Interactions Between Opioids and Antiretrovirals

Antiretroviral Pharmacokinetic Characteristics (summary):

	Protease Inhibitors (PIs) atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitors** dolutegravir (Tivicay®),[14], elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[15], raltegravir (Isentress®)[16]
Metabolism	Mainly CYP3A4	Efavirenz, nevirapine: CYP3A4, 2B6 (minor) Etravirine: CYP3A4, CYP2C9, and CYP2C19. Rilpivirine: CYP3A4 (major), as well as CYP2C19, 1A2, 2C8/9/10 (minor).	Dolutegravir: UGT1A1, CYP3A4 (10-15%). Elvitegravir: CYP3A, UGT1A1/3 Cobicistat: CYP3A, 2D6 (minor) Raltegravir: UGT1A1
Hepatic Inhibitor	Mainly CYP3A4 (darunavir, indinavir, nelfinavir, amprenavir >> saquinavir) Atazanavir: 3A4, UGT1A1 >>2C8 (weak) Caution when unboosted atazanavir is coadministered with drugs that are 2C8 substrates with narrow therapeutic indices (e.g., paclitaxel, repaglinide); clinically significant interactions with 2C8 substrates are not expected when atazanavir is boosted with ritonavir. Nelfinavir: 2B6 in vitro. Ritonavir: CYP3A4 (potent)> >2D6 >2C9 >2C19 >2A6 >1A2>2E1. At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition.[5] Ritonavir inhibits CYP2B6 in vitro,[17] but induces 2B6 in vivo.[18] Tipranavir: 2D6[19]	Efavirenz: 2C9, 2C19[10] (? Clinical significance). Etravirine[11]: CYP2C9 (weak), CYP2C19 (moderate), p-glycoprotein (weak) Delavirdine (Rescriptor®)[20]; 3A4 (potent)	Cobicistat: CYP3A, CYP2D6; also p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Dolutegravir inhibits the renal organic cation transporter, OCT2.[14] Raltegravir has no inhibitory or inductive potential in vitro.[16]
Hepatic Inducer	Nelfinavir: UGT, 2B6, 2C8, 2C9/19[21] Ritonavir: UGT, CYP1A2, CYP2C9/19, 2B6	Efavirenz: 3A4 (potent), 2B6[22] and UGT1A1[23] Etravirine[11]: 3A4 (weak)	Dolutegravir does not induce CYP1A2, CYP2B6, or CYP3A4 in vitro.[14]

Interactions Between Opioids and Antiretrovirals

	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitors
	Tipranavir: mixed induction/inhibition effects; often acts as inducer of CYP3A4 (potent) and UGT, even when boosted with ritonavir[9]	Nevirapine[12]: 3A4, 2B6 (potent) Rilpivirine: 2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak).[24] A clinically relevant effect on CYP enzyme activity is considered unlikely with the 25 mg dose.[13]	Elvitegravir: CYP2C9 (modest) Raltegravir has no inhibitory or inductive potential in vitro.[16]

	Narcotic Route of Metabolism[25] 26, 27	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
Alfentanil **Alfenta®**	Parent: CYP3A	potential ↑ alfentanil concentration	potential ↓ alfentanil concentration	potential ↑ alfentanil concentration
Buprenorphine ***Partial agonist*** **BuTrans®** (Transdermal Patch) **Suboxone®** (buprenorphine/ naloxone)	Parent: CYP3A4, 2C8 Metabolite (active): norbuprenorphine inhibits CYP3A4, 2D6 (this inhibition is not likely to lead to clinically significant interactions);[28] buprenorphine and norbuprenorphine undergo glucuronidation.[29]	potential ↑ buprenorphine concentration. Case report of 3 subjects on **atazanavir 300/ritonavir 100 mg** who experienced symptoms of opiate excess when initiated on buprenorphine 8-14 mg/day. In all cases, symptoms improved with reduction of buprenorphine to 8 mg daily or every other day. Potential mechanism may be due to CYP3A4 inhibition by atazanavir or ritonavir, or inhibition of glucuronidation by atazanavir. Until further data are available, initiate buprenorphine at reduced doses and titrate slowly.[30] A prospective, open-label, multiple dose study assessed the kinetics of buprenorphine (BUP) + **ATV 400 mg**	potential ↓ buprenorphine concentration In 7 HIV-negative volunteers, there was a lack of a clinically significant interaction with **nevirapine** (9% ↓ AUC of buprenorphine and 14% ↓ AUC of norbuprenorphine). Standard doses of both agents are recommended.[38] In a study of HIV-negative opioid-dependent patients receiving chronic buprenorphine/naloxone, the addition of **efavirenz** 600 mg per day for 15 days resulted in a 50% ↓ in the AUC of buprenorphine and 71% ↓ AUC of norbuprenorphine.[39] Despite	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

	Narcotic Route of Metabolism[25] 26, 27	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitor** (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
		or ATV/r 300mg/100mg daily in opioid dependent buprenorphine/naloxone maintained HIV negative volunteers. In order to determine the effect of BUP on the kinetics of ATV +/- RTV, subjects were compared with non-opioid dependent healthy controls (n=10 per group). Results: • BUP treatment did not significantly alter ATV or RTV concentrations (~31% ↓ in AUC and ~33% ↓ in Cmin of ATV when BUP was given concomitantly). • The coadministration of ATV +/- RTV with BUP for 5 days significantly ↑ BUP and BUP metabolite levels. ○ ATV + BUP: BUP AUC ↑ 1.9 fold; BUP Cmax ↑ 1.6 fold; BUP Cmin ↑ 2 fold ○ ATV/r + BUP: BUP AUC ↑ 1.7 fold; BUP Cmax ↑ 1.37 fold; BUP Cmin ↑ 1.7 fold 3 participants reported increased sedation with the combination. It is unclear why this occurred. Concentrations of BUP/metabolites were not higher in these 3 subjects compared to the other 7 subjects who did not develop sedation. The authors caution that buprenorphine dose reduction may be required when given with ATV +/-RTV.[31] A prospective cohort study did not observe hepatic pharmacodynamic	these significant decreases in the presence of efavirenz, no participants showed evidence of opiate withdrawal symptoms. Efavirenz kinetics were not affected by buprenorphine. When **etravirine** 200 mg BID was added to stable individualized buprenorphine/ naloxone maintenance therapy in 16 subjects, the Cmin, Cmax and AUC24h of buprenorphine were decreased by 40%, 11% and 25%, respectively, compared to treatment with buprenorphine/naloxone alone. For norbuprenorphine, Cmin was decreased by 24% after co-administration with etravirine, while Cmax and AUC24h were comparable between both treatments. Parent/metabolite ratios of Cmin, Cmax and AUC24h were decreased by 22%, 17% and 15%, respectively, after the combined intake of buprenorphine/naloxone and etravirine. The U.S. Product Monograph states that etravirine and buprenorphine or buprenorphine/naloxone may be co-administered without dose adjustments; however, clinical monitoring for withdrawal symptoms is recommended as	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.[41] 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.[42]

	Narcotic Route of Metabolism[25] 26, 27	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitor** (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
		interactions (i.e. significant elevations in liver transaminases) in patients on buprenorphine/naloxone with **atazanavir ± ritonavir**.[32] In 17 HIV-negative subjects on stable buprenorphine/naloxone, the addition of **darunavir 600/100 mg BID** for 7 days led to 71% ↑ Cmin, 36% ↑ Cmax and 46% ↑ AUC of norbuprenorphine, while kinetics of buprenorphine and naloxone were comparable to baseline. Clinical significance of ↑ norbuphrenorphine exposure is unknown, close monitoring is recommended with this combination.[33] In 21 opioid-dependent, buprenorphine-naloxone-maintained, HIV-negative volunteers, the impact of **darunavir/ritonavir 800/100 mg QD** (n=11) or **fosamprenavir/ritonavir 1400/200 mg QD** (n=10) for 15 days on the kinetics of buprenorphine and its metabolites were assessed. In the presence of PI therapy, there were no changes in buprenorphine or PI plasma levels and no significant changes in medication adverse effects or opioid withdrawal. Increased concentrations of the inactive metabolite buprenorphine-3-glucuronide suggested that darunavir-ritonavir and fosamprenavir-ritonavir induced glucuronidation. Dose adjustments are not likely to be necessary.[34]	buprenorphine (or buprenorphine/naloxone) maintenance therapy may need to be adjusted in some patients.[11] In a study of HIV-negative opioid-dependent patients receiving chronic buprenorphine/naloxone, the addition of **delavirdine** 600 mg BID for 7 days resulted in 325% ↑ AUC of buprenorphine but a 61% ↓ AUC of norbuprenorphine, with an overall net effect of 87% ↑ exposure to buprenorphine plus norbuprenorphine.[39] A significant increase in the reporting of drowsiness was observed. Delavirdine kinetics were not affected by buprenorphine. Other: In 27 opioid-dependent, buprenorphine/naloxone-maintained, HIV-negative volunteers, no significant changes in buprenorphine pharmacokinetics were observed following **ddI, 3TC and tenofovir** administration, and buprenorphine had no statistically significant effect on NRTI concentrations.[40]	

	Narcotic Route of Metabolism[25] 26, 27	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitor** (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
		In a study of 10 HIV-negative opioid-dependent patients receiving chronic buprenorphine/naloxone, the addition of **lopinavir/ritonavir 400/100 mg BID** for 7 days did not affect buprenorphine or norbuprenorphine AUC (norbuprenorphine Cmax ↓). No participants showed evidence of opiate withdrawal symptoms or toxicity. Lopinavir/ritonavir AUC ↑ 15% in the presence of buprenorphine, not likely clinically significant.[35] In the same study, the addition of **ritonavir** 100 mg BID for 7 days resulted in 57% ↑ in buprenorphine AUC and ↑ norbuprenorphine AUC. No participants showed evidence of opiate withdrawal symptoms or toxicity. Ritonavir AUC was not affected by buprenorphine.[35] In 12 HIV-negative subjects on stable buprenorphine/naloxone therapy, administration of **lopinavir/r 800/100 mg QD** for 10 days did not have any significant impact on naloxone AUC or Cmax, buprenorphine AUC or Cmax, and AUC of norbuprenorphine. Cmax of norbuprenorphine was significantly reduced in the presence of LPVr (3.11 vs 5.29 ng/mL, $p<0.05$) but objective opioid withdrawal was not observed. Lopinavir Cmax and AUC were not significantly different compared to		

	Narcotic Route of Metabolism[25] 26, 27	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitor** (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
		historical controls. Therefore, this combination may be coadministered without dose adjustment.[36] In a study of 10 HIV-negative opioid-dependent patients receiving chronic buprenorphine/naloxone, the addition of **nelfinavir** 1250 mg BID for 5 days did not affect buprenorphine or norbuprenorphine AUC (Cmax ↓ norbuprenorphine). No participants showed evidence of opiate withdrawal symptoms Nelfinavir AUC was not affected by buprenorphine.[35] In a study of HIV-negative opioid-dependent patients receiving chronic buprenorphine/naloxone, the addition of **tipranavir 500/ritonavir 200 mg BID** for 7 days resulted in ~80% ↓ AUC, Cmax and C24h of norbuprenorphine (the major metabolite of buprenorphine) and 44% ↓ AUC and 36% ↓ Cmax of naloxone. There was no clinical evidence of opioid withdrawal and no need to modify buprenorphine dose. In the presence of buprenorphine/naloxone, tipranavir AUC ↓ 19% and Cmin ↑ 3%, and ritonavir AUC ↓ 36% compared to historical controls.[37] No modification of buprenorphine/naloxone is required when co-administered with tipranavir/r, but tipranavir may be less effective due to decreased tipranavir plasma concentrations; coadminister		

	Narcotic Route of Metabolism[25] 26, 27	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitor** (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
		combination with caution.[37]		
Butorphanol **Apo®-Butorphanol** ***Agonist/ Antagonist***	Parent: Extensive liver metabolism via oxidation and conjugation to inactive metabolites	unknown	unknown	unknown
Codeine	Parent: UGT (to codeine-6-glucuronide); >CYP2D6 (to morphine-active) >CYP3A (to norcodeine-active) Rapid metabolizers of codeine via 2D6 may lead to high levels of morphine and toxicity.	Unlikely with unboosted PIs. Net effect unknown with ritonavir, as ritonavir may induce UGT and inhibit CYP3A.	Unlikely	Net effect unknown. Inhibition of 2D6 and 3A4 may ↓ formation of active metabolite.
Diphenoxylate **Lomotil®**	Parent: ester hydrolysis Metabolite (active): difenoxine (UGT)	No anticipated effect with unboosted atazanavir or fosamprenavir. Nelfinavir or ritonavir-boosted PIs may ↓ metabolite concentration via UGT induction.	no anticipated effect	no anticipated effect
Fentanyl **Duragesic®**	Parent: CYP3A	potential ↑ narcotic concentration 174% ↑ fentanyl AUC with **ritonavir 900 mg/day**. Monitor for respiratory and CNS depression.[43] Concentrations of fentanyl are expected to increase with **ritonavir** coadministration. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when **ritonavir** is co-administered with fentanyl, including extended release, transdermal or transmucosal preparations.[7]	potential ↓ narcotic concentration	potential ↑ narcotic concentration
Heroin	**Heroin** (diacetylmorphine)	No anticipated effect with unboosted atazanavir or fosamprenavir.	No anticipated effect.	Potential ↑ opiate.

	Narcotic Route of Metabolism[25] 26, 27	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitor** (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
	undergoes deacetylation to 6-monoacetylase morphine and morphine. Morphine undergoes glucuronidation(UGT) to morphine-6-glucuronide. Parent: Deacetylase Metabolite: UGT (6-monoacetylase morphine) Morphine and morphine-6-glucuronide are also P-glycoprotein substrates.	**Nelfinavir or ritonavir**: may facilitate the conversion of morphine to the active metabolite morphine-6-glucuronide via induction of UGT; clinical significance is unknown.[44] **Ritonavir** is a potent inhibitor of P-glycoprotein, therefore it may potentiate the effects of opiates in the CNS.[44]		
Hydrocodone Hycodan®	Parent: CYP2D6, 3A Metabolite (active): hydromorphone via 2D6 Poor metabolizers of 2D6 will not produce hydromorphone and derive little/no analgesic benefit	potential ↑ hydrocodone concentration Ritonavir may ↓ metabolite concentration (hydromorphone), clinical significance unclear.	potential ↓ hydrocodone concentration	potential ↑ hydrocodone concentration Cobicistat may ↓ metabolite concentration (hydromorphone), clinical significance unclear.
Hydromorphone Dilaudid® Jurnista®	Parent: UGT> ketoreductase	No anticipated effect with unboosted atazanavir or fosamprenavir. **Nelfinavir and ritonavir** may ↓ hydromorphone concentration via UGT induction.	no anticipated effect	no anticipated effect
Levomethadyl (LAAM; levo-alpha-acetyl	Parent: CYP3A4 Metabolites: norLAAM, dinorLAAM[45]	potential ↑ narcotic concentration Single dose study of ketoconazole and	potential ↓ narcotic concentration	potential ↑ narcotic concentration

	Narcotic Route of Metabolism[25] 26, 27	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitor** (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
methadol) Orlaam® USA **Note: product D/C due to severe cardiac events (April 2004)**		LAAM resulted in 5.29-fold ↑ LAAM AUC, 2.25-fold ↑ norLAAM AUC, and 1.21-fold ↑ dinorLAAM AUC. Could result in serious cardiac effects. **AVOID with CYP3A4 inhibitors**.[46] **Nelfinavir**: ↓ LAAM & dinorLAAM concentrations; ↑ norLAAM concentrations. No change in nelfinavir concentrations.[47] Interaction not clinically significant.		
Loperamide Imodium®	Parent: CYP 2C8, 3A4, UGT, Pgp	In healthy subjects, loperamide 16 mg plus **ritonavir 200 mg BID** for 5.5 days led to ↑ AUC of both loperamide and its metabolite by 121% and 44%, respectively. However, the respiratory response to loperamide in combination with RTV was not different from that to loperamide alone, and there was no evidence that loperamide had opioid effects in the central nervous system.[48] In healthy subjects, loperamide 16mg and **saquinavir 600mg** resulted in a 46.3% ↓ saquinavir Cmax and 53.7 ↓ in saquinavir AUC and 40% ↑ in loperamide AUC. The decrease in saquinavir AUC may be due to decreased absorption mediated by the effect of loperamide on the GI tract. Avoid use for a prolonged period of time.[49] In healthy subjects, loperamide 16 mg plus **tipranavir** 750 mg BID for 5.5 days or **tipranavir 750 mg/ritonavir**	no anticipated effect	potential ↑ narcotic concentration

	Narcotic Route of Metabolism[25] 26, 27	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitor** (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
		200 mg BID for 10.5 days led to ↓ loperamide AUC by 51% and 63%, respectively, and ↓ AUC of its metabolite by 72% and 77% compared to loperamide administered alone. The respiratory response to loperamide in combination with TPV and/or RTV was not different from that to loperamide alone, and there was no evidence that loperamide had opioid effects in the central nervous system. Loperamide can be safely coadministered with tipranavir/ritonavir.[48]		
Meperidine Demerol®	Parent: CYP2B6>>3A4>2C19 Metabolite: normeperidine[50]	potential ↑ meperidine concentration with unboosted PIs. With ritonavir-boosted PIs, may see ↓ meperidine concentration due to enzyme induction. **Meperidine is no longer contraindicated** in Norvir® product monograph. Single dose study with meperidine 50mg and **ritonavir 500mg BID** x 10 days showed a 67% ↓ meperidine AUC, and 47% ↑ normeperidine AUC.[51] **Therapy can likely be cautiously initiated for short periods; however, potential for diminished analgesia and normeperidine toxicity (i.e. seizures) with prolonged or high-dose therapy, particularly in renal dysfunction. Therefore, close monitoring is still suggested. Long-**	potential ↓ narcotic concentration.	potential ↑ narcotic concentration

	Narcotic Route of Metabolism[25] 26, 27	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
		term co-administration is not recommended. **Tipranavir/rtv:** ↓ meperidine and ↑ normeperidine.[9]		
Methadone	Parent: CYP3A, 2B6 (*S* isomer), 2C19 (*R** isomer), 2D6 Inhibits: CYP2D6 (weak) * The *R* isomer is active	**(refer to separate chart on Methadone-Antiretroviral Drug Interactions)**		
Morphine	Parent: UGT Metabolite (active): morphine-6-glucuronide (renal)	No anticipated effect with unboosted atazanavir and fosamprenavir. **Nelfinavir and ritonavir** may ↓ morphine concentration and ↑ active metabolite concentration.	no anticipated effect	no anticipated effect
Nalbuphine **Nubain®** ***Agonist/ antagonist***	Parent: liver metabolism to inactive metabolites	unknown	unknown	unknown
Naloxone ***Opioid antagonist*** **Suboxone®** (buprenorphine/ naloxone) **Targin®** (naloxone/ oxycodone)	Parent: UGT	No anticipated effect with unboosted atazanavir and fosamprenavir. **Nelfinavir and ritonavir** may ↓ naloxone concentration. **Also see entries under "Buprenorphine" for interaction data with buprenorphine/naloxone**.	no anticipated effect	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

	Narcotic Route of Metabolism[25] 26, 27	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitor** (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
				required when coadministering with elvitegravir/cobicistat.[52]
Naltrexone ***Opioid antagonist*** **ReVia®**	Parent: Not via CYP450; metabolized via dihydrodiol dehydrogenase Metabolite (active): 6-B-naltrexol	unlikely An HIV cohort study naltrexone was only rarely associated with hepatotoxicity (i.e. significant elevations in liver transaminases). The majority of patients were also hepatitis C co-infected, had an alcohol dependency and were on antiretroviral therapy (including PIs and NNRTIs).[53]	unlikely An HIV cohort study naltrexone was only rarely associated with hepatotoxicity (i.e. significant elevations in liver transaminases). The majority of patients were also hepatitis C co-infected, had an alcohol dependency and were on antiretroviral therapy (including PIs and NNRTIs).[53]	unlikely
Oxycodone **OxyContin®** **OxyNEO®** **Supeudol®** **Endocet®** **Percocet®** (acetaminophen/ oxycodone) **Targin®** (naloxone/ oxycodone)	Parent: CYP2D6, 3A4 Metabolites (active): oxymorphone via 2D6; noroxycodone via 3A4. Poor 2D6 metabolizers will not get analgesic effect.	potential ↑ oxycodone concentration In a randomized study of healthy volunteers, **ritonavir 300 mg, lopinavir/ritonavir 400/100 mg** or placebo **BID** was given for 4 days, with 10 mg oxycodone administered orally on day 3. Ritonavir and lopinavir/ritonavir increased oxycodone AUC 3.0-fold (range 1.9- to 4.3-fold; P <0.001) and 2.6-fold (range 1.9- to 3.3-fold; P <0.001), respectively. Both ritonavir (P <0.001) and lopinavir/ritonavir (P <0.05) increased the self-reported drug effect of oxycodone. Therefore, oxycodone dose reduction may be needed during concomitant use of ritonavir-containing therapy to avoid opioid-related adverse effects.[54]	potential ↓ oxycodone concentration	potential ↑ oxycodone concentration
Pentazocine	Parent: extensive liver metabolism with	unknown	unknown	unknown

Interactions Between Opioids and Antiretrovirals

	Narcotic Route of Metabolism[25] 26, 27	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitor** (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
Agonist/ antagonist **Talwin®**	inactive glucuronide metabolite			
Propoxyphene Darvon-N® ***(discontinued in 2010 due to risk of QT prolongation)***	Parent: extensive liver metabolism Metabolite (active): norpropoxyphene	unknown	unknown	unknown
Tramadol **Ralivia®, Tridural®, Ultram®, Zytram XL®** **Tramacet®** (acetaminophen/ tramadol)	Parent: CYP 3A4, 2B6, CYP2D6 Metabolite (active): O-desmethyl tramadol via 2D6[55] Inhibition of 2D6 may lead to ↓ therapeutic response	potential ↑ tramadol concentration	potential ↓ tramadol concentration	potential ↑ tramadol concentration

Key: CYP= Hepatic Cytochrome P450 isoenzyme; AD= Alcohol dehydrogenase; AUC= area under the concentration-time curve. Substrate= route of hepatic elimination of that specific drug (specified by a specific cytochrome P450 isoenzyme); inducer= leads to more rapid clearance of substrates of a specific hepatic isoenzyme (lowers levels of the respective drug and may lead to decreased efficacy); inhibitor= leads to decreased clearance of substrates of a specific hepatic isoenzyme (increases levels of a respective drug and may lead to toxicity). UGT= Uridine diphosphate glucuronyltransferase

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.

References:

1. Bristol-Myers Squibb Canada. Reyataz (atazanavir) Product Monograph. Montreal, QC July 4, 2013.

2. Janssen Inc. Prezista (darunavir) Product Monograph. Toronto, Ontario November 28, 2012.

3. ViiV Healthcare ULC. Telzir (fosamprenavir) Prescribing Information. Montreal, QC February 11, 2014.

4. Merck Frosst Canada Ltd. Crixivan (indinavir) Product Monograph. Kirkland, QC April 17, 2012.

5. AbbVie Corporation. Kaletra (lopinavir/ritonavir) Prescribing Information. Saint Laurent, Canada November 1, 2012.

6. Pfizer Canada Inc. Viracept (nelfinavir) Product Monograph. Kirkland, QC March 4, 2011.

7. AbbVie Corporation. Norvir (ritonavir) Prescribing Information. Saint-Laurent, QC December 18, 2012.

8. Hoffmann-La Roche Ltd. Invirase (saquinavir) Product Monograph. Mississauga, ON May 11, 2012.

9. Boehringer Ingelheim. Aptivus (tipranavir) Product Monograph. Burlington, ON March 11, 2011.

10. Bristol-Myers Squibb Canada. Sustiva (efavirenz) Prescribing Information. Montreal, QC June 11, 2012.

11. Janssen Inc. Intelence (etravirine) Product Monograph. Titusville, NJ November 16, 2013.

12. Boehringer Ingelheim (Canada) Ltd. Viramune and Viramune XR (nevirapine) Product Monograph. Burlington, ON May 30, 2011.

13. Janssen Inc. Edurant (rilpivirine) Product Monograph. Toronto, ON July 20, 2011.

14. ViiV Healthcare ULC. Tivicay (dolutegravir) Prescribing Information. Research Triangle Park, NC August, 2013.

15. Gilead Sciences Inc. Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) Prescribing Information. Foster City, CA August, 2012.

16. Merck Frosst Canada Ltd. Isentress (raltegravir) Prescribing Information. Kirkland, QC January 28, 2014.

17. Hesse LM, von Moltke LL, Shader RI, et al. Ritonavir, efavirenz, and nelfinavir inhibit CYP2B6 activity in vitro: potential drug interactions with bupropion. Drug Metabolism & Disposition 2001;29:100-02.

18. Kharasch ED, Mitchell D, Coles R, et al. Rapid clinical induction of hepatic cytochrome P4502B6 activity by ritonavir. Antimicrob Agents Chemother 2008;52(5):1663-9.

19. Vourvahis M, Dumond J, Patterson K, et al. Effects of tipranavir/ritonavir on the activity of cytochrome p450 enzymes 1A2, 2C9 and 2D6 in healthy volunteers [abstract 52]. 8th International Workshop on Clinical Pharmacology of HIV Therapy, April 16-18, 2007, Budapest, Hungary.

20. ViiV Healthcare ULC. Rescriptor (delavirdine) Product Monograph. Montreal, QC December 15, 2009.

21. Dixit V, Hariparsad N, Li F, et al. Cytochrome P450 enzymes and transporters induced by anti-human immunodeficiency virus protease inhibitors in human hepatocytes: implications for predicting clinical drug interactions. Drug Metab Dispos 2007;35(10):1853-9.

22. Robertson SM, Maldarelli F, Natarajan V, et al. Efavirenz induces CYP2B6-mediated hydroxylation of bupropion in healthy subjects. J Acquir Immune Defic Syndr 2008;49(5):513-9.

23. Lee L, Soon GH, Shen P, et al. Effect of efavirenz and darunavir/ritonavir on bilirubin levels in healthy adult volunteers: role of induction of UGT1A1 and bile efflux transporters [abstract 27]. 11th International Workshop on Clinical Pharmacology of HIV Therapy, April 5-7, 2010, Sorrento, Italy.

24. Crauwels HM, Van Heeswijk R, Stevens T, et al. The effect of TMC278, a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) on CYP3A activity in vivo [abstract P_28]. 10th International Workshop on Clinical Pharmacology of HIV Therapy, April 15-17, 2009, Amsterdam.

25. Bertz RJ, Granneman GR. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. Clinical Pharmacokinetics 1997;32(3):210-58.

26. Bruce RD, Altice FL, Gourevitch MN, et al. Pharmacokinetic drug interactions between opiod agonist therapy and antiretroviral medications: implications and management for clinical practice. . J Acquir Immune Defic Syndr 2006;41:563-72.

27. Micromedex 2.0 [database on the Internet]. Thomson Reuters (Healthcare) Inc. 2012 [cited June 10].

28. Reckitt Benckiser Pharmaceuticals Inc. Subutex & Suboxone Product Monograph. Richmond, VA 2002.

29. Chang Y, Moody D, McCance-Katz EF. Novel metabolites of buprenorphine detected in human liver microsomes and human urine. Drug Metab Dispos 2006;34(3):440-8.

30. Bruce RD, Altice FL. Three case reports of a clinical pharmacokinetic interaction with buprenorphine and atazanavir plus ritonavir. AIDS 2006;20:783-4.

31. McCance-Katz EF, Moody DE, Morse GD, et al. Interaction between buprenorphine and atazanavir or atazanavir/ritonavir. Drug Alcohol Depend 2007;91(2-3):269-78.

32. Vergara-Rodriguez P, Tozzi MJ, Botsko M, et al. Hepatic safety and lack of antiretroviral interactions with buprenorphine/naloxone in HIV-infected opioid-dependent patients. J Acq Immune Def Syndr 2011;56(Suppl 1):S62-7.

33. Sekar V, Tomaka F, Lefebevre E, et al. Pharmacokinetic interactions between darunavir/ritonavir and opioid maintenace therapy using methadone or buprenorphine/naloxone. J Clin Pharmacol 2011;51(2):271-8.

34. Gruber VA, Rainey PM, Moody DE, et al. Interactions between buprenorphine and the protease inhibitors darunavir-ritonavir and fosamprenavir-ritonavir. Clin Infect Dis 2011;Nov 18 [Epub ahead of print].

35. McCance-Katz EF, Moody D, Smith P, et al. Interactions between buprenorphine and antiretrovirals. II. The protease inhibitors nelfinavir, lopinavir/ritonavir, and ritonavir. Clin Infec Dis 2006;43(Suppl 4):S235-46.

36. Bruce RD, Altice F, Moody D, et al. Pharmacokinetic interactions between buprenorphine/naloxone and once-daily lopinavir/ritonavir. J Acquir Immune Defic Syndr 2010;54:511-14.

37. Bruce R, Altice F, Moody D, et al. Pharmacokinetic interactions between buprenorphine/naloxone and tipranavir/ritonavir in HIV-negative subjects chronically receiving buprenorphine/naloxone. Drug Alcohol Depend 2009;105:234-9.

38. McCance-Katz EF, Moody DE, Morse GD, et al. Lack of clinically significant drug interactions between nevirapine and buprenorphine. Am J Addict 2010;19(1):30-7.

39. McCance-Katz EF, Moody D, Morse G, et al. Interactions between buprenorphine and antiretrovirals. I. The nonnucleoside reverse-transcriptase inhibitors efavirenz and delavirdine Clin Infec Dis 2006;43(Suppl 4):S224-34.

40. Baker J, Rainey PM, Moody D, et al. Interactions between buprenorphine and antiretrovirals: nucleos(t)ide reverse transcriptase inhibitors didanosine, lamivudine and tenofovir. Am J Addict 2010 Jan 1;19(1):17-29.

41. Bruce RD, Moody D, Chodkowski D, et al. Pharmacokinetic interactions between buprenorphine/naloxone and raltegravir [abstract MOPE176]. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, July 17-20, 2011, Rome, Italy.

42. Bruce RD, Winkle P, Custodio J, et al. The pharmacokinetic and pharmacodynamic interactions between buprenorphine/naloxone and elvitegravir/cobicistat in subjects receiving chronic buprenorphine/naloxone treatment. J Acq Immune Def Syndr 2013;63(4):480-4.

43. Olkkola KT, Palkama VJ, Neuvonen PJ. Ritonavir's role in reducing fentanyl clearance and prolonging its half-life. Anesthesiology 1999;91:681-85.

44. Kashuba ADM, Lim ML. Interactions between heroin and antiretrovirals. Medscape Portals, Inc, Medscape HIV/AIDS 2002;8(1).

45. Roxane Laboratories I. Orlaam Product Monograph. Columbus, OH 2001.

46. Moody DE, Walsh SL, Rollins DE, et al. Ketoconazole, a cytochrome P450 3A4 inhibitor, markedly increases concentrations of levo-acetyl-alpha-methadol in opioid-naïve individuals. Clinical Pharmacology and Therapeutics 2004;76(2):154-66.

47. McCance-Katz EF, Rainey PM, Smith P, et al. Drug interactions between opioids and antiretroviral medications: interaction between methadone, LAAM, and nelfinavir. American Journal of Addictions 2004;13(2):163-80.

48. Mukwaya G, MacGregor TR, Hoelscher D, et al. Interaction of ritonavir-boosted tipranavir with loperamide does not result in loperamide-associated neurologic side effects in healthy volunteers. Antimicrob Agents Chemother 2005 December;49(12):4903-10.

49. Mikus G, Schmidt L, Burhenne J, et al. Reduction of saquinavir exposure by coadministration of loperamide: a two-way pharmacokinetic interaction. Clin Pharmacokinet 2004;43(14):1015-24.

50. Ramirez J, Innocenti F, Schuetz, et al. CYP2B6, CYP3A4, and CYP2C19 are responsible for the in vitro N-demethylation of meperidine in human liver microsomes. Drug Metab Dispos 2004;32:930-6.

51. Piscitelli S, Rock-Kress D, Bertz R, et al. The effect of ritonavir on the pharmacokinetics of meperidine and normeperidine. Pharmacotherapy 2000;20(5):549-53.

52. Bruce RD, Winkle P, Custodio J, et al. Pharmacokinetics of cobicistat-boosted elvitegravir administered in combination with methadone or buprenorphine/naloxone [abstract A-1250]. 52th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 9-12, 2012, San Francisco, CA.

53. Tetrault JM, Tate JP, McGinnis KA, et al. Hepatic safety and antiretroviral effectiveness in HIV-infected patients receiving naltrexone. Alcohol Clin Exp Res 2012;36(2):318-24.

54. Nieminen TH, Hagelberg NM, Saari TI, et al. Oxycodone concentrations are greatly increased by the concomitant use of ritonavir or lopinavir/ritonavir. Eur J Clin Pharmacol 2010;66(10):977-85.

55. Biovail Pharmaceuticals. Ralivia (tramadol) Prescribing Information. Mississauga, ON June 27, 2008.