

DRUG INTERACTIONS WITH INTEGRASE INHIBITORS

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137)	Raltegravir (MK-0518), Isentress®
Usual/Studied Dose(s)	50 mg QD (integrase-naïve), 50 mg BID being studied for integrase-experienced patients	150 mg QD (boosted with cobicistat 150 mg)	400 mg po BID
Kinetic Characteristics	Dolutegravir is a substrate of UGT1A1 (primary pathway) and CYP3A4 (10-15%).	Elvitegravir is metabolized via a combination of oxidative (CYP3A) and glucuronidation pathways. It is known to be a moderate inducer of CYP3A, but not an inhibitor. It is boosted with ritonavir.	Raltegravir is primarily metabolized by glucuronidation (UGT1A1) and has no inhibitory or inductive potential in vitro. ¹
Food	Dolutegravir absorption is modestly increased with food according to fat content. Dolutegravir AUC ↑ 33%, 41% and 66% when administered with low-fat (300 kcal, 7% fat), moderate fat (600 kcal, 30% fat) and high fat food (870 kcal, 53% fat), respectively. Dolutegravir may be administered with or without food and without regard to fat content. ²	When administered as a fixed dose combination tablet with emtricitabine, tenofovir and the pharmacoenhancer GS-9350 in healthy volunteers, elvitegravir AUC _{inf} and C _{max} ↑ by 34% and 22%, respectively, with a light meal and by 87% and 56% with a high-fat meal. ³	Moderate and high-fat meals had no clinically meaningful effect on the PK parameters.

1) ANTIRETROVIRALS

Atazanavir	<p>In a randomized, open-label, two-period, crossover study, healthy adult subjects received dolutegravir 30 mg QD for 5 days, followed by the addition of either atazanavir 300/100 mg QD or atazanavir 400 mg QD for 14 days.</p> <p>Coadministration with ATV/RTV resulted in ↑ AUC 62%, ↑ C_{max} 34% and ↑ C_{trough} 121% of dolutegravir. Coadministration with atazanavir 400 mg QD resulted in ↑ AUC 91%, ↑ C_{max} 50% and ↑ C_{trough} 90% of dolutegravir.</p> <p>The combinations were well tolerated. No dose adjustment is necessary when dolutegravir is coadministered with boosted or unboosted atazanavir.⁴</p>	<p>Randomized, crossover, multiple dose study in healthy subjects (n=14) to investigate whether atazanavir could effectively boost EVG levels</p> <ul style="list-style-type: none"> • EVG/ATV 300mg/400mg daily VS EVG/r 300mg/100g daily: ↑ C_{max}: 8%, ↑AUC: 7%, ↓ C_{min} 10.1% • ATV and RTV showed similar inhibition of CYP 3A activity using midazolam probe • ATV + EVG VS historical controls: ↓ ATV AUC 30%, ↓ ATV C_{min}: 46%, potential of EVG to induce ATV metabolism? This requires further study. <p>Atazanavir 400mg daily has potential to boost EVG levels when RTV sparing regimen desired.⁵</p>	<p>In two healthy volunteer studies, raltegravir kinetics were measured in the presence of steady-state boosted or unboosted atazanavir. In the presence of chronic atazanavir 400 mg QD, single dose raltegravir 100 mg resulted in raltegravir AUC ↑ 72%, C_{max} ↑ 53%, C₁₂ ↑ 95% compared to raltegravir alone.</p> <p>In an open-label, random order, crossover study, healthy volunteers received either RAL 400 mg BID or RAL 400/ATV 400 mg QD each for 7 days. In the presence of ATV, RAL C_{max} ↑ 37% (p=0.4), C_{min} ↓ 68% (P<0.001), AUC unchanged, and formation of RAL-glucuronide was significantly decreased. RAL pk showed</p>
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			<p>high interindividual variability and significant intra-individual diurnal variation.⁶</p> <p>In an open-label, fixed sequence study, HIV-infected subjects received ATV 400 mg QD for 2 weeks, followed by ATV 400/RAL 800 mg QD for 10 days. Concomitant tenofovir, proton-pump inhibitors and other interacting drugs were not allowed. Compared to historical data of RAL 400 mg single dose, RAL C_{max} ↑ 2.81-fold, AUC ↑ 18%, C_{trough} ↓ 85%. 4/15 subjects had RAL C_{trough} <33 nM. Atazanavir concentrations were not reported.⁷</p> <p>In an open-label, sequential, two-period study, 17 HIV-infected, virally suppressed subjects with no history of virologic failure received ATV 600 mg daily plus RAL 400 mg BID for 2 weeks then 800 mg daily plus ATV 600 mg QD for 4 weeks, concomitantly with 3TC or FTC. The AUC over 24 hours of QD RAL was not significantly different from that of BID RAL, while the C_{max} was 33% higher and C_{min} was 81% lower with QD vs. BID RAL. Atazanavir kinetics were similar with both RAL dosing regimens. All patients maintained an undetectable viral load and the regimens were well tolerated.⁸</p> <p>In 21 HIV-infected treatment-experienced subjects who switched to ATV 200/RAL 400 mg BID due to resistance or toxicity issues, mean ATV AUC was 6257 ng/mL.hr, C_{trough} was 227 ng/mL (122-332), with 24% having ATV</p>

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			<p>Ctrough <150 ng/mL. Mean RAL AUC was 9085 ng/mL.h and Ctrough 132 ng/mL. 62% subjects had VL<50 at study entry, all reached undetectable after 2 weeks.⁹</p> <p>In healthy subjects, coadministration of atazanavir 300 mg BID and raltegravir 400 mg BID resulted in 11% ↓ Cmax, 17% ↓ AUC and 29% ↓ Cmin of atazanavir compared to atazanavir 300 mg BID alone; mean ATV Cmin was 817 ng/mL. Raltegravir AUC ↑ 54%, Cmax ↑ 39% and Cmin ↑ 48% when given with atazanavir. Mean QRS and PR interval increases were observed with atazanavir alone, and remained when raltegravir was coadministered; the clinical relevance of these changes is unclear.¹⁰</p> <p>In 22 HIV-positive subjects who switched to atazanavir 300 mg BID plus raltegravir 400 mg BID, steady-state pharmacokinetics were assessed. Geometric mean atazanavir AUC, Cmax and C12h were 14454 ng.h/mL, 2275 ng/mL and 419 ng/mL, respectively. Raltegravir geometric mean AUC, Cmax and C12 were 7112 ng.h/mL, 1680 ng/mL and 62 ng/mL, respectively. Three subjects (14%) had atazanavir Ctrough <100 ng/mL. At the time of switch, 79% of patients had VL<50 copies/mL; by 24 weeks, all subjects had undetectable viral loads.¹¹</p>
Atazanavir/ ritonavir	In a randomized, open-label, two-period, crossover study, healthy adult subjects received dolutegravir 30 mg	Two kinetic studies with ATV/r + EVG were completed in healthy subjects: <ul style="list-style-type: none"> • Study 1: EVG 200/100mg 	In a healthy volunteer study, raltegravir 400 mg BID plus atazanavir 300/ritonavir 100 mg QD for 10 days resulted in

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	<p>QD for 5 days, followed by the addition of either atazanavir 300/100 mg QD or atazanavir 400 mg QD for 14 days.</p> <p>Coadministration with ATV/RTV resulted in ↑ AUC 62%, ↑ Cmax 34% and ↑ Ctrough 121% of dolutegravir. Coadministration with atazanavir 400 mg QD resulted in ↑ AUC 91%, ↑ Cmax 50% and ↑ Ctrough 90% of dolutegravir.</p> <p>The combinations were well tolerated. No dose adjustment is necessary when dolutegravir is coadministered with boosted or unboosted atazanavir.⁴</p>	<p>daily + ATV/r 300/100mg daily. Combination led to ↑ EVG exposures compared to EVG 200/100mg daily alone. Proposed mechanism: inhibition of UGT1A1/3 metabolism by ATV/r. Combination also led to modestly ↓ ATV exposures compared to ATV/r 300/100mg daily alone.</p> <ul style="list-style-type: none"> • Study 2: EVG 85/100 mg daily + ATV/r 300/100mg daily. Combination led to equivalent EVG exposures compared to the usual EVG 150mg daily dose. ATV exposure unchanged with EVG 85mg daily compared to ATV/r 300/100mg alone. Authors state an 85mg dose of EVG should be used when given with ATV/r.¹² 	<p>modest increases in raltegravir plasma levels (AUC ↑ 41%, Cmax ↑ 24%, C12 ↑ 77%) compared to raltegravir alone.¹³ These interactions are not considered clinically meaningful. Based on these data, UGT1A1 inhibitors such as atazanavir and tenofovir may be coadministered with raltegravir without adjustment in the dose of raltegravir.¹⁴</p>
Darunavir/ ritonavir	<p>In an open-label, multiple dose, 2-period, 2-sequence crossover study, healthy subjects received dolutegravir 30 mg QD for 5 days followed by randomization to lopinavir/ritonavir 400/100 mg BID or darunavir/ritonavir 600/100 mg BID plus dolutegravir 30 mg QD for 14 days. Steady-state dolutegravir kinetics were not altered in the presence of lopinavir/ritonavir. In the presence of darunavir/ritonavir, dolutegravir AUC ↓ 22%, Cmax ↓ 11% and Ctrough ↓ 38%; these changes were considered not clinically significant.</p> <p>No dosage adjustment for dolutegravir is required when used with lopinavir/ritonavir or darunavir/ritonavir.¹⁵</p>	<p>In a crossover study, healthy volunteers were randomized to receive either elvitegravir 125 mg/ritonavir 100 mg QD, darunavir 600 mg/ritonavir 100 mg BID, or elvitegravir 125 mg QD plus darunavir 600 mg/ritonavir 100 mg BID, each for 14 days. Treatment was well tolerated, and there were no clinically-relevant effects on PK parameters for either drug suggesting that this combination can be co-administered without dose adjustment.¹⁶</p>	<p>In an open-label, sequential 2-period study, 18 healthy subjects received raltegravir 400 mg BID for 4 days followed by raltegravir 400 mg BID plus darunavir 600/ritonavir 100 mg BID for 12 days. Eight subjects developed rash (7 mild-moderate, 1 serious) between days 8-12 of period 2, and only six subjects completed the study. Based on limited data, raltegravir exposure appeared to be slightly decreased in the presence of darunavir/ritonavir (raltegravir AUC ↓ 29%, Cmax ↓ 33%, Cmin ↑ 38%), while darunavir parameters were similar to historical controls.¹⁷</p> <p>In 29 HIV-positive subjects receiving regimens including raltegravir, raltegravir/darunavir 600 mg/ritonavir 100 mg BID, or</p>

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			<p>raltegravir/darunavir/ritonavir/ etravirine BID, no differences in raltegravir Ctrough were noted between the groups.¹⁸</p> <p>14 HIV-positive patients on stable cART with VL<50 copies/mL participated in a 3 period, phase I pk study of TDF/FTC plus DRVr 800/100 mg QD (period 1), TDF/FTC/DRVr plus RAL 400 mg BID (period 2), and DRVr/RAL (period 3). Intensive PK were performed at steady-state in each period. No statistically significant differences in PK parameters were observed between period 2 versus 1. In period 3, darunavir Ctrough ↓ 36% and $t_{1/2}$ ↓ 31% compared to period 1, while DRV AUC, Cmax and RTV pk were not significantly changed. No difference in RAL pk was observed between periods 2 & 3. Four subjects had DRV Ctrough < 550 ng/mL (IC50 for PI-resistant virus) in period 3 only, all levels were >55 ng/mL.¹⁹</p> <p>In 15 HIV-positive subjects receiving DRV 800/100 mg QD plus RAL 400 mg BID, favourable pharmacokinetics of both drugs were observed and all patients had VL<37 copies/mL at week 24.²⁰</p> <p>In 24 HIV-positive subjects, no evidence of a pharmacokinetic interaction was found between DRVr 800/100 mg QD plus RAL 400 mg BID or 800 mg QD.²¹</p> <p>In 55 HIV-positive patients receiving darunavir-containing regimens with either NRTI or</p>

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			<p>raltegravir, 117 darunavir Ctrough samples were measured. The mean (\pm sd) darunavir concentration was higher in the NRTI group as compared to the raltegravir group (4.20 ± 2.35 vs. 2.63 ± 1.84 mg/L, $p=0.018$).</p> <p>However, the proportion of subjects with VL<50 copies/mL was higher in the raltegravir vs. NRTI arm (76.5% vs. 44%, respectively, $p=0.041$). In a multivariate linear regression model, raltegravir was independently related to lower darunavir levels. The mechanism for this unexpected interaction is unclear, but does not appear to be virologically significant.²²</p>
Efavirenz	<p>In an open-label, single sequence crossover study, healthy volunteers received dolutegravir 50 mg once daily for 5 days followed by dolutegravir 50 mg and efavirenz 600 mg QD for 14 days. In the presence of efavirenz, dolutegravir AUC \downarrow 57%, C_{max} \downarrow 39% and C_{trough} \downarrow 75%, likely via enzyme induction of UGT1A1 and CYP3A4. Dolutegravir concentrations remained 4-5 fold higher than the protein-adjusted IC₉₀ for WT virus. No dose adjustment required for coadministration in integrase-naïve patients.²³</p>		<p>In a placebo-controlled, 2 period study in 12 subjects who received 400 mg raltegravir alone or in combination with 600 mg EFV for 14 days, raltegravir kinetic parameters were modestly reduced in the presence of EFV:</p> <p>C_{12 hr} GMR [90% CI] = 0.79 [0.49, 1.28], AUC_{0-∞} = 0.64 [0.52, 0.80] and C_{max} = 0.64 [0.41, 0.98]. There were no substantial differences in T_{max} or t_{1/2}. This interaction is likely not clinically meaningful.²⁴ Based on these data, efavirenz may be coadministered with raltegravir without dose adjustment.¹⁴</p>
Etravirine (TMC125)	<p>In an open-label, two-period, crossover study, healthy adult subjects received dolutegravir 50 mg QD for 5 days, then added etravirine 200 mg BID with food for 14 days. In the presence of etravirine, dolutegravir AUC \downarrow 70%, C_{max} \downarrow 52% and C_{trough} \downarrow 88%.</p>	<p>In healthy subjects, no clinically relevant PK changes were observed for elvitegravir/ritonavir 150/100mg daily and etravirine 200mg BID compared to either drug administered alone. These 2 antiretrovirals can be used together without dose adjustment.²⁶</p>	<p>In healthy subjects, raltegravir 400 mg BID and etravirine 200 mg BID for 4 days resulted in modest decreases in raltegravir concentrations (AUC \downarrow 10%, 11% \downarrow C_{max}, 34% \downarrow C_{12h}) compared to raltegravir alone, while etravirine levels were not altered. These changes are not considered to be</p>

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	<p>In a second randomized, open-label crossover study, healthy subjects began with dolutegravir 50 mg QD for 5 days, then added etravirine 200 mg BID plus either lopinavir/ritonavir 400/100 mg BID or darunavir 600/100 mg BID for 14 days. Dolutegravir kinetics were not significantly altered when given with etravirine plus lopinavir/ritonavir. When coadministered with etravirine plus darunavir/ritonavir, dolutegravir AUC ↓ 25%, C_{max} ↓ 12% and C_{trough} ↓ 37%. These changes were considered not clinically significant.</p> <p>Dolutegravir may be coadministered with etravirine without a dosage adjustment if lopinavir/ritonavir or darunavir/ritonavir is concurrently administered.²⁵</p>		<p>clinically meaningful; etravirine may be coadministered with raltegravir without dose adjustment.²⁷</p> <p>In 29 HIV-positive subjects receiving regimens including raltegravir, raltegravir/darunavir 600 mg/ritonavir 100 mg BID, or raltegravir/darunavir/ritonavir/etravirine BID, no differences in raltegravir C_{trough} were noted between the groups.¹⁸</p> <p>A pharmacokinetic substudy was conducted in 10 HIV-positive subjects participating in the ANRS TRIO study. Patients received raltegravir 400 mg BID and darunavir 600/100 mg BID on day 1, and etravirine 200 mg BID was added on day 7. PK parameters were measured on days 6 and 28. Raltegravir and darunavir PK (C_{max}, C_{min} and AUC) were not significantly different in the presence of etravirine.²⁸</p>
Fosamprenavir	<p>Healthy volunteers received dolutegravir 50 mg daily for 5 days followed by the addition of fosamprenavir/r 700/100 mg BID for 10 days. In the presence of fosamprenavir/r, dolutegravir AUC ↓ 35%, C_{max} ↓ 24% and C_T ↓ 49%, while amprenavir pharmacokinetics were similar to historical values. Despite the reductions, dolutegravir concentrations remained well above the protein-adjusted IC₉₀ for wild-type HIV, and no dose adjustment is needed when dolutegravir is co-administered with fosamprenavir/r in integrase inhibitor-naïve subjects.²⁹</p>	<p>Healthy volunteers were randomized to receive either elvitegravir 125 mg/ritonavir 100 mg QD followed by elvitegravir 125 mg QD plus fosamprenavir 700 mg/ritonavir 100 mg BID, or fosamprenavir 700 mg/ritonavir 100 mg BID followed by elvitegravir 125 mg QD plus fosamprenavir 700 mg/ritonavir 100 mg BID, each for 14 days. Treatment was well tolerated, and there were no clinically relevant effects on PK parameters for either drug suggesting that this combination can be co-administered without dose adjustment.³⁰</p>	<p>In an open-label, 3-period study, subjects received raltegravir 400mg BID for 7days, then were randomized to 14 days of either fosamprenavir 1400mg BID, FPV/r 700mg/100mg BID, or FPV/r 1400mg/100mg QD alone or with RAL; subjects continued their randomized dose of FPV for 14 more days, adding or removing RAL based on receipt in Period 2. With fosamprenavir, raltegravir PK decreased, especially at higher RTV doses, but RAL GM C_{min} were 3-9.4-fold >RAL IC₉₅ for WT HIV (14.6ng/mL). With RAL, amprenavir PK decreased modestly; APV GM C_{min} for FPV/r 700/100 BID and FPV/r 1400/100 QD were 2.1-7.8-</p>

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			fold >APV EC ₉₀ documented for PI-naïve HIV+ pts (228ng/mL). The clinical implications of these results have yet to be determined. ³¹
Lersivirine (UK-453,061, a next-generation NNRTI)			Healthy volunteers were randomized to receive lersivirine 1000 mg QD, raltegravir 400 mg BID or the combination, each for 10 days. Lersivirine exposures were not affected by raltegravir (AUC ↓ 2%, C _{max} ↑ 5%), while raltegravir AUC ↓ 15%, C _{max} ↓ 28% and C _{min} ↑ 25% in the presence of lersivirine. A clinically relevant interaction is unlikely. ³²
Lopinavir/ ritonavir	In an open-label, multiple dose, 2-period, 2-sequence crossover study, healthy subjects received dolutegravir 30 mg QD for 5 days followed by randomization to lopinavir/ritonavir 400/100 mg BID or darunavir/ritonavir 600/100 mg BID plus dolutegravir 30 mg QD for 14 days. Steady-state dolutegravir kinetics were not altered in the presence of lopinavir/ritonavir. In the presence of darunavir/ritonavir, dolutegravir AUC ↓ 22%, C _{max} ↓ 11% and C _{trough} ↓ 38%; these changes were considered not clinically significant. No dosage adjustment for dolutegravir is required when used with lopinavir/ritonavir or darunavir/ritonavir. ¹⁵	Healthy volunteers (n=27) were randomized to receive either elvitegravir (EVG)/ritonavir 125/100mg daily for 2 weeks, then EVG/r 125/100 mg daily plus LPV/r 400/100mg BID for 2 weeks (group 1) or LPV/r 400/100mg BID for 2 weeks, then EVG/r 125/100 mg daily plus LPV/r 400/100mg BID for 2 weeks (group 2). EVG exposures were significantly increased in the presence of LPV/r: 75% ↑ AUC _{tau} , 52% ↑ C _{max} , 1382% ↑ C _{tau} , possibly via inhibition of UGT1A1/3 metabolism. LPV and RTV exposures were unchanged. Based on simulations, the authors recommend the dose of EVG be ↓ to 85mg daily when used with LPV/r. ³³	Open label, 3 period, sequential, crossover, multiple dose study in healthy subjects (n=12) to investigate kinetics of RAL 400 mg BID +/- LPV/r 400 mg/100mg BID. LPV/r had no effect on RAL AUC (RAL alone vs. combo: 5.3mg/L.h VS 5.4 mg/L.h) or C _{max} (RAL alone vs combo: 1698ng/ml VS 1687 ng/ml). Concomitant use of LPV/r led to ↓ RAL C _{12h} 30% (49.4ng/ml VS 34.4ng/ml). Raltegravir C _{min} stayed above IC ₉₅ (15ng/ml). Dose adjustment not recommended. ³⁴
Maraviroc		In a randomized, healthy subject study (n=28), volunteers received EVG/r 150/100mg QD for 10 days followed by EVG 150/100mg QD plus maraviroc 150mg BID for 10 days or vice versa. No clinically relevant changes	In an open-label, fixed sequence study, healthy subjects (n=18) received raltegravir 400 mg BID for 3 days, then maraviroc 300 mg BID for 6 days, then both drugs together for 3 days. Plasma drug concentrations

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		<p>in EVG/rtv kinetics were observed with the combination, while maraviroc exposures were ↑ in the presence of EVG/r (maraviroc AUC ↑ 2.15 fold, Cmax ↑ 2.86 fold). Therefore, reduce maraviroc dose to 150mg BID when used with EVG/r (same as dose recommendation for MVC + other CYP 3A4 inhibitors).³⁵</p>	<p>were measured on the last day of each phase. When maraviroc and raltegravir were co-administered, mean maraviroc AUC ↓ 14% and Cmax ↓ 20% and mean raltegravir AUC ↓ 37% and Cmax ↓ 33% respective relative to each drug administered alone. The mechanism may be via decreased absorption or increase in first-pass metabolism.</p> <p>The authors considered these changes not to be clinically significant, and dose adjustments are not suggested. Monitoring for safety and efficacy is recommended with this combination.³⁶</p>
Nevirapine			Drugs may be coadministered. No Raltegravir dose modification is required. ¹⁴
Nucleoside reverse transcriptase inhibitors		<p>In healthy subjects, elvitegravir 200 mg/ritonavir 100 mg QD did not have significant effects on the kinetics of single doses of abacavir or stavudine, or multiple dose zidovudine. Didanosine AUC ↓ 14%, Cmin ↓ 25% in the presence of elvitegravir/ritonavir. Elvitegravir exposure was not significantly affected by coadministration of the NRTIs. Elvitegravir may be coadministered with abacavir, didanosine, stavudine and zidovudine without dose adjustment.³⁷</p>	
Ritonavir		In healthy volunteers, ritonavir doses of 50, 100, and 200 mg plus elvitegravir 125 mg led to 41%, 54% and 56% ↓, respectively in apparent oral clearance of elvitegravir relative to 20 mg ritonavir. A	In a placebo-controlled, 2 period study in 12 subjects, the combination of 400 mg raltegravir and 100 mg RTV BID did not affect raltegravir parameters compared to raltegravir 400 mg

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		ritonavir dose approaching 100 mg provided maximal inhibition of CYP activity. These data support a once-daily ritonavir dose of 100 mg when combined with elvitegravir. ³⁸	administered alone. ²⁴
Tenofovir	No clinically relevant drug interaction observed when healthy subjects received dolutegravir 50 mg QD and tenofovir 300 mg QD for 5 days compared to either drug administered alone. Dolutegravir and tenofovir can be coadministered without dose adjustment. ³⁹	No clinically relevant drug interaction observed when healthy subjects (n=24) received GS-9137 50 mg/rtv 100 mg QD with or without emtricitabine 200 mg/tenofovir 300 mg QD. ⁴⁰ Combination may be coadministered without dosage adjustment.	In an open-label, 3-period study in 10 healthy subjects, combination of 400 mg raltegravir BID and 300 mg QD of tenofovir for 4 days led to modest increases in raltegravir AUC (49%) and Cmax (64%) while Cmin was unchanged; tenofovir AUC ↓ 10% and Cmin ↓ 13%. ⁴¹ Dose adjustment likely not necessary.
Tipranavir	In an open-label, single sequence crossover study, healthy volunteers received dolutegravir 50 mg once daily for 5 days, then tipranavir/ritonavir 500/200 mg BID for 7 days, followed by dolutegravir 50 mg QD and tipranavir/ritonavir 500/200 mg BID for 5 days. In the presence of tipranavir/ritonavir, dolutegravir AUC ↓ 59%, Cmax ↓ 46% and Ctough ↓ 76%, likely via enzyme induction of UGT1A1 and CYP3A4. Four of 18 subjects discontinued the study due to increases in ALT during the TPV/r dosing alone. Dolutegravir concentrations remained 4-5 fold higher than the protein-adjusted IC90 for WT virus. No dose adjustment required for coadministration in integrase-naïve patients. ²³	In a crossover study, healthy volunteers were randomized to receive either elvitegravir 200 mg/ritonavir 100 mg QD, tipranavir 500 mg/ritonavir 200 mg BID, or elvitegravir 200 mg QD plus tipranavir 500 mg/ritonavir 200 mg BID, each for 14 days. Treatment was well tolerated, and there were no clinically relevant effects on PK parameters for either drug suggesting that this combination can be co-administered without dose adjustment. ¹⁶	In an open-label, 3 period study in 15 healthy subjects, addition of 400 mg raltegravir BID to steady-state TPV 500/rtv 200 mg BID for 4 days led to a 55% ↓ in raltegravir Cmin, while AUC ↓ 24% and Cmax ↓ 18%. The combination was generally well tolerated. ⁴² Although this result is borderline for clinical significance for C12 hr, there are considerable safety and efficacy data available for the concomitant use of tipranavir and raltegravir from the Phase III studies, which support the efficacy of this combination. There was no clinically meaningful difference in the efficacy profile of raltegravir with or without coadministration of tipranavir. Based on these data, tipranavir may be coadministered with raltegravir without dose adjustment. In an open-label study of 7 treatment-experienced patients initiating salvage therapy, optimized background therapy (OBT)

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			and raltegravir 400 mg BID were initiated, with tipranavir 500/ritonavir 200 mg BID added on 4 days later; intensive 12-hour PK was performed at days 4 and 19. In the presence of steady-state tipranavir/ritonavir, raltegravir AUC ↓ 28%, Cmax ↑ 5% and C12 ↑ 7% compared to raltegravir without TPV/r. At week 24, viral load was <50 in all patients (n=6) who completed the study; 1 patient discontinued at week 3 due to GI intolerance. Two subjects developed grade 3 transaminase elevations which resolved (1 spontaneously, one upon dose reduction to tipranavir 500/100 mg BID). ⁴³

2) OTHER AGENTS

Acid-reducing agents	<p>Healthy volunteers received four single-dose treatments: dolutegravir (DTG) 50 mg alone, DTG 50 mg with a multivitamin (One a Day Maximum), DTG 50 mg with a liquid antacid (Maalox Advanced Maximum Strength), and DTG 50 mg 2 hours before an antacid. Dolutegravir AUC was ↓ by 33% when coadministered with a multivitamin. Dolutegravir AUC was ↓ 74% with simultaneous antacid administration, and ↓ 26% with staggered antacid administration.⁴⁴</p> <p>In an open-label study, healthy subjects received a single fasted dose of dolutegravir 50 mg, followed by omeprazole 40 mg once daily fasted for 5 days and a second single fasted dose of dolutegravir 50mg administered 2 hours</p>	<p>In a study of healthy volunteers, subjects received elvitegravir 50 mg/ritonavir 100 mg alone or with antacid (administered simultaneously or 2-4 before) or omeprazole 40 mg (given simultaneously). Simultaneous administration with antacid led to 45% ↓ AUC, 47% ↓ Cmax and 41% ↓ Cmin of elvitegravir. Separating antacid administration by 2 hours decreased elvitegravir exposure by 10-20%, while separating antacid administration by 4 hours did not affect elvitegravir exposure. Simultaneous administration of omeprazole did not affect elvitegravir exposure, while omeprazole concentrations were consistent with historical controls.⁴⁵</p> <p>Elvitegravir/ritonavir should</p>	<p>In a prospective crossover study, healthy volunteers received single-dose raltegravir 400 mg with and without an antacid (Maalox Plus® Extra Strength). In the presence of an antacid, raltegravir AUC0-12 was unchanged, but Tmax occurred sooner and C12 was reduced by 65% (p<0.0001) and 75% of subjects had C12<15 ng/mL (RAL IC95). The clinical relevance of this interaction is unclear. Further studies are needed to determine if this interaction remains after multiple dosing to steady state, and if it is mitigated by temporal separation.⁴⁷</p> <p>In healthy subjects who received omeprazole 20 mg daily for 4 days followed by a single dose of raltegravir 400 mg two hours after omeprazole on day 5,</p>
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	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137)	Raltegravir (MK-0518), Isentress®
	<p>following omeprazole on day 5. The combination was well tolerated. Omeprazole co-administration had no significant effect on dolutegravir exposure. Increased gastric pH by omeprazole had no effect on dolutegravir absorption; therefore, dolutegravir may be co-administered with PPIs or H2-antagonists without dose adjustment.⁴⁴</p> <p>Dolutegravir can be taken with proton pump inhibitors, H2-antagonists and multivitamins without dose adjustment but should be administered 2 hours before or 6 hours after antacids.</p>	<p>be separated by at least 2 (preferably 4) hours from antacids or vitamin or mineral supplements containing calcium, zinc or iron by at least 2 hours.⁴⁵</p> <p>In healthy subjects, the effects of omeprazole 20 mg QD or famotidine 40 mg QD were studied on the kinetics of elvitegravir/cobicistat. The exposures of EVG/cobi were not significantly altered when omeprazole was administered 2 hours before or 12 hours apart, or when famotidine was administered simultaneously or 12 hours apart.⁴⁶</p> <p>Elvitegravir/ritonavir and elvitegravir/cobicistat may be given with omeprazole without dosage adjustment.</p> <p>Elvitegravir/ritonavir and elvitegravir/cobicistat should be administered simultaneously with or 12 hours apart from H2-receptor antagonists.</p>	<p>raltegravir AUC ↑ 3-fold, Cmax ↑ 4-fold and Cmin ↑ 46% in the presence of omeprazole. Raltegravir T_{max} and t_{1/2} were not significantly affected. The mechanism is likely a consequence of increased bioavailability as raltegravir solubility is higher at higher gastric pH levels.⁴⁸</p> <p>HIV-positive subjects stable on raltegravir 400 mg BID received single dose famotidine 20 mg or omeprazole 20 mg once daily for 5 days (each given 2 hours prior to raltegravir). Coadministration of famotidine resulted in 45% ↑ AUC, 60% ↑ Cmax and 6% ↑ Ctrough of raltegravir. In the presence of omeprazole, raltegravir AUC, Cmax and Ctrough were increased by 39%, 51% and 24%, respectively. These increases are not likely clinically significant, and raltegravir may be coadministered with famotidine or omeprazole without dose adjustment.⁴⁹</p>
Buprenorphine/ naloxone			<p>In 12 HIV-negative subjects stabilized on at least 3 weeks of buprenorphine/naloxone therapy, administration of raltegravir 400 mg BID did not significantly affect AUC and Cmax of buprenorphine and norbuprenorphine compared to baseline values, while Tmax of both buprenorphine and norbuprenorphine increased significantly. Naloxone AUC and Cmax concentrations were also unchanged in the presence of steady-state raltegravir, and objective opioid withdrawal was not observed. The AUC0-24h and Cmin of RAL did not significantly differ from</p>

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137)	Raltegravir (MK-0518), Isentress®
			historical controls (5553 vs. 4428 hr*ng/mL) and (1070 vs. 1266 ng/mL). As such, buprenorphine/naloxone and raltegravir can be safely co-administered without dosage modification. ⁵⁰
Glucocorticoids			Drugs may be coadministered. No Raltegravir dose modification is required. ¹⁴
Ketoconazole		In a healthy volunteer study, subjects received elvitegravir 150/100 mg daily alone and then with ketoconazole 200 mg BID, each for 10 days, followed by 4 more days of ketoconazole 200 mg BID alone. In the presence of ketoconazole, modest increases in elvitegravir exposures were observed: 17% ↑ Cmax, 48% ↑ AUC, 67% ↑Ctau. Based on these results, clinically relevant drug interactions are not expected with EVG/r and additional CYP3A4 inhibitors. A maximum ketoconazole dose of 200 mg once daily is recommended when coadministering with boosted elvitegravir. ⁵¹	
Lamotrigine			In healthy subjects, raltegravir 400 mg BID for five days did not affect the pharmacokinetics of single dose lamotrigine 100 mg. The mean ratio of the AUC of lamotrigine-2N-glucuronide to lamotrigine was similar when lamotrigine was taken alone (0.35) or when taken with raltegravir (0.36). Raltegravir does not influence the glucuronidation of lamotrigine. ⁵²
Methadone			No dose adjustment is required for methadone when co-administered with raltegravir. ⁵³
Midazolam			In healthy volunteers, coadministration of raltegravir

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137)	Raltegravir (MK-0518), Isentress®
			400 mg BID with single dose midazolam 2 mg did not affect midazolam kinetics, confirming the lack of CYP3A4 inhibition/inducing activity of raltegravir.
Oral contraceptives		In healthy female subjects on OrthTri-Cyclen Lo® (norgestimate-NGM/ethinyl estradiol-EE 25 ug) for at least 2 months, the fixed dose tablet of elvitegravir/cobicistat/FTC/tenofovir ("quad") was co-administered daily on days 12-21 of the second cycle. When coadministered with the Quad, there was a 25% ↓ EE AUC and a 2-fold ↑ AUC and Cmax of NGM-active metabolite relative to NGM/EE administered alone. Elvitegravir and cobicistat concentrations were similar to historical controls. Compared to baseline, there was no change in progesterone levels, a similar ↓ in FSH and a larger ↓ in LH during treatment with the Quad + NGM/EE vs. NGM/EE alone. The authors recommend that an oral contraceptive containing at least 30 ug of EE be used when taking the Quad tablet. ⁵⁴	Coadministration of Ortho Tri-Cyclen™ (or generic equivalent) plus raltegravir 400 mg BID in healthy female subjects for 21 days did not substantially alter plasma exposure levels of either ethinyl estradiol or norelgestromin. It is unlikely for an alteration in the efficacy of Ortho Tri-Cycle™ for contraception to occur upon coadministration with raltegravir. ⁵⁵
Phenobarbital			Phenobarbital: The impact on UGT1A1 is unknown. Use with caution. ¹⁴
Phenytoin			The impact on UGT1A1 is unknown. Use with caution. ¹⁴
Pioglitazone			Drugs may be coadministered. No Raltegravir dose modification is required. ¹⁴
Pravastatin			In healthy adults who received pravastatin 40 mg QD plus raltegravir 400 mg BID for 4 days, pravastatin exposures were not significantly affected in the presence of raltegravir. Raltegravir AUC ↑ 13%, Cmax ↑ 31% and C12 ↓ 41% when

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137)	Raltegravir (MK-0518), Isentress®
			coadministered with pravastatin; however, since raltegravir efficacy is better correlated with AUC, this interaction is not likely to be clinically significant, and no dose adjustments are required. ⁵⁶
Ribavirin			In a retrospective analysis of 12 HIV/HCV co-infected subjects on RAL 400 mg BID prior to initiating ribavirin/pegylated interferon therapy, median RAL Ctrough was 0.071 mg/L at baseline and 0.051 mg/L when coadministered with ribavirin/peg IFN (p=0.98). Viral load remained undetectable and early HCV virologic response occurred in 8 patients. The combination was well tolerated, and no patient experienced major hepatic toxicity. ⁵⁷
Rifabutin		<p>Randomized, sequential, crossover study in HIV negative healthy volunteers:</p> <ul style="list-style-type: none"> • Treatment A: EVG/r 300mg/100mg daily (n=19) • Treatment B: EVG/r 300mg/100mg +/- rifabutin 150mg every other day (n=19) • Treatment C: Rifabutin 300mg daily (n=18) <p>EVG/r + RFB (150mg every other day): equivalent EVG AUC and RFB AUC relative to EVG/r or RFB (300mg daily) PK alone. Total antimycobacterial AUC ↑ 50% during coadministration. This is consistent with data from drug interaction studies with other RTV boosted agents.⁵⁸</p> <p>Decrease rifabutin to 150mg every other day or 150mg three times weekly when administered with EVG/r.</p>	In healthy adults who received raltegravir 400 mg BID with or without rifabutin 300 mg daily, coadministration of rifabutin resulted in 20% ↓ Cmin, 19% ↑ AUC and 39% ↑ Cmax of raltegravir; these changes are not considered to be clinically significant, and rifabutin may be coadministered with raltegravir without dose adjustment. ^{1, 59}
Ribavirin			In 14 healthy subjects who received raltegravir 400 mg

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137)	Raltegravir (MK-0518), Isentress®
			BID for 5 days plus single dose ribavirin 800 mg, raltegravir pharmacokinetics were not significantly affected by ribavirin. Ribavirin Cmax ↓ 21% and Tmax ↑ 39%, while Cmin and AUC were unchanged in the presence of raltegravir. This is unlikely to be of clinical significance or have an impact on the antiviral effects of ribavirin in HIV-1 and HCV co-infected subjects. ⁶⁰
Rifampin			In healthy subjects, single dose raltegravir 400 mg in the presence of rifampin 600 mg daily led to 61% ↓ Ctrough, 40% ↓ AUC and 38% ↓ Cmax of raltegravir. When raltegravir 800 mg BID was coadministered with rifampin 600 mg daily for 14 days, raltegravir C12 was ↓ 53%, AUC ↑ 27% and Cmax ↑ 62% in the presence of rifampin. ⁶¹ Product monograph recommends increasing raltegravir dose to 800 mg twice daily during coadministration with rifampin.¹ Administration of raltegravir 800 mg BID in two HIV-positive subjects receiving rifampin 600 mg QD for treatment of active tuberculosis resulted in raltegravir kinetic parameters comparable to historical data in HIV-positive subjects taking raltegravir 400 mg BID without rifampin. In the two cases, raltegravir was well tolerated. ⁶²
Sirolimus			Raltegravir may avoid interactions with certain immunosuppressives as it is primarily metabolized via glucuronidation and not by

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137)	Raltegravir (MK-0518), Isentress®
			CYP3A4. Case report of the successful use of raltegravir/3TC/abacavir and sirolimus in a 49 year old HIV/HCV+ patient who underwent liver transplantation. The patient was switched to this regimen after a series of medication modifications. Patient had developed renal insufficiency with hyperpotasemia and metabolic acidosis due to increased tacrolimus levels (> 25 ng/ml) related to atazanavir use. ⁶³
St Johns Wort			Drugs may be coadministered. No Raltegravir dose modification is required. ¹⁴
Telaprevir			In an open-label cross-over study in 20 HIV/HCV-negative healthy volunteers, co-administration of raltegravir 400 mg BID and telaprevir 750 mg q8h for 6 days with food did not affect telaprevir pharmacokinetics, while raltegravir exposures were increased (Cmin ↑ 78%, Cmax ↑ 26% and AUC ↑ 31%) possibly due to inhibition of intestinal P-gp by telaprevir. Exposure to raltegravir-glucuronide was similarly increased. This effect was not considered to be clinically relevant. ⁶⁴

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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