## DRUG INTERACTIONS WITH INTEGRASE INHIBITORS

| | **Dolutegravir (S/GSK 1349572), Tivicay®, Triumeq®** (coformulated with abacavir/lamivudine) | **Elvitegravir (GS-9137), Stribild®** (coformulated with cobicistat/tenofovir/ emtricitabine) | **Raltegravir (MK-0518), Isentress®** |
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| Usual/Studied Dose(s) | 50 mg QD (integrase-naïve), 50 mg BID (for integrase-resistant 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%). It is not a CYP inducer in vitro and at clinically relevant concentrations does not inhibit CYP, UGT or major transporters except for OCT2 and MATE1.<br>Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp in vitro.[1] | Elvitegravir is metabolized via a combination of oxidative (CYP3A) and glucoronidation pathways. It is a modest inducer of CYP2C9 and may decrease the plasma concentrations of CYP2C9 substrates. | Raltegravir is primarily metabolized by glucuronidation (UGT1A1) and has no inhibitory or inductive potential in vitro.[2] |
| 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.[3] | When administered as a fixed dose combination tablet with emtricitabine, tenofovir and cobicistat 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.[4]<br><br>Take with food. | Moderate and high-fat meals had no clinically meaningful effect on the PK parameters. |
| **1) ANTIRETROVIRALS** | | | |
| Atazanavir | 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.<br><br>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 | <u>Using ritonavir as a booster</u>: Randomized, crossover, multiple dose study in healthy subjects (n=14) to investigate whether atazanavir could effectively boost EVG levels<br>• EVG 300 mg/ATV 400 mg daily vs. EVG 300 mg/ ritonavir 100 mg daily: ↑ Cmax: 8%, ↑AUC: 7%, ↓ Cmin 10.1%<br>• ATV and RTV showed similar inhibition of CYP 3A activity using midazolam probe<br>• ATV + EVG vs. historical controls: ↓ ATV AUC | 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%, Cmax ↑ 53%, C12 ↑ 95% compared to raltegravir alone.<br><br>In an open-label, random order, crossover study, healthy volunteers received either RAL 400 mg BID or |

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| | 90% of dolutegravir.<br><br>The combinations were well tolerated. No dose adjustment is necessary when dolutegravir is coadministered with boosted or unboosted atazanavir.[5] | 30%, ↓ ATV Cmin: 46%, potential of EVG to induce ATV metabolism? This requires further study.<br>Atazanavir 400mg daily has potential to boost EVG levels when RTV sparing regimen desired.[6]<br><br><u>Using cobicistat as a booster</u>: A fixed sequence, crossover study in healthy subjects compared **EVG 85/co 150 mg plus ATV 300 mg QD** to either EVG 150/co 150 mg QD or ATV 300/ritonavir 100 mg QD:<br>• ***EVG 85/co 150/ATV 300 mg QD vs. EVG 150/co 150 mg QD:*** 17% ↑ AUC, 16% ↓ Cmax, 83% ↑ Ctau of EVG<br>• ***EVG 85/co 150/ATV 300 mg QD vs. ATV 300/ritonavir 100 mg QD:*** 10% ↓ AUC, 24% ↓ Cmax, 19% ↓ Ctau of atazanavir; changes not considered clinically relevant<br>All ATV, EVG, cobicistat PK were comparable with reference/historical data.[7] | **RAL 400/ATV 400 mg QD** each for 7 days. In the presence of ATV, RAL Cmax ↑ 37% (p=0.4), Cmin ↓ 68% (P<0.001), AUC unchanged, and formation of RAL-glucuronide was significantly decreased. RAL pk showed high interindividual variability and significant intra-individual diurnal variation.[8]<br><br>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 Cmax ↑ 2.81-fold, AUC ↑ 18%, Ctrough ↓ 85%. 4/15 subjects had RAL Ctrough <33 nM. Atazanavir concentrations were not reported.[9]<br><br>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 Cmax was 33% higher and Cmin was 81% lower with QD vs. BID RAL. Atazanavir kinetics were similar with both RAL dosing regimens. All patients maintained an undetectable |

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| | | | viral load and the regimens were well tolerated.[10]<br><br>Six HIV-infected patients on **ATV 300/100 mg QD** were intensified **with RAL 400 mg QD** for 10 days. RAL exposure was adequate in most patients with only 1 Ctrough <15 ng/mL (IC95). Atazanavir concentrations were similar to historical controls and all Ctrough>150 ng/mL.[11]<br><br>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, Ctrough was 227 ng/mL (122-332), with 24% having ATV 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.[12]<br><br>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 |

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| | | | unclear.[13]<br><br>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.[14] |
| Atazanavir/ ritonavir | 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.<br><br>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.<br><br>The combinations were well tolerated. No dose adjustment is necessary when dolutegravir is coadministered with boosted or unboosted atazanavir.[5] | Two kinetic studies with ATV/r + EVG were completed in healthy subjects:<br>• **Study 1:** EVG 200/100mg 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.<br>• **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.<br>Authors state an 85mg dose | In a healthy volunteer study, raltegravir 400 mg BID plus **atazanavir 300/ritonavir 100 mg QD** for 10 days resulted in modest increases in raltegravir plasma levels (AUC ↑ 41%, Cmax ↑ 24%, C12 ↑ 77%) compared to raltegravir alone.[16] 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.[2] |

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| | | of EVG should be used when given with ATV/r.[15] | |
| Darunavir/ 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%, Cmax ↓ 11% and Ctrough ↓ 38%; these changes were considered not clinically significant.<br><br>No dosage adjustment for dolutegravir is required when used with lopinavir/ritonavir or darunavir/ritonavir.[17, 18] | 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.[19]<br><br>In a fixed-sequence crossover study assessing the kinetics of **darunavir 600/cobicistat 150 mg BID plus either elvitegravir 150 mg QD or etravirine 200 mg BID** vs. darunavir 600/ cobicistat 150 mg BID alone:<br>• darunavir exposures were not significantly affected by coadministration with either elvitegravir or etravirine<br>• elvitegravir and etravirine exposures were comparable to historical reference data[20]<br><br>Kinetics of **darunavir 800 mg and elvitegravir 150/ cobicistat 150 mg once daily**:<br>• elvitegravir Ctrough 52% ↓ and AUC ↓ 20% vs. elvitegravir/cobicistat/TDF-FTC (Stribild®)<br>• darunavir Ctrough ↓ 21% and AUC ↓ 3% vs. darunavir 800/cobicistat 150 mg QD[20] | 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.[21]<br><br>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 Ctrough were noted between the groups.[22]<br><br>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 |

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| | | Clinical significance unclear. Use combination with caution until further data available. | 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.[23]<br><br>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.[24]<br><br>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**.[25]<br><br>In 55 HIV-positive patients receiving darunavir-containing regimens with either NRTI or raltegravir, 117 darunavir Ctrough samples were measured. The mean (± 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). 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 |

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| | | | this unexpected interaction is unclear, but does not appear to be virologically significant.[26] |
| Efavirenz | In an open-label, single sequence crossover study, healthy volunteers received dolutegravir 50 mg once daily for 5 days followed by DTG 50 mg and efavirenz 600 mg QD for 14 days. In the presence of efavirenz, DTG AUC ↓ 57%, Cmax ↓ 39% and Ctrough ↓ 75%, likely via enzyme induction of UGT1A1 and CYP3A4. Dolutegravir concentrations remained 4-5 fold higher than the protein-adjusted IC90 for WT virus.[27]<br><br>A dose adjustment to dolutegravir 50 mg BID is recommended in treatment-naïve or treatment-experienced, INSTI-naïve patients. Alternative combinations that do not include metabolic inducers should be considered where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[18]<br><br>In pharmacokinetic simulation models, dolutegravir and efavirenz concentrations were predicted following a switch from efavirenz 600 mg daily to dolutegravir 50 mg daily. Following the switch, efavirenz concentrations stayed above the MEC up to 3 days and dolutegravir Ctrough achieved MEC 3 days post switch. Since dolutegravir Ctrough achieved MEC before efavirenz concentrations fell | Three-period study in healthy subjects of EVG/COBI/ FTC/TDF (Quad) for 1 week followed by washout, efavirenz/FTC/TDF (Atripla®) for 2 weeks, then Quad for 5 weeks. Following the switch from Atripla® to the Quad, elvitegravir exposures were lower:<br>• Day 35: AUC ↓ 37%, Cmax ↓ 19%, Ctau ↓ 67%<br>• Day 42: AUC ↓ 29%, Cmax ↓ 11%, Ctau ↓ 54%<br>Cobicistat Ctau was ↓ 35% at day 14 post-switch. AUC of EVG glucuronidated metabolite were ↑ 46% and ↑ 32% on days 35 and 42, respectively. Mean EVG Ctrough was ~3-fold and ~5-fold > than protein-adjusted IC95 of 45 ng/mL on days 35 and 42, respectively, and 7-8 fold ↑ at 5 weeks post switch.[29] | 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:<br>$C_{12\,hr}$ GMR [90% CI] = 0.79 [0.49, 1.28], $AUC_{0-\infty}$ = 0.64 [0.52, 0.80] and $C_{max}$ = 0.64 [0.41, 0.98]. There were no substantial differences in $T_{max}$ or $t_{½}$. This interaction is likely not clinically meaningful.[30] Based on these data, efavirenz may be coadministered with raltegravir without dose adjustment.[2] |

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| | below MEC, dolutegravir 50 mg QD may be initiated immediately following efavirenz discontinuation.[28] | | |
| Etravirine | 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 ↓ 70%, Cmax ↓ 52% and Ctrough ↓ 88%.<br><br>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%, Cmax ↓ 12% and Ctrough ↓ 37%. These changes were considered not clinically significant.[31]<br><br>Dolutegravir may be coadministered with etravirine without a dosage adjustment if atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is concurrently administered.[18] | 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.[32] | In healthy subjects, raltegravir 400 mg BID and etravirine 200 mg BID for 4 days resulted in modest decreases in raltegravir concentrations (AUC ↓ 10%, 11% ↓ Cmax, 34% ↓ C12h) compared to raltegravir alone, while etravirine levels were not altered. These changes are not considered to be clinically meaningful; etravirine may be coadministered with raltegravir without dose adjustment.[33]<br><br>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 Ctrough were noted between the groups.[22]<br><br>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 (Cmax, Cmin and AUC) were not significantly different in the presence of etravirine.[34] |
| Fosamprenavir/ ritonavir | 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 | Healthy volunteers were randomized to receive either elvitegravir 125 mg/ritonavir 100 mg QD followed by elvitegravir 125 mg QD plus | In an open-label, 3-period study, subjects received raltegravir 400mg BID for 7days, then were randomized to 14 days of either |

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| | presence of fosamprenavir/r, dolutegravir AUC ↓ 35%, Cmax ↓ 24% and Cτ ↓ 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.[35]<br><br>A dose adjustment of dolutegravir to 50 mg twice daily is recommended in treatment-naïve or treatment-experienced, INSTI-naïve patients. Alternative combinations that do not include metabolic inducers should be considered where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[18] | 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.[36] | 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 $IC_{95}$ 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-fold >APV $EC_{90}$ documented for PI-naïve HIV+ pts (228ng/mL). The clinical implications of these results have yet to be determined.[37] |
| 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%, Cmax ↑ 5%), while raltegravir AUC ↓ 15%, Cmax ↓ 28% and Cmin ↑ 25% in the presence of lersivirine. A clinically relevant interaction is unlikely.[38] |
| 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 | 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 | 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 Cmax (RAL alone vs combo: 1698ng/ml VS 1687 ng/ml). |

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| | 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.<br><br>No dosage adjustment for dolutegravir is required when used with lopinavir/ritonavir or darunavir/ritonavir.[17] | (group 2). EVG exposures were significantly increased in the presence of LPV/r: 75% ↑ $AUC_{tau,}$ 52% ↑ Cmax, 1382% ↑ Ctau, possibly via inhibition of UGT1A1/3 metabolism. LPV and RTV exposures were unchanged.<br>Based on simulations, the authors recommend the dose of EVG be ↓ to 85mg daily when used with LPV/r.[39] | Concomitant use of LPV/r led to ↓ RAL C12h 30% (49.4ng/ml VS 34.4ng/ml). Raltegravir Cmin stayed above IC95 (15ng/ml). Dose adjustment not recommended.[40] |
| 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 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).[41] | 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 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.<br><br>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.[42] |
| Nevirapine | In 10 adult HIV-infected subjects on stable abacavir/3TC and nevirapine 400 mg daily, dolutegravir 50 | | Drugs may be coadministered. No Raltegravir dose modification is required.[2] |

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| | mg daily was added for 5 days; nevirapine was then discontinued while dolutegravir continued to be administered with abacavir/3TC for 2 weeks. Dolutegravir exposures were significantly reduced (19% ↓ AUC, 34% ↓ Ctrough) with coadministration of nevirapine. No dosing recommendations were provided by the investigators, but dolutegravir 50 mg BID could be considered.[43]<br><br>NB: currently, the dolutegravir product monograph states that coadministration with nevirapine should be avoided because there are insufficient data to make dosing recommendations.[18] | | The pharmacokinetics of raltegravir 400/nevirapine 200 mg BID (n=21) and raltegravir/nevirapine 800/400 mg QD (n=10) were assessed in a cohort of HIV+ subjects. Patients in the QD group showed significantly lower RAL [28 ng/mL (17-79) vs 152 ng/mL (56-285), $p$ = 0.002] but similar NVP concentrations [5969 ng/mL (3957-7228) versus 5250 ng/mL (3890-8020), $p$ = 0.88], as compared to the BID group. One raltegravir Ctrough was below the IC95 (15 ng/mL) in the QD arm, while exposures in the BID arm were consistent with previous data.[44] |
| Nucleoside reverse transcriptase inhibitors | | 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.[45] | |
| Rilpivirine | In an open-label, two-cohort, single sequence crossover study, healthy subjects, received either DTG 50mg daily for 5days or S/GSK1265744 30mg daily for 12 days (Period 1), rilpivirine 25 mg daily for 11-12 days (Period 2) and rilpivirine 25 | | In healthy volunteers, coadministration of rilpivirine 25 mg QD and raltegravir 400 mg BID for 11 days did not significantly alter the pharmacokinetics of either drug compared to each drug administered alone. The combination may be |

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| | mg daily plus DTG 50 mg daily or S/GSK1265744 30 mg daily for 12 days (Period 3); all doses were administered following a moderate fat meal. The combinations of RPV + DTG and RPV + S/GSK1265744 were well-tolerated and no significant changes in the PK parameters of any drug were observed.[46] | | administered without dose adjustment.[47] |
| 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 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.[48] | 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 administered alone.[30]<br><br>The effect of ritonavir 100 mg BID on the kinetics of single-dose raltegravir 400 mg was studied in 12 healthy volunteers. Coadministration resulted in 22% ↑ AUC, 20% ↓ Cmax and 3.57-fold ↑ C12 of raltegravir.[49] |
| 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.[18, 50] | 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.[51] 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%.[52] 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 | 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. | 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 |

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| | presence of tipranavir/ritonavir, dolutegravir AUC ↓ 59%, Cmax ↓ 46% and Ctrough ↓ 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.[27]<br><br>A dose adjustment of dolutegravir to 50 mg twice daily is recommended in treatment-naïve or treatment-experienced, INSTI-naïve patients. Alternative combinations that do not include metabolic inducers should be considered where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[18] | 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.[19]<br><br>In a fixed-sequence crossover study, the pharmacokinetics of **tipranavir 500 mg BID with either cobicistat 150 mg BID or ritonavir 200 mg BID** were assessed. When boosted with cobicistat, tipranavir concentrations were significantly lower (Ctau ↓ 85.6%, AUC ↓ 53.8%, Cmax ↓ 37.8%) compared to those achieved when boosted with ritonavir. Avoid combination until further information is available.[20] | well tolerated.[53] 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.<br><br>In an open-label study of 7 treatment-experienced patients initiating salvage therapy, optimized background therapy (OBT) 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).[54] |
| **2) OTHER AGENTS** | | | |

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| Antacids (NB: see separate entries for H2-blockers and Proton-pump inhibitors) | 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.[55]<br><br>In a randomized, open-label pharmacokinetic study, coadministration of dolutegravir with **1200 mg calcium carbonate or 324 mg ferrous fumarate** under fed conditions resulted in plasma exposures comparable to dolutegravir given alone or given 2 hours prior to calcium or iron in the fasted state. In the fasted state, dolutegravir exposures were ↓ 37% to 39% when coadministered with calcium and ↓ 54% to 57% when coadministered with iron, compared to dolutegravir given alone, respectively.[56]<br><br>**Dolutegravir should be administered 2 hours before or 6 hours after medications containing polyvalent cations (e.g., Mg, Al, Fe, or Ca) including cation-containing antacids or laxatives, sucralfate, oral iron or calcium supplements, and buffered** | 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.[57]<br><br>**Elvitegravir should be separated by at least 2 hours from antacids containing aluminum, magnesium hydroxide, or calcium carbonate.**[58] | In a prospective crossover study, healthy volunteers received single-dose raltegravir 400 mg with and without an **aluminum/magnesium antacid** (Maalox Plus® Extra Strength). In the presence of the 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).[59] Taking an aluminum and magnesium antacid within 6 hours of raltegravir administration significantly decreased raltegravir plasma levels. Manufacturer states that **concomitant or staggered administration of antacids containing aluminium and/or magnesium is not recommended**.[2]<br><br>When a calcium carbonate antacid was administered 2 hours prior to raltegravir, raltegravir C12 ↓ 32%, but this interaction was not considered clinically meaningful. **May give raltegravir with antacids containing calcium carbonate**.[2] |

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| | **medications.[18] Dolutegravir can be administered without regard to multivitamins.** | | |
| Buprenorphine/ naloxone | | In 18 subjects on stable buprenorphine/naloxone who received **elvitegravir 150 mg/cobicistat 150 mg daily** for 10 days, buprenorphine AUC ↑ 35%, Cmax ↑ 12%, Ctau ↑ 66%, norbuprenorphine AUC ↑ 42%, Cmax ↑ 24%, Ctau ↑ 57%, while naloxone AUC and Cmax ↓ 28%. These changes were not considered clinically significant, and no dose adjustments are required when coadministering with elvitegravir/cobicistat.[60] | 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 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.[61] |
| Calcium channel blockers (including amlodipine, diltiazem, felodipine, nifedipine, verapamil, etc.) | Clinically significant interaction not anticipated. | Potential for increased concentrations of calcium channel blockers when coadministered with cobicistat. Use combination with caution and clinical monitoring; adjust calcium channel blocker dose if required.[62] | In a pharmacokinetic study in healthy volunteers, coadministration of raltegravir 400 mg twice daily plus amlodipine 5 mg once daily for 7 days did not result in significant changes in exposures of either drug. Combination may be given without dosage adjustment.[63] |
| Carbamazepine | In healthy volunteers, dolutegravir exposures were significantly reduced in the presence of carbamazepine (49% decrease AUC, 33% decrease Cmax, 73% decrease Ctrough). Integrase-naïve subjects | Healthy subjects (n=14) received the following treatments sequentially over 41 days: elvitegravir/cobicistat 150/150 mg daily for 10 days, carbamazepine 100 mg BID for 3 days then carbamazepine 200 mg BID | The impact on UGT1A1 is unknown. Use with caution.[2] |

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| | taking carbamazepine should receive dolutegravir 50mg twice daily.[64]<br><br>Oxcarbamazepine is predicted to decrease dolutegravir Cmin by 32% but this is not considered clinically significant; therefore, no dose adjustment of dolutegravir is recommended with coadministration.[64] | for 18 days, followed by elvitegravir/cobicistat 150/150 mg daily plus carbamazepine 200 mg BID for 10 days. With coadministration, elvitegravir and cobicistat exposures were decreased significantly (AUC decreased 69%, Cmax decreased 45%, Ctau decreased 97%, and AUC decreased 84%, Cmax decreased 72%, Ctau decreased 91%, respectively). Of note, elvitegravir Ctau was below the protein binding adjusted IC95 (45 ng/mL) in 11 of 12 subjects.<br><br>Carbamazepine AUC increased 43%, Cmax increased 40% and Ctau increased 51% while exposures of the carbamazepine epoxide metabolite were modestly decreased (35% decrease AUC) in the presence of elvitegravir/cobicistat.<br><br>**Combination is contraindicated**.[65] | |
| Colchicine | | Potential ↑ colchicine concentrations. Do not coadminister in patients with renal or hepatic impairment. Refer to monograph for specific dosing recommendations.[58] | |
| Corticosteroids (oral/inhaled, injectable or topical) e.g., betamethasone, budesonide, dexamethasone, fluticasone, prednisone, triamcinolone | In an open-label, healthy volunteer study, subjects received dolutegravir 50 mg daily alone for 5 days and then with concomitant **prednisone** for 10 days (prednisone at 60 mg daily for 5 days, followed by a 5-day taper). Dolutegravir AUC, Cmax and C24 were ↑ 11%, 6% and 17%, respectively when coadministered with prednisone. These changes | **Systemic dexamethasone** may ↓ elvitegravir and cobicistat concentrations.[58] Avoid coadministration if possible.<br><br>Case report of adrenal suppression in a 39 year old HIV-infected male on elvitegravir/cobicistat/tenofovir /emtricitabine who received **intranasal fluticasone nasal drops** 800 ug BID. | Drugs may be coadministered. No raltegravir dose modification is required.[2] |

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| | were not clinically significant.<br><br>No dose adjustment is required for dolutegravir coadministered with prednisone.[66]<br><br>Similarly, no clinically significant interaction anticipated with other corticosteroids. | Fluticasone nasal drops were changed to beclomethasone nasal spray with recovery of adrenal axis suppression.[67]<br><br>Due to the potential for ↑ **fluticasone** concentrations; consider alternative corticosteroid[58] such as beclomethasone. | |
| Digoxin | | Administration of digoxin 0.5 mg single dose with cobicistat 150 mg once daily resulted in 41% ↑ Cmax and 8% ↑ AUC of digoxin. Use combination with caution, monitor digoxin drug concentrations.[58] | No interaction anticipated. |
| H2 blockers (including cimetidine, famotidine, nizatidine, ranitidine, etc.)<br><br>**equivalent doses:*<br>*<u>H2RAs (treatment)</u>:*<br>*Famotidine 20 mg BID or 40 mg qhs*<br>*Nizatidine 150 mg BID or 300 mg qhs*<br>*Ranitidine 150 mg BID or 300 mg qhs*<br><br>*<u>H2RAs (maintenance qhs dosing)</u>:*<br>*Famotidine 20 mg*<br>*Nizatidine 150 mg*<br>*Ranitidine 150 mg* | **Dolutegravir can be taken with H2-antagonists without dose adjustment.**[18] | 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.[57]<br><br>**Elvitegravir/ritonavir and elvitegravir/cobicistat may be given with H2-blockers without dosage adjustment.** | 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**.[68] |
| HmgCoA reductase inhibitors (statins):<br><br>atorvastatin<br>lovastatin<br>pravastatin | | <u>Using cobicistat as a booster</u>: Fixed sequence, crossover study in healthy subjects of EVG 150/co 150 mg daily alone or with single dose **rosuvastatin 10 mg**. With coadministration: | 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 |

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| rosuvastatin<br>simvastatin | | • Kinetics of EVG were unaffected<br>• 89% ↑ Cmax, 38% ↑ AUC of rosuvastatin<br>Dose adjustment likely not necessary.[7]<br><br>Potential for ↑ **atorvastatin** concentrations; initiate with lowest starting dose of atorvastatin and titrate to response.[58]<br><br>**Stribild® is contraindicated with lovastatin and simvastatin.[58]** | 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.[69] |
| Ketoconazole | | In a healthy volunteer study, subjects received elvitegravir 150/ritonavir 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% ↑Cmin. A maximum ketoconazole dose of 200 mg once daily is recommended when coadministering with boosted elvitegravir.[70] | The effect of ketoconazole 200 mg BID on the kinetics of single-dose raltegravir 400 mg was studied in 12 healthy volunteers. Coadministration resulted in 94% ↑ AUC, 75% ↑ Cmax and 3.35-fold ↑ C12 of raltegravir.[49] |
| 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.[71] |
| Methadone | No effect in vivo on pharmacokinetics of | A pharmacokinetic study was conducted in 11 subjects on | No dose adjustment is required for methadone when |

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| | methadone.[72]<br><br>In an open-label, 2-period study in adult opiate-dependent, HIV$^-$ subjects, subjects received their current individual doses of methadone once daily for 3 days followed by dolutegravir 50 mg BID for 5 days with stable methadone therapy. Kinetics of R- and S-methadone were not altered by concomitant dolutegravir and there were no clinically relevant differences in pharmacodynamic measures. No dose adjustment in methadone is required when given in combination with dolutegravir.[73] | stable methadone (80-120 mg/day) who received elvitegravir 150 mg/cobicistat 150 mg daily for 10 days. The kinetics of R-methadone were unaffected in the presence of elvitegravir/cobicistat (AUC ↑ 7%, Cmin ↑ 10%); elvitegravir and cobicistat exposures were similar to historical controls. No dose adjustments are needed.[74] | co-administered with raltegravir.[75] |
| Midazolam | No effect in vivo on pharmacokinetics of midazolam.[72] | **Oral midazolam is contraindicated.**<br><br>Parenteral midazolam: potential for ↑ midazolam concentrations. Coadministration should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.[58] | In healthy volunteers, coadministration of raltegravir 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 a randomized, 2-period, double-blind, placebo-controlled, crossover study conducted within a single menstrual cycle, healthy female subjects received Ortho-Cyclen (ethinyl estradiol [EE] 0.035 mg and norgestimate 0.25 mg) throughout the study and were randomized to receive dolutegravir 50 mg BID or | 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 was co-administered daily on days 12-21 of the second cycle. When coadministered with Stribild®, there was a 25% ↓ EE AUC and a 2-fold ↑ AUC and Cmax | 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 |

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| | placebo with food every 12 hours for 10 days followed by Ortho-Cyclen only on day 11. From days 12 to 21, subjects who had taken DTG were switched to placebo, and subjects who had taken placebo were switched to DTG, which subjects took every 12 hours with food. Luteinizing hormone, follicle stimulating hormone, and progesterone levels were collected on days 1, 10, 11, 21, and 22. The PK of EE and norelgestromin (NGMN) were not altered by concomitant dolutegravir and there were no clinically relevant differences in pharmacodynamic measures. Oral contraceptives can be co-administered with dolutegravir 50 mg once or twice daily without dose adjustment.[73] | 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 investigators recommend that an oral contraceptive containing at least 30 ug of EE be used when taking Stribild®.[76]<br><br>Consider risks and benefits of coadministering nergestimate/ ethinyl estradiol. Consider alternative (non-hormonal) methods of contraception.[58] | coadministration with raltegravir.[77] |
| Phosphodiester-ase 5 (PDE5) inhibitors<br><br>Avanafil<br>Sildenafil<br>Tadalafil<br>Vardenafil | No interaction anticipated. | <u>For treatment of pulmonary arterial hypertension:</u>[58]<br>• sildenafil: contraindicated<br>• tadalafil: if already on Stribild®, start tadalafil 20 mg daily, ↑ to 40 mg daily based on tolerability. If on tadalafil and starting Stribild®, stop tadalafil at least 24 hours prior; after at least 1 week, resume tadalafil at 20 mg daily, ↑ to 40 mg daily based on tolerability.<br><br><u>For erectile dysfunction:</u>[58]<br>• sildenafil: 25 mg every 48 hours<br>• vardenafil: 2.5 mg every 72 hours<br>• tadalafil: 10 mg every 72 hours<br><br><u>For benign prostatic</u> | No interaction anticipated. |

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| | | <u>hypertrophy (BPH) - tadalafil:</u><br>• Standard dose of 5 mg daily may be used in those taking protease inhibitors or other potent CYP3A4 inhibitors. The dose may be decreased to 2.5 mg/day based on individual tolerability.[78] | |
| Phenobarbital | Based on modelling with clinical correlation, integrase-naïve subjects taking phenobarbital should receive dolutegravir 50mg twice daily.[64] | Potential for significant ↓ in elvitegravir and cobicistat concentrations. Consider alternate anticonvulsants.[58] | The impact on UGT1A1 is unknown. Use with caution.[2] |
| Phenytoin | Based on modelling with clinical correlation, integrase-naïve subjects taking phenytoin should receive dolutegravir 50mg twice daily.[64] | Potential for significant ↓ in elvitegravir and cobicistat concentrations. Consider alternate anticonvulsants.[58] | The impact on UGT1A1 is unknown. Use with caution.[2] |
| Pioglitazone | | | Drugs may be coadministered. No Raltegravir dose modification is required.[2] |
| Proton-pump inhibitors (PPIs), including esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, etc.<br>**equivalent doses:*<br><u>*PPIs (daily standard dose):*</u><br>*Esomeprazole 20 mg*<br>*Lansoprazole 30 mg*<br>*Omeprazole 20 mg*<br>*Pantoprazole 40 mg*<br>*Rabeprazole 20 mg* | 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 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.[55]<br><br>**Dolutegravir can be taken with proton pump inhibitors** | 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.[57]<br><br>**Elvitegravir/ritonavir and elvitegravir/cobicistat may be given with proton pump inhibitors without dosage adjustment.** | 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, raltegravir AUC ↑ 3-fold, Cmax ↑ 4-fold and Cmin ↑ 46% in the presence of omeprazole. Raltegravir $T_{max}$ and $t_{½}$ were not significantly affected. The mechanism is likely a consequence of increased bioavailability as raltegravir solubility is higher at higher gastric pH levels.[79]<br><br>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). |

| | Dolutegravir (S/GSK 1349572), Tivicay®, Triumeq® (coformulated with abacavir/lamivudine) | Elvitegravir (GS-9137), Stribild® (coformulated with cobicistat/tenofovir/ emtricitabine) | Raltegravir (MK-0518), Isentress® |
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| | **without dose adjustment.**[18] | | 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**.[68] |
| 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.[80]<br><br>In 14 healthy subjects who received raltegravir 400 mg 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.[81] |
| Rifabutin | In healthy volunteers, coadministration of | <u>Using ritonavir as a booster:</u><br>Randomized, sequential, | In healthy adults who received raltegravir 400 mg BID with or |

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| | dolutegravir 50 mg QD alone or with rifabutin 300 mg QD for 14 days resulted in 5% ↓ AUC, 15% ↑ Cmax and 30% ↓ Ctau of dolutegravir. This change is unlikely to be clinically significant effect in integrase-naïve patients.[82] | crossover study in HIV negative healthy volunteers:<br>• Treatment A: EVG/r 300mg/100mg daily (n=19)<br>• Treatment B: EVG/r 300mg/100mg +/- rifabutin 150mg every other day (n=19)<br>• Treatment C: Rifabutin 300mg daily (n=18)<br>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.[83] **Decrease rifabutin to 150mg every other day or 150mg three times weekly when administered with EVG/r.**<br><br><u>Using cobicistat as a booster</u>: Fixed sequence, crossover study in healthy subjects of EVG 150/co 150 mg daily alone, then with **rifabutin 150 mg q2d**, followed by rifabutin 300 mg QD after a 10-day washout. With coadministration of EVG 150/co 150 mg and rifabutin 150 mg q2d:<br>• 67% ↓ Ctrough of EVG<br>• Rifabutin exposures comparable to rifabutin 300 mg QD alone<br>• 4.8-6.3-fold ↑ exposures of 25-desacetyl-RFB, resulting in 21% higher total antimycobacterial activity.[7]<br><br>In a subsequent healthy volunteer study, <u>twice daily</u> | 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.[2, 85] |

| | Dolutegravir (S/GSK 1349572), Tivicay®, Triumeq® (coformulated with abacavir/lamivudine) | Elvitegravir (GS-9137), Stribild® (coformulated with cobicistat/tenofovir/ emtricitabine) | Raltegravir (MK-0518), Isentress® |
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| | | cobicistat was utilized to overcome the induction effect of rifabutin on elvitegravir exposures. Subjects received elvitegravir 150 mg daily, cobicistat 150 mg BID plus rifabutin 150 mg q2days for 13 days. Elvitegravir AUC and Cmax were not significantly changed and Ctau was 59% higher compared to elvitegravir 150 mg/cobicistat 150 mg administered alone. Rifabutin AUC and Cmax were not significantly changed and Ctau was 41% higher and exposures of 25-desacetyl-RFB were 12-fold higher compared to rifabutin 300 mg daily, resulting in <2-fold increase in total antimycobacterial activity. No Grade 2, 3, 4 or serious adverse events were observed.[84]<br><br>**Consider cobicistat 150 mg BID with elvitegravir 150 mg daily when coadministering with rifabutin 150 mg every 2 days.** | |
| Rifampin | In open-label, three-period, fixed-sequence, single center pharmacokinetic (PK) drug interaction study, healthy volunteers received dolutegravir 50 mg once daily for 7 days (period 1), then DTG 50 mg twice daily for 7 days (period 2), then DTG 50 mg twice daily together with rifampin 600 mg once daily (period 3) for 14 days. Dolutegravir 50 mg BID plus rifampin achieved mean AUC 33% ↑ and Ctau 22% ↑ versus DTG 50 mg daily alone. There were no discontinuations for adverse events (AEs) and no Grade 3 | **Combination is contraindicated.**[58] | 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.[86] **Product monograph recommends increasing raltegravir dose to 800 mg twice daily during coadministration with rifampin.**[2] **Use combination** |

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| | or higher AEs.[82]<br><br>Dolutegravir 50 mg twice daily is recommended in treatment-naïve or treatment-experienced, INSTI-naïve patients. Alternatives to rifampin should be used where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[18] | | **with caution, particularly among patients with high HIV viral loads who are just beginning antiretroviral therapy.**[87]<br><br>The effect of rifampin 600 mg QD on the kinetics of single-dose raltegravir 400 mg was studied in 12 healthy volunteers. Coadministration resulted in 55% ↓ C12, 40% ↓ AUC and 25% ↓ Cmax of raltegravir.[49]<br><br>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.[88]<br><br>In a prospective, randomized open-label study of 153 HIV-positive adults receiving rifampicin-based treatment for tuberculosis, subjects received raltegravir 400 mg BID, raltegravir 800 mg BID or efavirenz 600 mg once daily with tenofovir and lamivudine. At week 24, virologic suppression (<50 copies/mL) was achieved in 76%, 78% and 63% of the groups, respectively. Rates of discontinuation due to adverse events were similar in the efavirenz and raltegravir 800 mg BID group (6% each).[89] In a pharmacokinetic substudy, raltegravir plasma concentrations were |

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| | | | decreased at the 400 mg BID dose with rifampin comparatively to raltegravir alone. There was a trend to higher raltegravir exposures in the 800 mg BID group.[90]<br><br>In the presence of **intermittent rifampin dosing** (3 times weekly), administration of **raltegravir 400 mg BID** resulted in 40% ↓ RAL C12, 16% ↑ Cmax and 8% ↑ AUC relative to raltegravir 400 mg BID alone, while **raltegravir 800 mg BID** in the presence of intermittent rifampin led to 11% ↓ RAL C12, 76% ↑ Cmax and 84% ↑ AUC. **Administer raltegravir 800 mg BID with daily or intermittent rifampin.**[91] |
| Rifapentine | | Potential for significant ↓ elvitegravir and cobicistat concentrations. Coadministration is not recommended.[58] | In a 3-period study in healthy volunteers, raltegravir 400 mg BID was administered alone or with rifapentine 900 mg taken once weekly or 600 mg daily (5 of 7 days/week). Once-weekly rifapentine co-administration resulted in a 73% ↑ AUC, 89% ↑ Cmax and 44% ↓ Cmin of raltegravir. Daily rifapentine coadministration did not change mean AUC or Cmax of raltegravir, but the $C_{min}$ ↓ 43%. Inter-patient variability was high. Rifapentine demonstrated less inductive effect on RAL concentrations than reported for rifampin.[92] |
| Sirolimus | | | Raltegravir may avoid interactions with certain immunosuppressives as it is primarily metabolized via glucuronidation and not by CYP3A4. |

| | **Dolutegravir (S/GSK 1349572), Tivicay®, Triumeq®** (coformulated with abacavir/lamivudine) | **Elvitegravir (GS-9137), Stribild®** (coformulated with cobicistat/tenofovir/ emtricitabine) | **Raltegravir (MK-0518), Isentress®** |
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| | | | 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.[93] |
| St John's Wort | Based on modelling with clinical correlation, integrase-naïve subjects taking St John's Wort should receive dolutegravir 50mg twice daily.[64] | **Combination is contraindicated.**[58] | Drugs may be coadministered. No Raltegravir dose modification is required.[2] |
| 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.[94] |
| Warfarin *(racemic mixture; R: CYP1A2, 3A, 2C19; S: 2C9 primarily)*<br><br>*NB:* The S- | No interaction anticipated. | Potential for warfarin concentrations to be affected.<br><br>Case report of a 42 year old HIV-positive male with recurrent DVT, on efavirenz/tenofovir/ emtricitabine and stable warfarin (average 50 | No interaction anticipated. |

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| enantiomer of warfarin exhibits 2 to 5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance. | | mg/week). After changing cART to elvitegravir/cobicistat/ tenofovir/emtricitabine due to ongoing CNS effects with efavirenz, the INR became subtherapeutic on day 20. The patient's warfarin dose was increased 60% in order to achieve a therapeutic INR.[95]<br><br>Monitor INR and adjust warfarin dose accordingly.[58] | |

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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