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Drug Interactions with Cobicistat- or Ritonavir-Boosted Elvitegravir

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Abstract

Cobicistat and ritonavir are structurally distinct compounds that both potently inhibit cytochrome P450 (CYP) 3A, the metabolizing enzyme primarily responsible for the elimination of several antiretroviral medications, and, as such, are pharmacokinetic boosters for antiretroviral agents that require longer dosing intervals. Recently, cobicistat was approved for the treatment of HIV-1 infection in treatment-naive adults as a component of a single-tablet regimen consisting of cobicistat-boosted elvitegravir plus emtricitabine and tenofovir disoproxil fumarate. While studies have demonstrated that boosting with either cobicistat or ritonavir results in comparable plasma exposure of the target antiretroviral agent, a better understanding of drug-drug interactions between cobicistat- and ritonavir-boosted antiretrovirals and other medications will inform treatment decisions in HIV-infected patients. In connection with their distinct structural properties, COBI and RTV differ with respect to their drug-drug interaction profiles. Compared with ritonavir, cobicistat lacks induction potential and is a more specific inhibitor of 3A and therefore, has reduced effects on other CYP isoforms. To date, more studies have assessed ritonavir drug-drug interactions with other medications than have assessed cobicistat drug-drug interactions. The objective of this article is to review the drug-drug interactions when cobicistat- or ritonavir-boosted elvitegravir, cobicistat, or elvitegravir/cobicistat/emtricitabine/tenofovir are coadministered with antiretroviral therapies or drugs that are either substrates, inducers, or inhibitors of the CYP3A metabolic pathway, as well as with drugs that alter intra-gastric pH or are substrates of P-gp, in order to inform the proper use of elvitegravir/cobicistat/emtricitabine/tenofovir. **(AIDS Rev. 2016;18:101-11)**

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Key words

Anti-HIV agent. Cobicistat. Drug interaction. Elvitegravir. Ritonavir. Tenofovir disoproxil fumarate.

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Introduction

Cobicistat (COBI) and ritonavir (RTV) potently inhibit cytochrome P450 (CYP) 3A, the metabolizing enzyme primarily responsible for the elimination of several antiretroviral medications substrates for CYP3A, such as elvitegravir (EVG), typically have limited bioavailability and a shortened half-life due to CYP3A-dependent clearance. However, COBI and RTV can enhance the systemic exposure of these agents by inhibiting CYP3A[1.] Studies have demonstrated that EVG, atazanavir (ATV), and darunavir (DRV) have comparable plasma pharmacokinetic parameters when boosted by either COBI or ritonavir (RTV)[2-4]. In contrast to RTV, COBI is devoid of HIV activity, is a weaker inhibitor of CYP2D6, and does not inhibit or induce other CYP enzymes. Furthermore, COBI does not induce uridine glucuronosyltransferase (UGT) and has similar inhibitory effects on the P-glycoprotein transporter (P-gp).[1,5]

In a growing number of countries, COBI is approved as a component of a single-tablet regimen for the treatment of HIV-1 infection in adults. This regimen consists of EVG (150 mg), COBI (150 mg), emtricitabine (FTC; 200 mg), and tenofovir disoproxil fumarate (TDF; 300 mg)[6]. The combination of EVG/COBI/FTC/TDF was first approved by the US Food and Drug Administration (FDA) in August 2012 based on the 48-week primary outcomes of two global phase III trials[6-8]. These trials demonstrated non-inferior efficacy of EVG/COBI/FTC/TDF compared with both efavirenz (EFV) plus FTC/TDF and RTV-boosted ATV plus FTC/TDF, and suggested that EVG/COBI/FTC/TDF had better tolerability. EVG/COBI/FTC/TDF was associated with a lower incidence of abnormal dreams, dizziness, insomnia, and rash than EFV plus FTC/TDF and lower incidence of diarrhea and ocular icterus than ATV/RTV plus FTC/TDF, although EVG/COBI/FTC/TDF had higher incidence of nausea compared to EFV plus FTC/TDF[7,8]. Furthermore, EVG/COBI/FTC/TDF demonstrated non-inferior efficacy after 96 weeks of treatment, consistent with findings at week 48[9,10]. Similarly, COBI-boosted ATV has demonstrated long-term non-inferior efficacy and comparable safety and tolerability to RTV-boosted ATV[11,12]. Also, COBI-boosted DRV (800 mg DRV/150 mg COBI), as a single-tablet formulation, has shown to have pharmacokinetic, efficacy, and safety profiles similar to DRV 800 mg with 100 mg RTV[13,14.]

A clearer understanding of drug-drug interactions between COBI- and RTV-boosted antiretrovirals and other medications will provide guidance for clinicians treating HIV-1-infected patients who have comorbidities and may be taking multiple medications. In connection with their distinct structural properties, COBI and RTV differ with respect to their drug-drug interaction profiles.

Drug-drug interactions

Understanding the pharmacodynamics and drug-drug interactions of COBI, RTV, and EVG is critical for predicting the safety and efficacy of administering these agents with concomitant medications. Drugs that induce CYP3A activity are expected to increase clearance of EVG, resulting in lower plasma concentrations, potentially decreasing EVG's therapeutic efficacy and leading to the development of viral resistance. Cobicistat is an inhibitor of CYP2D6 as well as P-gp, breast cancer resistance protein (BCRP), and the organic anion transporters P1B1 (OATP1B1) and OATP1B35,[15,16.] As a result, coadministration of COBI with drugs that are primarily metabolized by CYP3A or CYP2D6, or are substrates of P-gp, BCRP, OATP1B1, or OATP1B3, may result in increased plasma concentrations of the coadministered agent. Elvitegravir is a modest inducer of CYP2C9; coadministration of EVG-containing treatment regimens may decrease the plasma concentration of drugs that are primarily metabolized by this enzyme[17]. Similarly, RTV inhibits CYP3A and CYP2D6 and induces CYP1A2, CYP2C9, CYP2C19, and CYP2B6, among other enzymes, including glucuronosyl transferase[18-21.] These induction effects are not observed with COBI. Hence, coadministration of RTV with drugs that are primarily metabolized by CYP3A or CYP2D6 will result in increased plasma concentrations, whereas coadministration of RTV with drugs that are primarily metabolized by CYP1A2, CYP2C9, CYP2C19, CYP2B6, and glucuronosyl transferase will result in decreased plasma concentrations, potentially leading to therapeutic failure of the agents reliant on the enzyme families induced by RTV.

Drug-drug interaction studies are primarily conducted in healthy volunteers to control as many factors as possible, such as the effect of disease status on drug metabolism. While a disease state may impact the ultimate response to a drug, including drug-drug interactions, the type and the magnitude of interactions are generally expected to be comparable in healthy volunteers and HIV-1-infected patients6. All drug-drug interaction studies discussed in this review were

Table 1. Plasma and geometric mean ratio pharmacokinetic parameters for cobicistat versus ritonavir-boosted antiretrovirals[2-4]

Coadministered drug	Dose of coadministered drug	Cobicistat or ritonavir booster dose	N	Plasma pharmacokinetic parameters of coadministered drug		
				C_{max}, ng/ml	AUC, ng h/ml	C_{min}, ng/ml
Elvitegravir	150 mg	Cobicistat 150 mg*	39	2,660 (27.6)	27,000 (29.4)	490 (52.9)
		Ritonavir 100 mg	38	2,500 (32.1)	22,500 (23.4)	410 (40.5)
		GMR (90% CI)		108 (100, 116)	118 (110, 126)	110 (95.3, 127)
Atazanavir	300 mg	Cobicistat 150 mg	34	4,880 (24.9)	55,900 (28.2)	1,330 (42.7)
		Ritonavir 100 mg	36	5,270 (23.6)	55,200 (27.6)	1,340 (40.8)
		GMR (90% CI)		92.3 (85.1, 100)	101 (94.5, 108)	97.6 (88.1, 108)
Darunavir	800 mg	Cobicistat 150 mg	33	7,740 (21.8)	81,100 (31.0)	1,330 (50.7)
		Ritonavir 100 mg	31	7,460 (20.3)	80,000 (34.0)	1,870 (83.3)
		GMR (90% CI)		103 (100, 106)	102 (97.4, 106)	69.4 (59.0, 81.7)

AUC: area under the curve; CI: confidence interval; C_{max}: maximum concentration; C_{min}: minimum concentration; GMR: geometric mean ratio.
*Fixed-dose combination of elvitegravir/cobicistat/emtricitabine/tenofovir (150/150/200/300 mg).

conducted with EVG/COBI/FTC/TDF, EVG coadministered with COBI or RTV, or COBI. The pharmacokinetic effects of COBI or RTV on EVG were considered bioequivalent, while the effects of EVG/COBI/FTC/TDF on coadministered drugs were extrapolated from studies assessing COBI- or RTV-boosted EVG5. This review focuses on clinically relevant drug-drug interactions when these commonly prescribed agents are coadministered with drugs that are either substrates, inducers, or inhibitors of the CYP3A metabolic pathway, as well as with drugs that alter intra-gastric pH, are substrates of P-gp, or represent other antiretroviral therapies (Tables 1-3). Studies were included if pharmacokinetic data was available. Theoretical or extrapolated drug-drug interactions, such as with fluticasone, were not included in this review, even though clinically relevant. Data on medications not widely prescribed are only discussed in the text and were excluded from the tables. This review will discuss drug-drug interaction studies involving EVG coadministered with COBI or RTV, including two HIV protease inhibitors, ATV and DRV, that are recommended in the HIV treatment guidelines as part of the preferred regimens by the Department of Health and Human Services[22].

Drug-drug interactions with CYP3A inhibitors

Atazanavir

The pharmacokinetic interactions between EVG and RTV- or COBI-boosted ATV were characterized in two studies. In the first study, 33 subjects received once-daily EVG/RTV (200 mg/100 mg), ATV/RTV (300 mg/100 mg), or EVG (200 mg) plus ATV/RTV (300/100 mg) for 14 days using a randomized crossover design[23]. When ritonavir-boosted EVG and ATV were coadministered, EVG mean AUC, C_{max}, and C_{trough} increased by 100, 85, and 188%, respectively, compared with EVG/RTV alone. This most likely resulted from ATV-mediated inhibition of UGT1A1, which serves as a secondary pathway for EVG metabolism. In contrast, ATV mean AUC, C_{max}, and C_{trough} were 21, 16, and 34% lower, respectively, when ATV was coadministered with EVG/RTV compared to EVG/ATV alone. While ATV pharmacokinetics were within the equivalence bounds determined for C_{max} and AUC, ATV C_{trough} was lower upon coadministration with EVG/RTV.

Given that EVG exposure was higher when coadministered with ATV/RTV, the second arm of the study (n=20) evaluated a reduced 85 mg EVG dose which was

Table 2. Relative effects of cobicistat versus ritonavir on the pharmacokinetics of elvitegravir when administered with other drugs

Coadministered drug and dose	Elvitegravir dose	Cobicistat or ritonavir booster dose	N	PK effect	GMR of elvitegravir pharmacokinetic parameters (90% CI) No effect = 1.00		
					C_{max}	AUC	C_{min}
Atazanavir							
300 mg once daily[24]	85 mg once daily	Cobicistat 150 mg once daily	18	↔	0.84 (0.61, 1.15)*	1.17 (0.88, 1.56)	1.83 (1.17, 2.86)
300 mg once daily[23]	85 mg once daily	Ritonavir 100 mg once daily	20	↔	0.90 (0.81, 1.02)	1.07 (0.95, 1.21)	1.38 (1.18, 1.61)
300 mg once daily[23]	200 mg once daily	Ritonavir 100 mg once daily	33	↑	1.85 (1.69, 2.03)	2.00 (1.85, 2.16)	2.88 (2.53, 3.27)
Antacid[39]							
20 ml single dose given simultaneously with elvitegravir	50 mg single dose	Ritonavir 100 mg single dose	11	↓	0.53 (0.47, 0.60)	0.55 (0.50, 0.60)	0.59 (0.52, 0.67)
20 ml single dose given four hours before elvitegravir			8	↔	0.95 (0.84, 1.07)	0.96 (0.88, 1.04)	1.04 (0.93, 1.17)
20 ml single dose given four hours after elvitegravir			10	↔	0.98 (0.88, 1.10)	0.98 (0.91, 1.06)	1.00 (0.90, 1.11)
20 ml single dose given two hours before elvitegravir			11	↔	0.82 (0.74, 0.91)	0.85 (0.79, 0.91)	0.90 (0.82, 0.99)
20 ml single dose given two hours after elvitegravir			10	↔	0.79 (0.71, 0.88)	0.80 (0.75, 0.86)	0.80 (0.73, 0.89)
Darunavir[25]							
600 mg twice daily	125 mg once daily	Ritonavir 100 mg twice daily	21	↔	1.13 (1.03, 1.24)	1.10 (0.99, 1.22)	1.18 (1.06, 1.31)
Famotidine[40]							
40 mg once daily given 12 hours after elvitegravir	150 mg once daily	Cobicistat 150 mg once daily	10	↔	1.02 (0.89, 1.17)	1.03 (0.95, 1.13)	1.18 (1.05, 1.32)
40 mg once daily given simultaneously with elvitegravir			16	↔	1.00 (0.92, 1.10)	1.03 (0.98, 1.08)	1.07 (0.98, 1.17)
Omeprazole							
40 mg once daily given two hours before elvitegravir[39]	50 mg once daily	Ritonavir 100 mg once daily	9	↔	0.93 (0.83, 1.04)	0.99 (0.91, 1.07)	0.94 (0.85, 1.04)
20 mg once daily given two hours before elvitegravir[40]	150 mg once daily	Cobicistat 50 mg once daily	11	↔	1.16 (1.04, 1.30)	1.10 (1.02, 1.19)	1.13 (0.96, 1.34)
20 mg once daily given 12 hours after elvitegravir[40]			11	↔	1.03 (0.92, 1.15)	1.05 (0.93, 1.18)	1.10 (0.92, 1.32)

(Continue)

Table 2. Relative effects of cobicistat versus ritonavir on the pharmacokinetics of elvitegravir when administered with other drugs *(continued)*

Coadministered drug and dose	Elvitegravir dose	Cobicistat or ritonavir booster dose	N	PK effect	GMR of elvitegravir pharmacokinetic parameters (90% CI) No effect = 1.00		
					C_{max}	AUC	C_{min}
Omeprazole							
150 mg once every other day	150 mg once daily	Cobicistat 150 mg once daily	12	↓	0.91 (0.84, 0.99)	0.79 (0.74, 0.85)	0.33 (0.27, 0.40)
Rosuvastatin[24]							
10 mg single dose	150 mg single dose	Cobicistat 150 mg once daily	10	↔	0.94 (0.83, 1.07)	1.02 (0.91, 1.14)	0.98 (0.83, 1.16)

AUC: area under the curve; CI: confidence interval; C_{max}: maximum concentration; C_{min}: minimum concentration; GMR: geometric mean ratio; PK: pharmacokinetic.
*Compared to elvitegravir/cobicistat 150 mg/150 mg.

expected to provide equivalent systemic exposure to EVG. Elvitegravir (85 mg) was coadministered with ATV/RTV (300/100 mg) and the resulting EVG exposure was compared to that following the other previously-described treatments, which were each administered for 10 days using a randomized crossover design[23]. The EVG mean AUC and C_{max} were similar, and C_{trough} was 38% higher upon coadministration with ATV/RTV. The EVG AUC and C_{max} were within bioequivalence boundaries, and the modestly higher C_{trough} was not considered to be clinically relevant for EVG safety or efficacy. Similarly, ATV mean AUC, C_{max}, and C_{trough} were all within bioequivalence boundaries.

To evaluate the ability of COBI to boost EVG and ATV, the pharmacokinetics of EVG/COBI (150 mg/150 mg) or ATV/RTV (150/100 mg) and EVG (85 mg) plus ATV/COBI (300/150 mg) were assessed in three cohorts (n = 18) using a fixed-sequence crossover design[24]. Following coadministration of EVG plus ATV/COBI, EVG mean $C_{max,}$ and AUC were similar, with the C_{trough} 83% higher compared with administration of EVG/COBI alone. Further, ATV mean C_{max}, AUC, and C_{trough} were also similar when compared to ATV/RTV administration. Despite slight changes in exposures, all EVG and ATV pharmacokinetic values were within protocol-specified lack-of-alteration boundaries, supporting the recommendation that EVG should be reduced to 85 mg daily when coadministered with ATV/COBI.

Darunavir

The pharmacokinetics of EVG/RTV (125/100 mg once daily), DRV/RTV (600/100 mg twice daily), and EVG (125 mg once daily) plus DRV/RTV (600/100 mg twice daily) were assessed in a randomized crossover study (n = 21) where each treatment was administered for 14 days[25]. When EVG plus DRV/RTV were coadministered, the mean C_{max}, AUC, and C_{trough} were 13, 10, and 18% higher for EVG, respectively, and were 11, 11, and 17% lower for DRV, respectively, compared with EVG/RTV or DRV/RTV administered alone. With the exception of DRV C_{trough}, the pharmacokinetic parameters for both agents were within the protocol-specified lack-of-alteration boundaries. The changes in DRV C_{trough} were similar, indicating it is unnecessary to adjust the dose of EVG or DRV/RTV when these agents are coadministered[25].

Similarly, there were no differences in the pharmacokinetics of DRV or COBI exposure when comparing DRV/COBI (600/150 mg twice daily) to EVG (150 mg once daily) plus DRV/COBI (600 /150 mg twice daily)[26]. In this randomized crossover study (n = 24), each treatment was administered for 10 days. Following coadministration of EVG plus DRV/COBI, DRV mean $C_{max,}$ AUC, and C_{trough} were similar compared with DRV/COBI alone. The EVG pharmacokinetic parameters were not calculated, but those for DRV were within protocol-specified lack-of-alteration boundaries. Together, these data indicate that coadministration of EVG plus COBI-boosted DRV may be a viable treatment option when DRV is limited to a 600 mg twice-daily dose.

However, when the dose of DRV was increased to 800 mg, DRV mean C_{trough} was 21% lower following coadministration of DRV/COBI plus EVG compared with DRV/COBI alone. Similarly, EVG C_{trough} and COBI

Table 3. Relative effects of cobicistat- or ritonavir-boosted elvitegravir or cobicistat on the pharmacokinetics of other drugs

Coadministered drug and dose	Elvitegravir dose	Cobicistat or ritonavir booster dose	N	PK effect	GMR of coadministered drug pharmacokinetic parameters (90% CI) No effect = 1.00		
					C_{max}	AUC	C_{min}
Atazanavir							
300 mg once daily[24]	85 mg once daily	Cobicistat 150 mg once daily	18	↔	0.76 (0.59, 0.97)	0.90 (0.73, 1.12)	0.80 (0.55, 1.17)
300 mg once daily[23]	85 mg once daily	Ritonavir 100 mg once daily	20	↔	0.96 (0.86, 1.08)	0.89 (0.80, 0.99)	0.82 (0.72, 0.95)
300 mg once daily[23]	200 mg once daily	Ritonavir 100 mg once daily	33	↔	0.84 (0.78, 0.90)	0.89 (0.80, 0.99)	0.65 (0.59, 0.72)
Buprenorphine/ Naloxone[33]							
Buprenorphine 16-24 mg once daily	150 mg once daily	Cobicistat 150 mg once daily	17	↑	1.12 (0.98, 1.27)	1.35 (1.18, 1.55)	1.66 (1.43, 1.93)
Nor-buprenorphine (primary metabolite of)			17	↑	1.24 (1.03, 1.49)	1.42 (1.22, 1.67)	1.57 (1.31, 1.88)
Naloxone 4-6 mg once daily			17	↓	0.72 (0.61, 0.85)	0.72 (0.59, 0.87)	ND
Darunavir							
800 mg once daily[26]	150 mg once daily	Cobicistat 150 mg once daily	–	↓	1.10 (N/D)	0.97 (N/D)	0.78 (N/D)
600 mg twice daily[26]	150 mg once daily	Cobicistat 150 mg twice daily	12	↔	1.01 (0.95, 1.07)	1.00 (0.94, 1.08)	0.95 (0.85, 1.07)
600 mg twice daily[25]	125 mg once daily	Ritonavir 100 mg twice daily	22	↔	0.89 (0.85, 0.94)	0.88 (0.82, 0.95)	0.82 (0.73, 0.92)
R-methadone (methadone: 80-120 mg once daily)	150 mg once daily	Cobicistat 150 mg once daily	11	↔	1.01 (0.91, 1.13)	1.07 (0.96, 1.19)	1.10 (0.95, 1.28)
S-methadone (methadone: 80-120 mg once daily)			11	↔	0.96 (0.87, 1.06)	1.00 (0.89, 1.12)	1.02 (0.89 1.17)
Norgestimate/ ethinyl estradiol[32]							
0.180, 0.215, or 0.250 norgestimate once daily	150 once daily	Cobicistat 150 mg once daily	15	↑	2.08 (2.00, 2.17)	2.26 (2.15, 2.37)	2.67 (2.43, 2.92)
0.025 mg ethinyl estradiol once daily			15	↓	0.94 (0.86, 1.04)	0.75 (0.69, 0.81)	0.56 (0.52, 0.61)
Rifabutin[24]							
150 mg once every other day	150 mg once daily	Cobicistat 150 mg once daily	12	↔	1.09 (0.98, 1.20)	0.92 (0.83, 1.03)	0.94 (0.85, 1.04)
25-O-desacetyl-rifabutin 150 mg once every other day			12	↑	4.84 (4.09, 5.74)	6.25 (4.09, 5.74)	4.94 (4.04, 6.04)
Rosuvastatin[24]							
10 mg single dose	150 mg single dose	Cobicistat 150 mg once daily	10	↔	1.89 (1.48, 2.42)	1.38 (1.14, 1.67)	ND

AUC: area under the curve; CI: confidence interval; C_{max}: maximum concentration; C_{min}: minimum concentration; GMR: geometric mean ratio; ND: no data; PK: pharmacokinetic.

mean AUC were 52% and 15-20% lower, respectively, compared with EVG/COBI/FTC/TDF administration[26]. While the DRV and EVG C_{trough} values were above the concentration necessary to produce 95% inhibition of the HIV-1 virus (DRV [EC50]: 55 ng/ml, EVG [IC95]: 45 ng/ml), these findings suggest coadministration of DRV at a dose of 800 mg and EVG/COBI/FTC/TDF should be avoided[27].

Drug-drug interactions with CYP3A inducers

Rifabutin

Rifabutin is an antimycobacterial agent that demonstrates similar efficacy, but less CYP3A induction, than rifampicin. Rifabutin is the preferred treatment for pulmonary tuberculosis in HIV-infected patients taking RTV-boosted protease inhibitors, given that coadministration with rifampicin profoundly decreases antiretroviral plasma exposure[28,29]. Using a fixed-sequence crossover design, the pharmacokinetics of rifabutin (300 mg once daily), EVG/COBI (150/150 mg once daily), and EVG/COBI (150/150 mg once daily) plus rifabutin (150 mg once every other day) were assessed in 12 subjects24. Following coadministration of rifabutin plus EVG/COBI, EVG mean C_{max}, and AUC were within bioequivalence boundaries, though C_{trough} was 67% lower than when EVG/COBI was given alone. The corresponding rifabutin pharmacokinetic parameters were comparable when rifabutin was administered alone. However, the C_{max}, AUC, and C_{trough} of the active rifabutin metabolite, 25-O-desacetylrifabutin, were 4.8-, 6.3-, and 4.9-fold higher, respectively, resulting in a 21% increase in antimycobacterial activity when rifabutin and EVG/COBI were coadministered. Notably, coadministration of EVG/COBI plus rifabutin resulted in an EVG C_{trough} of 164 ng/ml. Although this is above the concentration necessary to produce 95% inhibition of HIV-1 virus (45 ng/ml), coadministration of rifabutin and EVG/COBI is not recommended[27].

Interactions with drugs metabolized by CYP3A

Ethinyl estradiol and norgestimate

Given previously documented drug-drug interactions with oral contraceptives[30,31], German, et al. assessed the drug-drug interactions between EVG/COBI/FTC/TDF and Ortho Tricyclen Lo, an oral hormonal contraceptive consisting of norgestimate (0.180, 0.215, or 0.250 mg) and ethinyl estradiol (0.025 mg)[32]. In this open-label, fixed-sequence, two-part study conducted in 12 subjects, the pharmacokinetics of ethinyl estradiol, norgestimate, EVG, and COBI were evaluated on day 21 of the menstrual cycle of subjects who had been taking Ortho Tricyclen Lo for a 28-day lead-in period or for at least one month prior to day 1 of study enrollment. Following coadministration of Ortho Tricyclen Lo plus EVG/COBI/FTC/TDF, mean C_{max}, AUC, and C_{trough} of norelgestromin, norgestimate's metabolite, were 109, 126, and 167% higher, respectively, compared with administration of the hormonal contraceptive alone. In contrast, the corresponding ethinyl estradiol pharmacokinetic parameters were 6, 25, and 4.5% lower, respectively. Based on these findings, the authors recommend that hormonal contraception contain at least 30 µg of ethinyl estradiol when coadministered with EVG/COBI/FTC/TDF.

Methadone and buprenorphine/naloxone

Methadone and buprenorphine/naloxone are commonly used opioid replacement therapies and are known to undergo drug interactions with RTV-boosted protease inhibitors[33-35]. To assess interactions with COBI-boosted EVG, methadone (80-120 mg once daily) and buprenorphine/naloxone (16-24/4-6 mg once daily) were administered alone or concomitantly with EVG/COBI (150/150 mg once daily) in 17 subjects[33]. In both the methadone and buprenorphine/naloxone treatment groups, opioid plus EVG/COBI did not produce significant differences in methadone, buprenorphine, or naloxone exposure based on the pharmacokinetic parameters, C_{max}, AUC, and C_{trough}. Coadministration of EVG/COBI modestly increased plasma exposures of both buprenorphine and norbuprenorphine, the primary metabolite of buprenorphine. Buprenorphine mean C_{max}, AUC, and C_{trough} were 35, 12, and 65% higher, respectively, and the corresponding parameters for norbuprenorphine were 42, 24, and 57% higher compared with either opioid administered alone. However, these effects were not considered clinically significant. Based on the lack of clinically relevant pharmacokinetic interactions observed between methadone or buprenorphine/naloxone and EVG/COBI, dose adjustments are not necessary when coadministering these agents.

Interactions with drugs not metabolized by CYP3A

Modifiers of gastric pH

The pharmacophore of HIV integrase inhibitors, such as EVG, forms a complex with divalent cations (e.g., Mg^{2+}) at the active site of the integrase enzyme, resulting in antiviral activity[36,37]. Due to high concentration of divalent cations in antacids, there may be significant drug interactions with agents like EVG. Given the prevalent use of acid-reducing medications among HIV-1-infected patients, the potential for local gastrointestinal interactions between EVG and antacids has been evaluated[37-39]. In a phase 1, open-label, crossover study, EVG/RTV (50/100 mg once daily) and an antacid (Maalox Max® 20 ml once daily) were given either simultaneously or staggered by two hours or four hours37,39. Simultaneous coadministration of EVG/RTV plus an antacid resulted in substantial reductions in EVG C_{max}, AUC, and C_{trough}, by 47, 45, and 41%, respectively, compared with EVG/RTV administration alone. However, this effect was mitigated by separating the doses by both two and four hours. When staggering the dose of antacids by two hours before or after EVG/RTV, the corresponding pharmacokinetic parameters were 18, 15, and 10% lower and 21, 20, and 19% lower, respectively. Furthermore, when staggering the doses by four hours before or after EVG/RTV, the respective values were 5% lower, 4% lower, and 4% higher, respectively, and 2% lower, 2% lower, and no change, respectively. In both instances, EVG exposures were within the predefined bioequivalence boundaries, indicating that coadministration of EVG/RTV and antacids should be separated by at least two hours.

Drug-drug interactions between EVG and H2-receptor antagonists or proton-pump inhibitors have also been evaluated to differentiate cation-based interactions from reductions in gastrointestinal acidity[39,40]. A randomized fixed-sequence and randomized two-way crossover study evaluated the pharmacokinetics of COBI- and RTV-boosted EVG when given either simultaneously or staggered with the proton-pump inhibitor omeprazole (EVG/COBI and EVG/RTV), or the H2-receptor antagonist famotidine (EVG/COBI). The EVG/COBI (150/150 mg once daily) plus omeprazole (20 or 40 mg) or famotidine (40 mg) had no effect on COBI or EVG exposure regardless of whether drug delivery was simultaneous or staggered by at least two hours. Similarly, EVG/RTV (50/100 mg once daily) plus omeprazole (20 or 40 mg) failed to alter EVG exposure when omeprazole was administered two hours prior to EVG/RTV. These findings indicate that the observed interaction between EVG and antacids was likely due to local complexation with cations in the gastrointestinal tract rather than a broader pH-based effect. Based on these findings, dosing restrictions are not necessary when administering EVG/COBI/FTC/TDF with either proton-pump inhibitors or H2-receptor antagonists.

Rosuvastatin

In order to provide dosing recommendations for EVG/COBI/FTC/TDF, Ramanathan, et al. evaluated drug-drug interactions between EVG/COBI and the non-CYP3A-metabolized statin rosuvastatin[24]. Using a fixed-sequence, crossover design (n = 10), EVG/COBI (150/150 mg once daily) and rosuvastatin (10 mg) were administered either alone or concomitantly. While coadministration of rosuvastatin with EVG/COBI increased rosuvastatin mean C_{max} and AUC by 89 and 38%, respectively, coadministration of these agents had no effect on EVG or COBI exposure compared with EVG/COBI alone (pharmacokinetic parameters not reported). However, there were no clinically relevant interactions between rosuvastatin and EVG/COBI, suggesting that dose adjustment of rosuvastatin is not necessary with EVG/COBI/FTC/TDF.

Desipramine and digoxin

To evaluate the ability of COBI to mediate non-CYP3A interactions, a metabolic probe study was conducted using the validated phenotypic probes desipramine (CYP2D6 probe) and digoxin (P-gp probe)[15,17]. In this randomized, open-label, crossover study, desipramine (50 mg) or digoxin (0.5 mg) was administered alone or with COBI (150 mg) on day 10 of COBI administration. Coadministration of COBI with desipramine increased mean desipramine AUC_{last}, AUC_{inf}, and C_{max} by 58, 65, and 24%, respectively, relative to desipramine alone. Similarly, COBI and digoxin coadministration increased mean digoxin AUC_{last}, AUC_{inf}, and C_{max} by 20, 8, and 41%, respectively. Based on the < 2-fold increase in desipramine exposure parameters, the authors concluded that COBI may be classified as a weak CYP2D6 inhibitor. The small increase in pharmacokinetic parameters for these probe drugs indicates that clinically relevant interactions between COBI and CYP2D6 and P-gp substrates are not anticipated and no dose adjustments are necessary when coadministering these agents or other agents dependent on 2D6 or P-gp with COBI.

Table 4. Summary of drug-drug interactions

Antiretroviral*	Concomitant medication	Potential management
EVG	ATV/COBI	Reduce EVG dose to 85 mg daily
EVG	DRV 600 mg with RTV 100 mg twice daily	No dose adjustment necessary
EVG	DRV 600 mg with COBI 150 mg twice daily	No dose adjustment necessary
EVG/COBI	DRV 800 mg daily	Coadministration not recommended
EVG/COBI	Rifabutin	Coadministration not recommended
EVG/COBI	Ethinyl estradiol	Coadministration acceptable if hormonal contraception contains at least 30 µg ethinyl estradiol
EVG/COBI	Methadone	No dose adjustment necessary
EVG/COBI	Buprenorphine/naloxone	No dose adjustment necessary
EVG/COBI	Antacids	Separate administration by at least 2 hours
EVG/COBI	Proton pump inhibitors	No dose adjustment necessary
EVG/COBI	H2-antagonists	No dose adjustment necessary
EVG/COBI	Rosuvastatin	No dose adjustment necessary
EVG/COBI	Desipramine	No dose adjustment necessary
EVG/COBI	Digoxin	No dose adjustment necessary
EVG/COBI	Bupropion	No dose adjustment necessary

*See tables 2 and 3 for EVG dose utilized in the pharmacokinetic studies.

Cobicistat and ritonavir as antiretroviral boosters

While COBI and RTV are both structurally distinct strong CYP3A inhibitors, more studies to date have assessed RTV drug-drug interactions with other medications than have assessed COBI drug-drug interactions. Because of this, caution is warranted when coadministering COBI with drugs that are either contraindicated or require dosage modification with RTV[41]. Additional information on medications contraindicated with EVG/COBI/FTC/TDF can be found in the STRIBILD™ package labeling[6]. Importantly, COBI-boosted EVG or EVG/COBI/FTC/TDF only induces CYP2C9, whereas RTV-boosted antiretrovirals may affect additional CYP enzymes, including CYP2B6. As a result, RTV may be contraindicated for use with a broader range of medications than COBI. For instance, the antidepressant and smoking cessation aid bupropion is primarily metabolized by CYP2B6. While the coadministration of bupropion with RTV results in decreased bupropion levels[42], coadministering EVG/COBI/FTC/TDF with bupropion is not expected to alter the plasma concentrations of bupropion.

Conclusions

The combination EVG/COBI/FTC/TDF has a long elimination half-life, with maximum plasma concentrations two to four hours after dosing and an oral bioavailability that is maximized under fed conditions6. Although this facilitates once-daily dosing, a longer half-life or use of a pharmacokinetic booster may raise concerns that if a drug-drug interaction occurs, it will take longer to resolve than without the boosting agent. Drug-drug interaction studies conducted to date demonstrate that COBI- and RTV-boosted EVG can be safely coadministered with a variety of medications, including other antiretroviral drugs. Based on the findings presented in this review, it appears that many drug-drug interactions are not expected to be of clinical relevance, cause safety concerns, or result in the

need for dose adjustment (Table 4). Nevertheless, some medications, such as potent inducers, may produce significant decreases in COBI and EVG exposure and as a result are contraindicated for coadministration with EVG/COBI/FTC/TDF, given the increased risk of virologic failure and the possible development of viral resistance. In other cases, agents with the potential for interactions with COBI- and RTV-boosted EVG may be taken provided there is sufficient temporal separation of drug intake. For instance, antacids should be coadministered at least two hours before or after intake of EVG/RTV, and by extrapolation, EVG/COBI/FTC/TDF. Due to the limited number of studies on drug-drug interactions with COBI-boosted EVG, caution is warranted when coadministering EVG/COBI/FTC/TDF with drugs that are contraindicated or require dosage modification with RTV, given that both COBI and RTV are potent 3A4 inhibitors. However, there are some differences in the drug interaction profiles of COBI and RTV, as has been observed for bupropion. Future studies are necessary to fully explore the drug-drug interactions between COBI- and RTV-boosted antiretrovirals and other medications in order to fully provide recommendations for clinicians treating HIV-1-infected patients who may be taking multiple treatment regimens. In the absence of forthcoming drug-drug interaction studies, clinicians may need to extrapolate from available RTV-based drug-drug interaction studies or consult with a clinical pharmacist or pharmacologist to advise on patient therapy.

Declaration of interest

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