ETR alone significantly decreased exposures of DTG by

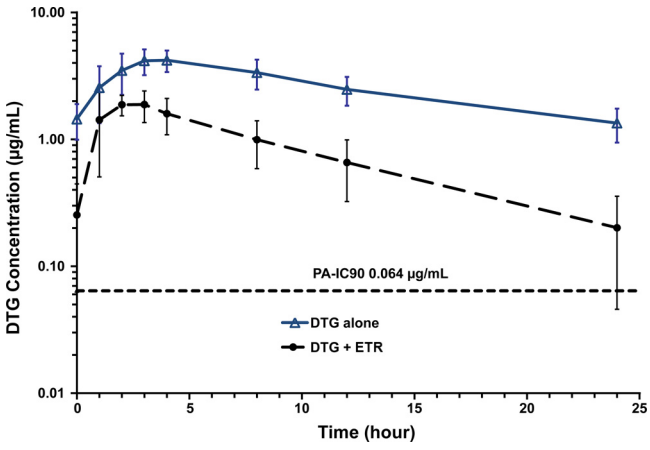

FIG. 1. Mean concentration-time profile of DTG alone and with coadministration of ETR.

TABLE 2. Pharmacokinetic parameters of DTG treatment with or without coadministration of ETR

Treatment regimen	*n*	Geometric mean (CV%)[a]					Median t_{max} (h)[b]
		$AUC_{0-\tau}$ (μg · h/ml)	C_{max} (μg/ml)	$C\tau$ (μg/ml)	CL/F (liters/h)	$t_{1/2}$ (h)	
DTG	15	60.4 (22)	4.34 (19)	1.29 (29)	0.83 (22)	12.4 (21)	3.00 (1.00–4.07)
DTG + ETR	15	17.8 (39)	2.10 (24)	0.16 (84)	2.81 (39)	6.39 (22)	2.00 (1.00–3.00)

[a] CV%, Percent coefficient of variation.
[b] The range is indicated in parentheses.

ca. 70% for $AUC_{0-\tau}$ and by ca. 90% for C_τ. All subjects demonstrated decreased exposures of DTG in the presence of ETR. Pharmacokinetic parameters for DTG in study 1 are shown in Table 2, and statistical comparisons of DTG PK parameters are shown in Table 3.

Figure 2 demonstrates DTG mean concentration-time profiles when administered alone and with ETR/LPV/RTV or ETR/DRV/RTV. When combined with one of these RTV-boosted PIs, the impact of ETR on DTG was markedly reduced. DTG coadministration with ETR/LPV/RTV had no effect on DTG steady-state plasma $AUC_{0-\tau}$ and C_{max}, whereas C_τ increased by 28%. DTG coadministration with ETR/DRV/RTV modestly decreased the plasma DTG $AUC_{0-\tau}$, C_{max}, and C_τ by 25, 12, and 37%, respectively. PK parameters of DTG in study 2 are shown in Table 4, and statistical comparisons of DTG PK parameters are shown in Table 5.

DISCUSSION

As DTG progresses into phase 3 clinical trials, evaluation of the drug interaction profile is warranted with compounds such as ETR. This combination is especially likely to be used in individuals who are resistant to raltegravir. ETR has a complex metabolic profile as it is a substrate of CYP3A4, CYP2C9, and CYP2C19; an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein (P-gp); and an inducer of CYP3A4 (6). Therefore, numerous drug interactions exist that prevent the coadministration with some antiretrovirals (Intelence package insert; Tibotec Therapeutics, a Division of Centocor Ortho Biotech Products, L.P.). The first study we conducted showed that ETR alone reduced the steady-state C_τ and $AUC_{0-\tau}$ of DTG by 88 and 71%, respectively. Although C_τ still remains ~3-fold above the protein-adjusted 90% inhibitory concentration (IC_{90}) (Fig. 1), this decrease could be clinically relevant, particularly in subjects failing raltegravir therapy. The mechanism for the reduction in DTG exposure by ETR is likely the result of net induction of multiple metabolic pathways. DTG is metabolized via UGT1A1 and CYP3A4 and is a P-gp substrate. Since CYP3A4 is likely a minor metabolic pathway and UGT1A1 is the major metabolic pathway for DTG, UGT1A1 induction is likely primarily contributing to the reduced exposures observed. In healthy subjects, ETR decreased the $AUC_{0-\tau}$ of raltegravir, which is a UGT1A1 substrate and is primarily metabolized by this pathway, by 10% (2). This decrease was not considered clinically significant; however, case reports of subjects having virologic failure on this combination have been reported (8). In all of these cases of virologic failure, raltegravir trough concentrations were markedly decreased compared to historical data. These data further suggest that ETR may induce UGT1A1, causing large reductions in raltegravir exposure in some patients.

Based on the large reduction in exposure of DTG when administered with ETR alone, it is recommended that this combination not be coadministered. Study 2 was therefore conducted to evaluate strategies to allow for their combined use. This second study evaluated whether combining DTG and ETR with an RTV-boosted PI could attenuate the interaction and allow for concomitant dosing of DTG and ETR. This strategy was based on literature demonstrating that an RTV-boosted PI could counteract the enzyme-inducing properties of a first-generation NNRTI, efavirenz (1, 4, 10).

Study 2 demonstrated that ETR coadministered with both RTV-boosted PI regimens affects the exposure of DTG to a lesser degree. Coadministration of ETR/LPV/RTV had no effect on the DTG $AUC_{0-\tau}$ and C_{max} and resulted in an approximately 28% increase in C_τ at steady state. ETR/DRV/RTV treatment yielded a net reduction in DTG exposure with a more prominent effect on C_τ (37% reduction) than on $AUC_{0-\tau}$

TABLE 3. Statistical comparisons of DTG pharmacokinetics with or without the coadministration of ETR

Plasma DTG PK parameter	GLS mean ratio (90% CI) for DTG + ETR vs DTG (n = 15)
$AUC_{0-\tau}$	0.294 (0.257–0.337)
C_{max}	0.484 (0.433–0.542)
$C\tau$	0.121 (0.093–0.157)
CL/F	3.40 (2.97–3.89)
$t_{1/2}$	0.516 (0.471–0.565)

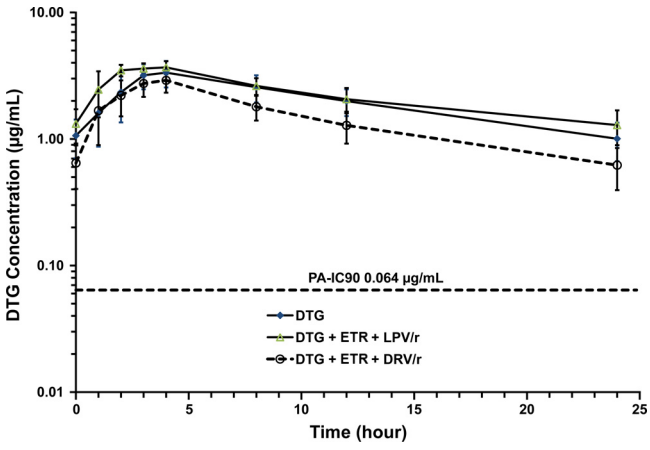

FIG. 2. Mean concentration-time profile of DTG alone and with coadministration of ETR/LPV/RTV or ETR/DRV/RTV.

TABLE 4. Pharmacokinetic parameters of DTG with or without the coadministration of either ETR/LPV/RTV or ETR/DRV/RTV

Treatment regimen	*n*	Geometric mean (CV%)[a]					Median t_{max} (h)[b]
		$AUC_{0-\tau}$ (μg · h/ml)	C_{max} (μg/ml)	$C\tau$ (μg/ml)	CL/F (liters/h)	$t_{1/2}$ (h)	
DTG (cohort 1)	8	47.8 (19)	3.52 (12)	0.97 (33)	1.05 (19)	11.3 (18)	3.50 (2.00–4.00)
DTG (cohort 2)	9	45.2 (22)	3.38 (26)	0.94 (40)	1.11 (22)	10.4 (17)	3.02 (1.00–12.00)
DTG q24h + ETR/LPV/RTV q12h	8	52.8 (18)	3.78 (12)	1.23 (32)	0.95 (18)	15.4 (25)	3.50 (1.00–4.00)
DTG q24h + ETR/DRV/RTV q12h	9	33.9 (22)	2.98 (18)	0.59 (33)	1.47 (22)	10.2 (16)	4.00 (1.00–4.00)

[a] CV%, Percent coefficient of variation.
[b] The range is indicated in parentheses.

(25% reduction) and C_{max} (12% reduction). These findings were similar to those from a previous study that showed LPV/RTV had no effect on DTG PK at steady state, whereas DRV/RTV showed a moderate net reduction in DTG PK (16). The complicated interplay of RTV-boosted PIs (LPV and DRV) and ETR likely explains the interactions observed with DTG. Specifically, the combination of multiple drugs with potent inducing and inhibitory properties on both enzymes and transport proteins led to a net overall change that is not clinically significant from DTG alone.

Since the coadministration of ETR/LPV/RTV had no effect on DTG plasma exposure and showed good tolerability, DTG can be coadministered with ETR/LPV/RTV with no dose adjustment. Although coadministration of ETR/DRV/RTV resulted in modestly decreased plasma DTG exposures, the magnitude of the interaction is not considered clinically significant because the geometric mean plasma DTG C_τ of 0.59 μg/ml for the combination is ~9-fold above the PA-IC_{90} (0.064 μg/ml) for wild-type HIV. In clinical studies, DTG showed potent antiviral activity (both short term and long term) at doses that provide an inhibitory quotient (the ratio of C_τ and PA-IC_{90}) of >3 (3, 7). Furthermore, a PK/pharmacodynamic analysis of DTG from a phase 2a study demonstrated that these exposures would still remain on the plateau of the concentration-response curve (15). Although the combination of DTG and ETR alone should be avoided, DTG can be coadministered with ETR/DRV/RTV with no dose adjustment. Although this recommendation has not been formally confirmed in HIV-infected subjects, it will be evaluated using population PK analyses in large-scale clinical trials.

DTG is currently being evaluated in phase 3 studies in HIV-infected patients. The attributes of once-daily administration and the potential to treat raltegravir-resistant subjects make it a promising investigational drug. Another important characteristic is the ability to coadminister DTG with other antiretrovirals without dose adjustment. These data provide further guidance for the concomitant use of DTG with key antiretrovirals in regimens for treatment-experienced subjects.

TABLE 5. Statistical comparisons of DTG pharmacokinetics with or without the coadministration of either ETR/LPV/RTV or ETR/DRV/RTV

Plasma DTG PK parameter	GLS mean ratio (90% CI)	
	ETR/LPV/RTV + DTG vs DTG in cohort 1 (*n* = 8)	ETR/DRV/RTV + DTG vs DTG in cohort 2 (*n* = 9)
$AUC_{0-\tau}$	1.11 (1.02–1.20)	0.750 (0.691–0.814)
C_{max}	1.07 (1.02–1.13)	0.882 (0.781–0.997)
$C\tau$	1.28 (1.13–1.45)	0.629 (0.523–0.758)
CL/F	0.905 (0.832–0.984)	1.33 (1.23–1.45)
$t_{1/2}$	1.36 (1.20–1.54)	0.993 (0.891–1.11)

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