

## Original article

# Pharmacokinetics of elvitegravir and etravirine following coadministration of ritonavir-boosted elvitegravir and etravirine

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**Background:** This crossover, open-label clinical study evaluated the potential for clinically relevant drug interactions between ritonavir-boosted elvitegravir (elvitegravir/r), an HIV integrase inhibitor, and etravirine, a non-nucleoside reverse transcriptase inhibitor.

**Methods:** Healthy volunteers were randomized into one of two groups, each with two arms. Group 1 ( $n=20$ ) followed a sequence of 10-day dosing of elvitegravir/r (150/100 mg once daily) and elvitegravir/r plus etravirine (200 mg twice daily) or the reverse ( $n=10$  per sequence). Group 2 ( $n=14$ ) followed a sequence of 10-day dosing of etravirine and etravirine plus elvitegravir/r or the reverse ( $n=7$  per sequence), all under fed conditions. Elvitegravir, ritonavir and etravirine pharmacokinetics were determined on days 10 and 20 using non-compartmental analyses. Lack of pharmacokinetic alteration bounds for 90% confidence intervals (CI) about the geometric mean ratio (GMR; coadministration versus alone) were 70–143% for elvitegravir and

ritonavir pharmacokinetics (maximum concentration [ $C_{max}$ ], concentration at the end of the dosing interval [ $C_{tau}$ ] and area under the plasma concentration–time curve [ $AUC_{tau}$ ; 0–24 h] and 80–125% for etravirine pharmacokinetics ( $AUC_{tau}$  0–12 h).

**Results:** Of the 34 enrolled participants, 31 completed the study. There were three discontinuations, but none were caused by adverse events (AEs). The most common treatment-emergent AE was headache. Elvitegravir pharmacokinetic GMR was 6–7% higher following elvitegravir/r plus etravirine dosing versus elvitegravir/r. The GMR for etravirine and ritonavir  $AUC_{tau}$  were 2.4% and 12.3% lower, respectively. Importantly, the 90% CI for elvitegravir and etravirine pharmacokinetics and  $AUC_{tau}$  and  $C_{max}$  for ritonavir were within the lack of alteration bounds.

**Conclusions:** Elvitegravir/r and etravirine do not undergo clinically relevant drug interactions and can be coadministered without dose adjustment.

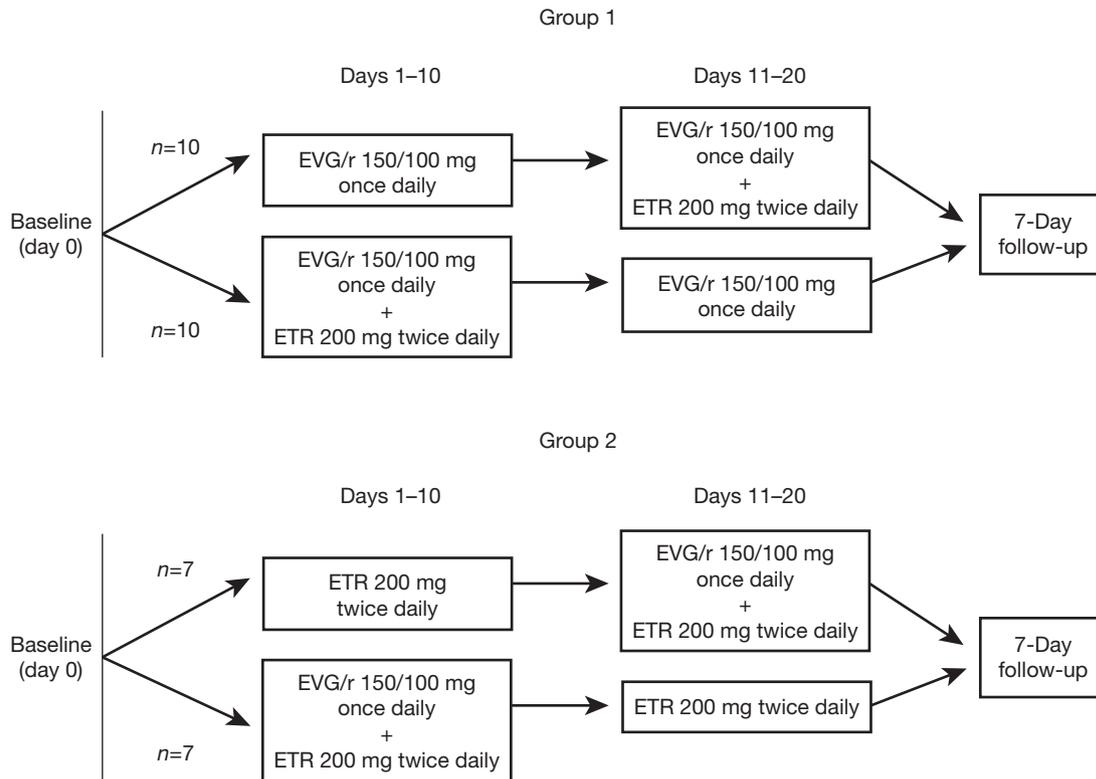
## Introduction

Integrase inhibitors are a novel class of antiretroviral agents for the treatment of HIV-infected patients, especially those harbouring multiclass-resistant virus [1,2]. Elvitegravir is a once-daily potent strand transfer inhibitor undergoing evaluation in Phase III clinical trials. Elvitegravir is metabolized by the cytochrome P450 enzyme, CYP3A4, and also by glucuronidation via uridine glucuronosyl transferase (UGT) 1A1/3 [3]. Once-daily administration of elvitegravir boosted with ritonavir 100 mg (elvitegravir/r) causes a 20-fold increase in elvitegravir plasma exposure over the dosing interval via inhibition of CYP3A4-mediated metabolism. In addition, mean elvitegravir trough concentration, which was the best determinant of antiviral activity in a 10-day

monotherapy study and a 48-week Phase II study, is approximately 10-fold above its *in vitro* protein binding adjusted 95% inhibition concentration ( $IC_{95}$ ) following 150/100 mg elvitegravir/r administration [4–6]. In the Phase II study of treatment-experienced HIV type-1 (HIV-1) patients, elvitegravir/r demonstrated a potent and durable reduction in HIV-1 viral load when coadministered with other active antiretroviral agents, and was well tolerated [7,8].

Etravirine (TMC125), a non-nucleoside reverse transcriptase inhibitor (NNRTI) that was recently approved by the US Food and Drug Administration (18 January 2008), is active against NNRTI-resistant virus in addition to wild-type virus [9,10]. In randomized,

Figure 1. Study design



Pharmacokinetic sampling was performed following study drug dosing on days 10 and 20. ETR, etravirine; EVG/r, ritonavir-boosted elvitegravir.

double-blind, placebo-controlled Phase III studies (DUET-1 and DUET-2), significantly more treatment-experienced adult HIV-1 patients with documented resistance to NNRTIs had an undetectable viral load (<50 copies/ml) with etravirine plus a background regimen compared with placebo and a background regimen [11,12]. Etravirine is metabolized primarily by CYP3A4 and the CYP2C subfamily (2C8, 2C9 and 2C19). Etravirine has been shown to induce CYP3A4 and its clinical coadministration has resulted in lower plasma exposures of CYP3A4 substrates (for example, atorvastatin, clarithromycin, maraviroc and sildenafil). Etravirine also mildly inhibits CYP2C9, CYP2C19 and the transporter, P-glycoprotein (Pgp) [13].

Given the antiviral activity of etravirine and elvitegravir/r against multiclass-resistant HIV-1 virus, their coadministration is desirable as there remains an unmet medical need for combinations of newer agents; however, their overlapping metabolic pathways first necessitate evaluation of clinically relevant drug interactions. The pharmacokinetics and safety of elvitegravir, ritonavir and etravirine were determined in this study following multiple dose administration of elvitegravir/r

(150/100 mg once daily) and etravirine (200 mg twice daily) alone and in combination.

## Methods

### Participants and study design

This was a Phase I, single-centre, open-label, crossover study in healthy male and female (non-pregnant and non-lactating) volunteers (aged 18–45 years, inclusive) performed at Seaview Research, Inc. (Miami, FL, USA). Eligible participants were administered the assigned study treatments as shown in Figure 1. The study protocol and informed consent document were reviewed and approved by the Independent Institutional Review Board Inc. (Plantation, FL, USA) and participants provided written informed consent before study participation. The major eligibility criteria were good health (based on medical history, physical exams and laboratory evaluations), non-smoking, normal 12-lead electrocardiogram, haemoglobin  $\geq 12.0$  g/dl, creatinine clearance  $\geq 80$  ml/min, no evidence of HIV, hepatitis B virus or hepatitis C virus infection and

use of at least two forms of contraception, including an effective barrier method. Exclusion criteria were plasma and blood donation within 7 and 56 days of study entry, respectively, history of significant sensitivity or allergy to drugs, history of alcohol abuse and use of prescription drugs within 30 days of study drug dosing (with the exception of vitamins, acetaminophen, ibuprofen and/or hormonal contraceptive).

In two groups, participants were randomized to the sequence of receiving elvitegravir/r 150/100 mg once daily and elvitegravir/r 150/100 mg once daily plus etravirine 200 mg twice daily (Group 1,  $n=10$  per sequence) or etravirine 200 mg twice daily and elvitegravir/r 150/100 mg once daily plus etravirine 200 mg twice daily (Group 2,  $n=7$  per sequence). Each study treatment was administered for 10 days. On days 10 and 20, following elvitegravir/r dosing and/or the morning dose of etravirine, the pharmacokinetics of elvitegravir and ritonavir were evaluated in Group 1 and that of etravirine evaluated in Group 2. The sampling scheme for Group 1 was pre-dose (0) and 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 18 and 24 h after dosing. The sampling scheme for Group 2 was pre-dose (0) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h after dosing. Morning doses of study drugs were administered under the supervision of clinic staff. Because elvitegravir and etravirine exposures are higher when taken with food, participants received study drugs immediately after a standardized morning meal (approximately 400 kcal) with 240 ml (8 fluid ounces) of water. On the days of pharmacokinetic sampling, participants fasted until collection of the 4 h post-dose blood draw was completed. Participants were allowed to consume water as desired, with the exception of 1 h before and 2 h after study drug dosing. Elvitegravir was supplied as 150 mg tablets, ritonavir as 100 mg soft gelatin capsules (Norvir®; Abbott Laboratories, North Chicago, IL, USA), and etravirine as 100 mg tablets, all for oral administration. Blood samples were collected in a Vacutainer® tube containing anticoagulant (spray-dried  $K_2EDTA$ ; Becton Dickinson, Franklin Lakes, NJ, USA) and inverted several times to mix the blood and the anticoagulant. Samples were kept on wet ice or refrigerated for  $\leq 30$  min and centrifuged for 10 min at a 1,200 relative centrifuge force ( $g$ -force) in a refrigerated centrifuge set at approximately 4°C to harvest plasma.

### Bioanalysis

Plasma concentrations of analytes were determined using validated HPLC/tandem mass spectrometry (MS/MS) bioanalytical assays at Gilead Sciences, Inc. (Durham, NC, USA; elvitegravir and ritonavir) or Johnson & Johnson Pharmaceutical Research and Development (Mechelen, Belgium; etravirine). Elvitegravir and etravirine assay conditions have been reported in detail

elsewhere [14,15]. In brief, assay conditions for ritonavir samples involved processing using solid-phase extraction and MS/MS detection using electrospray ionization. The assay calibration curve was linear between 5–5,000 ng/ml. Accuracy, expressed as percentage bias, ranged from -8 to 13.9% (intraassay) and -2.0 to 9.4% (interassay). Corresponding estimates for precision were 3.3–11.3% and 8.0–11.6%, respectively. The precursor to product ion transition was 721  $m/z \rightarrow 268$   $m/z$ .

### Pharmacokinetic analyses

Pharmacokinetic parameters of elvitegravir, ritonavir and etravirine were estimated by application of a non-linear curve-fitting software package (WinNonlin® software, Professional Edition, Version 5.0.1; Pharsight Corporation, Mountain View, CA, USA) using non-compartmental methods. Parameters included maximum observed plasma concentration ( $C_{max}$ ), time to reach maximum concentration ( $T_{max}$ ), area under the plasma concentration–time curve over the dosing interval ( $AUC_{tau}$ ; calculated using the linear up-log down trapezoidal method; 0–24 h for elvitegravir and ritonavir and 0–12 h for etravirine), elimination half-life ( $T_{1/2}$ ) and concentration at the end of the dosing interval ( $C_{tau}$ ).

### Statistical analyses

A parametric (normal theory) analysis of variance (ANOVA), using a mixed effects model appropriate for a crossover design, was fit to the natural logarithmic transformations of  $AUC_{tau}$ ,  $C_{max}$  and  $C_{tau}$  of elvitegravir, etravirine and ritonavir. Sample size of the study was based on variability estimates of  $C_{max}$ ,  $AUC_{tau}$  and  $C_{tau}$  for elvitegravir (Group 1) and  $AUC_{tau}$  for etravirine (Group 2), and accounted for potential dropouts. The final sample size provided at least 90% power to conclude a lack of pharmacokinetic alteration based on the expected geometric mean ratio (GMR) of treatments (coadministered versus alone) of 1.0 and associated 90% confidence interval (CI) of 70–143% for elvitegravir and 80–125% for etravirine. The 90% CI boundaries for lack of pharmacokinetic alteration of 70–143% were chosen based on the efficacy of elvitegravir/r in a Phase II study [7] that evaluated multiple elvitegravir doses (125, 50 and 20 mg) and the cumulative safety data at the 125 mg dose and higher doses evaluated in Phase I studies. The boundaries for etravirine were the classical bioequivalence criteria of 80–125% based on the understanding of the relationship between etravirine exposure and antiviral response. The pharmacokinetics of ritonavir, used at a subtherapeutic dose as a pharmacokinetic booster, was evaluated using exploratory 90% CI boundaries of 70–143%. Participants with an evaluable pharmacokinetic profile for the coadministered versus alone

treatment pair were included in the pharmacokinetic analysis sets.

## Results

### Demographics

In total, 34 participants were enrolled in the study (Group 1,  $n=20$ ; Group 2,  $n=14$ ). The mean age was 33 years (range 18–45) and participants were distributed equally by sex. Median body mass index at screening was 26.0 kg/m<sup>2</sup> (range 20.7–30.0). Overall, 32 participants (94%) were White and 2 participants (6%) were Black. All participants in Group 2 and 17 of 20 in Group 1 completed the study (three participants withdrew consent and discontinued the study prematurely).

### Safety

The most common treatment-emergent adverse events (AEs) were headache and/or nausea. In Group 1, six participants (31.6%) and two participants (10.5%), respectively, had AEs during elvitegravir/r plus etravirine and elvitegravir/r alone. Headache was the only event reported in more than one participant during either treatment (two participants on elvitegravir/r plus etravirine and none on elvitegravir/r alone). In Group 2, five participants (35.7%) and four participants (28.6%), respectively, had AEs during treatment with etravirine plus elvitegravir/r and etravirine alone. Headache and nausea were the only events that occurred in more than one participant during either treatment (headache occurred in two participants during each treatment and nausea occurred in two participants receiving etravirine and one participant receiving elvitegravir/r plus etravirine). All AEs were grade 1 (mild) in severity, with the exception of one grade 2 event of dysmenorrhoea that was considered unrelated to study treatment. No deaths, serious AEs, grade 3 or 4 AEs or discontinuations because of AEs occurred. No clinically relevant treatment-related changes from pre-dose were observed for any clinical laboratory or vital sign parameters.

### Pharmacokinetics

#### *Elvitegravir*

The plasma concentration–time profiles of elvitegravir after administration of multiple elvitegravir/r doses alone and in combination with etravirine are presented in Figure 2A. Corresponding elvitegravir pharmacokinetic parameters are presented in Table 1. Peak elvitegravir concentrations were observed 4.0–4.5 h following dosing and elvitegravir  $T_{1/2}$  was similar across treatments (8.0 and 8.2 h without and with etravirine, respectively). Consistent with the overlapping elvitegravir concentration–time profiles between treatments, the GMR (%) and 90% CI for elvitegravir plasma

$C_{max}$ ,  $AUC_{tau}$  and  $C_{tau}$  were contained within the lack of pharmacokinetic alteration bounds of 70–143%, indicating that elvitegravir pharmacokinetics were unaffected by etravirine coadministration.

#### *Etravirine*

The plasma concentration–time profiles of etravirine following multiple dose administration alone and with elvitegravir/r are presented in Figure 2B and etravirine pharmacokinetic parameters are presented in Table 1. Etravirine reached peak plasma concentrations 4.0–4.5 h after dosing and displayed similar  $T_{1/2}$  values (9.5 and 7.9 h without and with elvitegravir/r, respectively) with overlapping interquartile ranges between the treatments. The GMR (%) and 90% CI for etravirine plasma  $C_{max}$ ,  $AUC_{tau}$  and  $C_{tau}$  were within the predefined lack of alteration bounds of 80–125%, indicating etravirine pharmacokinetics were unaffected by elvitegravir/r coadministration.

#### *Ritonavir*

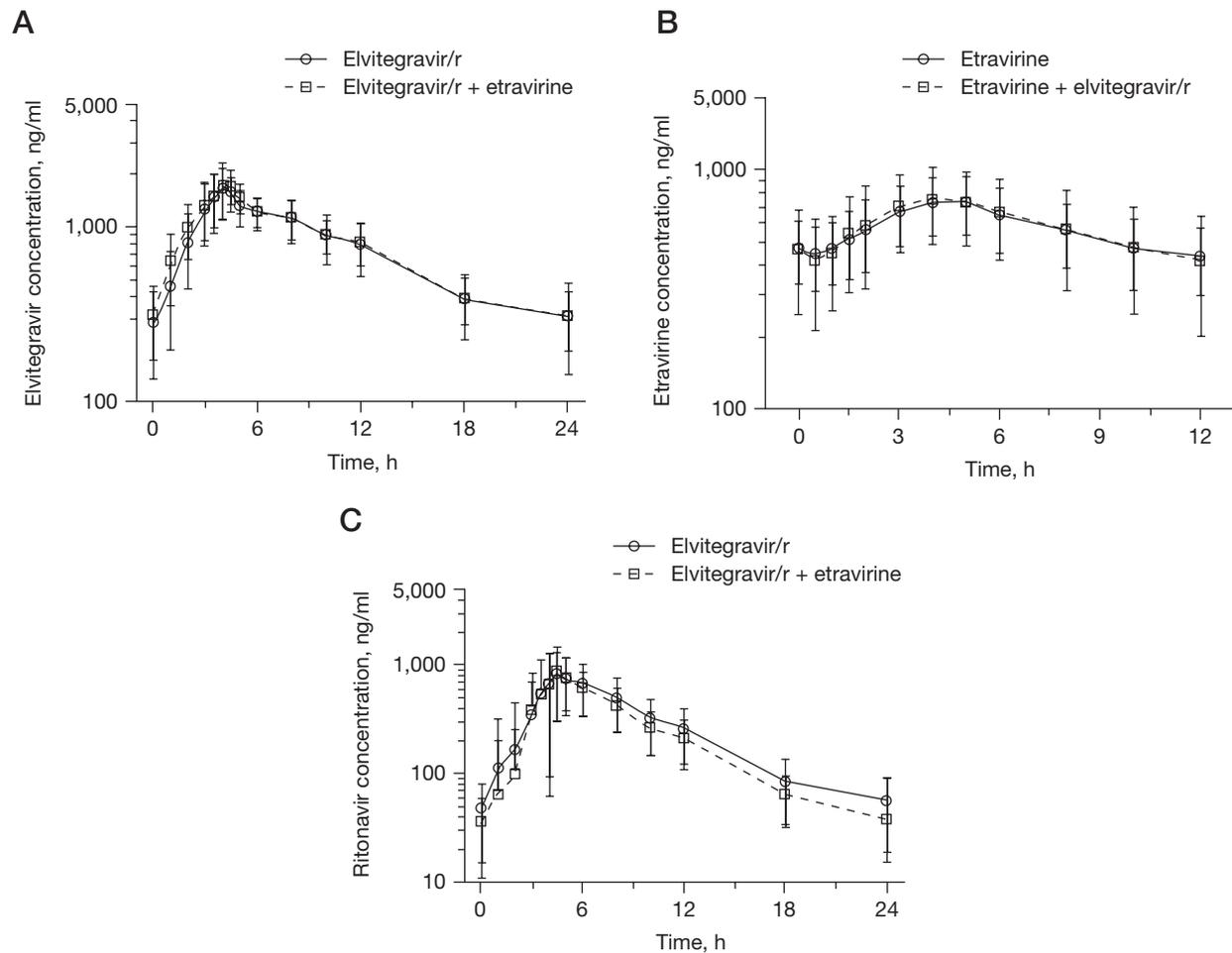
Ritonavir plasma concentration–time profiles following multiple dose administration of elvitegravir/r alone and in combination with etravirine are presented in Figure 2C and pharmacokinetic parameters are presented in Table 1. Plasma profiles of ritonavir were similar between the two treatments, with concentrations slightly lower in the combination arm. Ritonavir  $T_{max}$  (4.5 h in both groups) and  $T_{1/2}$  (4.6 and 4.3 h with elvitegravir/r and with elvitegravir/r and etravirine, respectively) were similar between the two study treatments. The GMR (%) and 90% CI for ritonavir  $C_{max}$  and  $AUC_{tau}$  were within the exploratory lack of alteration boundaries of 70–143%, whereas  $C_{tau}$  was lower in the combination treatment.

## Discussion

The potent antiviral activity independently demonstrated for elvitegravir and etravirine, each in combination with other antiretrovirals, in treatment-experienced HIV-infected patients coupled with the present data offers the potential to coadminister these two new antiretrovirals in patients with limited treatment options. This study showed that coadministration of elvitegravir/r and etravirine does not alter the pharmacokinetics of elvitegravir or etravirine based on predefined criteria. Following administration of study treatments, AEs were primarily grade 1, with no grade 3 or 4 AEs, serious AEs or discontinuations because of AEs, indicating that the study treatments were well tolerated.

Review of etravirine drug interaction data with HIV protease inhibitors provides a context for the present interaction data with elvitegravir/r [13]. Etravirine  $AUC_{tau}$  values decreased 76% and 37% with

Figure 2. Plasma concentration–time profiles for elvitegravir, etravirine and ritonavir



(A) Elvitegravir plasma concentration–time profiles (mean  $\pm$ SD; Group 1,  $n=17$ ) after administration of ritonavir-boosted elvitegravir (elvitegravir/r; 150/100 mg once daily) with or without etravirine (200 mg twice daily). (B) Etravirine plasma concentration–time profiles (mean  $\pm$ SD; Group 2,  $n=14$ ) after administration of etravirine (200 mg twice daily) with or without elvitegravir/r (150/100 mg once daily). (C) Ritonavir plasma concentration–time profiles (mean  $\pm$ SD; Group 1,  $n=17$ ) after administration of elvitegravir/r (150/100 mg/ml) with or without etravirine (200 mg twice daily).

tipranavir/r and darunavir/r, respectively, and increased approximately 50% with atazanavir [13]. Changes in amprenavir exposures (69% increase with fosamprenavir dosing) and atazanavir (38% decrease in minimum plasma concentration) have been observed upon coadministration with etravirine [16]. In comparison, etravirine and elvitegravir pharmacokinetics were not altered upon etravirine plus elvitegravir/r coadministration. Data for etravirine with HIV protease inhibitors illustrate that the involvement of multiple enzymes or transporters, as well as their mixed inhibitory or inductive effects, often confounds mechanistic delineation in three-way drug–drug interactions. Despite some overlap in their metabolic routes, etravirine and elvitegravir pharmacokinetics are unaffected upon coadministration. Although etravirine is a weak inducer of CYP3A,

coadministration of a low boosting dose (for example, 100 mg once daily) of ritonavir fully countered the potential inductive effect of etravirine. These results underscore the need for clinical evaluation of three-way interactions. Results of this study also reinforce the lack of a significant role of Pgp or the CYP2C subfamily (inhibited by etravirine) in elvitegravir disposition, in agreement with a lack of pharmacokinetic changes in elvitegravir upon coadministration with tipranavir/r, a net Pgp inducer at steady-state, or omeprazole, the proton pump inhibitor and prototypical CYP2C19 substrate and inhibitor [17,18]. Elvitegravir/r has previously been shown to lack clinically relevant drug interactions with nucleos(t)ide reverse transcriptase inhibitors and several ritonavir-boosted protease inhibitors [15,17,19–21]. Accordingly, the observed

**Table 1.** Pharmacokinetic parameters of elvitegravir, etravirine and ritonavir following multiple dose administration of ritonavir-boosted elvitegravir or etravirine alone and in combination

Parameter	Elvitegravir			ETR	Etravirine			Ritonavir		
	EVG/r	EVG/r + ETR	GMR, % (90% CI)		EVG/r + ETR	GMR, % (90% CI)	EVG/r + ETR	GMR, % (90% CI)		
Mean C <sub>max</sub> <sup>a</sup> , ng/ml	1,700	1,830	107	852	865	102	970	956	97.6	
(CV, %)	(28.2)	(28.4)	(101–113)	(44.1)	(42.0)	(85.8–120)	(57.1)	(61.9)	(86.2–110)	
Mean AUC <sub>tau</sub> <sup>*</sup> , ng•h/ml	17,600	18,500	106	6,960	7,050	97.6	6,350	5,550	87.7	
(CV, %)	(27.3)	(19.5)	(99.9–113)	(31.4)	(42.7)	(88.3–108)	(46.9)	(44.9)	(80.8–95.1)	
Mean C <sub>tau</sub> <sup>a</sup> , ng/ml	311	311	106	433	418	89.6	55.3	36.9	70.6	
(CV, %) <sup>†</sup>	(53.4)	(36.8)	(97.0–116)	(31.2)	(51.7)	(82.7–97.1)	(65.7)	(58.8)	(63.7–78.2)	
Median T <sub>max</sub> <sup>a</sup> , h	4.0	4.5	NA	4.5	4.0	NA	4.5	4.5	NA	
(IQR)	(4.0–4.5)	(4.0–4.5)		(4.0–5.0)	(3.0–5.0)		(4.0–5.0)	(4.0–5.0)		
Median T <sub>1/2</sub> <sup>a</sup> , h	8.0	8.2	NA	9.5	7.9	NA	4.6	4.3	NA	
(IQR)	(6.6–8.8)	(6.8–9.2)		(8.2–11.2)	(6.2–10.3)		(4.3–5.1)	(4.1–4.5)		

Ritonavir-boosted elvitegravir (EVG/r)  $n=17$ , etravirine (ETR)  $n=14$ . Data were rounded to be presented as three significant figures. <sup>a</sup>0–24 h for EVG and ritonavir; 0–12 h for ETR. <sup>\*</sup>24 h after dosing for EVG and ritonavir; 12 h after dosing for ETR. AUC<sub>tau</sub><sup>\*</sup>, area under the plasma concentration–time curve over the dosing interval; CI, confidence interval; C<sub>tau</sub><sup>a</sup>, concentration at the end of the dosing interval; CV, coefficient of variation; GMR, geometric mean ratio; IQR, interquartile range; NA, not applicable; T<sub>max</sub><sup>a</sup>, time to maximum concentration; T<sub>1/2</sub><sup>a</sup>, elimination half-life.

lack of alteration in elvitegravir pharmacokinetics in this study is consistent with its established metabolic and transport properties.

The processes affecting etravirine pharmacokinetics upon elvitegravir/r coadministration are multifactorial. Data from etravirine protease inhibitor studies (atazanavir and ritonavir-boosted atazanavir) suggest that elvitegravir/r, a net inhibitor of CYP3A4, might increase etravirine systemic concentrations [22]. However, low-dose ritonavir (100 mg twice daily) has been shown to induce CYP2C9 and 2C19, which contribute towards etravirine metabolism [23]. Similarly, etravirine exposures (AUC<sub>tau</sub>) are 50% higher with the CYP3A inhibitor atazanavir 400 mg, but only 30% higher with ritonavir-boosted atazanavir 300/100 mg despite greater than twofold higher atazanavir exposures with the latter treatment. Furthermore, etravirine undergoes glucuronidation, a pathway known to be induced by ritonavir [24–26]. Anecdotal evidence also suggests induction of glucuronidation by low-dose ritonavir (100 mg) [27], although the magnitude of this effect is unknown because of a paucity of direct clinical interaction data between glucuronidation substrates and low-dose ritonavir. Thus, ritonavir might display dose-dependent mixed inhibitory or inductive effects towards the multiple CYP (CYP3A and CYP2C) and glucuronidation enzymes involved in etravirine metabolism. The lack of observed pharmacokinetic alteration when etravirine is coadministered with elvitegravir/r is probably a net result of this complex interplay.

In conclusion, elvitegravir/r and etravirine do not undergo clinically relevant drug–drug interactions. Therefore, these agents could be coadministered without dose adjustment in HIV-infected patients.

## Acknowledgements

Some of the data from this study were presented at the *47th Interscience Conference on Antimicrobial Agents and Chemotherapy*, 17–20 September 2007, Chicago, IL, USA. Financial support for the clinical study discussed in this manuscript was provided by Gilead Sciences, Inc.

## Disclosure statement

SR, SW and BPK are employees of Gilead Sciences, Inc. (Foster City, CA, USA). TNK and RM are employees of Tibotec, Inc. (Yardley, PA, USA).

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Accepted for publication 21 August 2008