Interactions Between Opioids and Protease Inhibitors /Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

	Narcotic Route of Metabolism[1, 2 3]	Mild-Moderate Enzyme Inhibitors Atazanavir-Reyataz®[4] Darunavir - Prezista®[5] Delavirdine-Rescriptor®[6]; Fosamprenavir - Telzir®;[7] Indinavir-Crixivan®[8]; Nelfinavir-Viracept®[9]; Saquinavir-Invirase®[10]	Potent Enzyme Inhibitors Ritonavir - Norvir®[11]; Lopinavir/Ritonavir – Kaletra®[12] Tipranavir/Ritonavir - Aptivus®/Norvir®[13]	Enzyme Inducers Nevirapine - Viramune®[14] Efavirenz-Sustiva® **[15] Etravirine - Intelence®[16] Tipranavir (unboosted) - Aptivus®[13]
Hepatic Substrate		Mainly CYP3A4	CYP3A4> 2D6	CYP3A4
Hepatic Inducer		UGT, 2C9/19 (nelfinavir only) Efavirenz: can act as both an inducer and inhibitor of CYP3A4, but induction properties prevail clinically.	UGT, CYP1A2, CYP2C9/19, 2B6	CYP3A4 Efavirenz: can act as both an inducer and inhibitor of CYP3A4, but induction properties prevail clinically. Tipranavir: when used alone, tipranavir induces CYP3A4 and UGT; when combined with ritonavir, the net effect is CYP3A4 inhibition.[13]
Hepatic Inhibitor		Mainly CYP3A4 (indinavir, nelfinavir, amprenavir, delavirdine, >> saquinavir) Efavirenz also inhibits 2C9, 2C19 (? Clinical significance). Nelfinavir inhibits 2B6 in vitro.	CYP3A4 (potent)> >2D6 >2C9 >2C19 >2A6 >1A2>2E1 At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition.[12] Ritonavir inhibits CYP2B6 in vitro,[17] but induces 2B6 in vivo.[18] Tipranavir: when used alone, tipranavir induces CYP3A4 and UGT; when combined with ritonavir, the net effect is CYP3A4 inhibition.[13]	Efavirenz inhibits CYP2B6 in vitro.
Alfentanil **Alfenta®**	Parent: CYP3A	potential ↑ alfentanil concentration	potential ↑ alfentanil concentration	potential ↓ alfentanil concentration
Buprenorphine **BuTrans®**	Parent: CYP3A4, 2C8 Metabolite (active):	potential ↑ buprenorphine concentration.	potential ↑ buprenorphine concentration	potential ↓ buprenorphine concentration

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Transdermal Patch, Suboxone® **Partial agonist** **Suboxone® (combined buprenorphine and naloxone)**	norbuprenorphine inhibits CYP3A4, 2D6 (this inhibition is not likely to lead to clinically significant interactions);[19] buprenorphine and norbuprenorphine undergo glucuronidation.[20]	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.[21] A prospective, open-label, multiple dose study assessed the kinetics of buprenorphine (BUP) + **ATV 400 mg 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	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.[21] 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	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.[29] 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.[23] Despite these significant decreases in the presence of efavirenz, no participants showed evidence of opiate withdrawal symptoms. Efavirenz kinetics were not affected by buprenorphine. 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

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		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.[22] 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	clinically significant.[25] 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.[25] 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 historical controls. Therefore, this combination may be coadministered without dose	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.[30] 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 combination with caution.[30]

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		norbuprenorphine.[23] A significant increase in the reporting of drowsiness was observed. Delavirdine kinetics were not affected by buprenorphine. 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.[24] 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.[25] <u>Other:</u>	adjustment.[28]	

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		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.[26] 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.[27]		

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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	Net effect unknown; ritonavir may induce UGT and inhibit CYP3A	Unlikely
Diphenoxylate Lomotil®	Parent: ester hydrolysis Metabolite (active): difenoxine (UGT)	no anticipated effect - nelfinavir may ↓ metabolite concentration	possible ↓ metabolite concentration	no anticipated effect with NNRTIs; tipranavir may ↓ metabolite concentration
Fentanyl Duragesic®	Parent: CYP3A	potential ↑ narcotic concentration	174% ↑ fentanyl AUC with ritonavir 900 mg/day. Monitor for respiratory and CNS depression.[31] 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.[11]	potential ↓ narcotic concentration
Heroin	**Heroin** (diacetylmorphine) undergoes deacetylation to 6-	no anticipated effect	**Ritonavir:** via induction of UGT, ritonavir may facilitate	no anticipated effect with NNRTIs; **tipranavir** may

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	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**: via induction of UGT, nelfinavir may facilitate the conversion of morphine to the active metabolite morphine-6-glucuronide; clinical significance is unknown.[32]	the conversion of morphine to the active metabolite morphine-6-glucuronide; clinical significance is unknown. RTV is a potent inhibitor of P-glycoprotein, therefore it may potentiate the effects of opiates in the CNS.[32]	facilitate the conversion of morphine to the active metabolite morphine-6-glucuronide via induction of UGT; clinical significance is unknown
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	potential ↑ hydrocodone concentration - may ↓ metabolite concentration (hydromorphone)	potential ↓ hydrocodone concentration
Hydromorphone Dilaudid®	Parent: UGT> ketoreductase	no anticipated effect - nelfinavir may ↓ hydromorphone concentration	possible ↓ hydromorphone concentration	no anticipated effect with NNRTIs; tipranavir may ↓ hydromorphone concentration
Levomethadyl (LAAM; levo-alpha-acetyl methadol) Orlaam® USA **Note: product D/C due to severe cardiac events (April 2004)**	Parent: CYP3A4 Metabolites: norLAAM, dinorLAAM[33]	*Nelfinavir:* ↓ LAAM & dinorLAAM concentrations; ↑ norLAAM concentrations. No change in nelfinavir concentrations.[34] Interaction not clinically significant.	potential ↑ narcotic concentration. Single dose study of ketoconazole and 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.**[35]	potential ↓ narcotic concentration

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Loperamide Imodium®	Parent: CYP 2C8, 3A4, UGT, Pgp	*Saquinavir (SQV):* In healthy subjects, loperamide 16mg and SQV 600mg resulted in a 46.3% ↓ SCV Cmax and 53.7 ↓ in SQV AUC and 40% ↑ in loperamide AUC. The decrease in SQV AUC may be due to decreased SQV absorption mediated by the effect of loperamide on the GI tract. Avoid use for a prolonged period of time.[36]	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.[37]	no anticipated effect with NNRTIs; In healthy subjects, loperamide 16 mg plus **tipranavir** 750 mg BID for 5.5 days or **tipranavir 750 mg/ritonavir 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.[37]
Meperidine Demerol®	Parent: CYP2B6>>3A4>2C19 Metabolite: normeperidine[38]	potential ↑ meperidine concentration; if PI is boosted with ritonavir, may see ↓ meperidine concentration due to enzyme induction	**No longer contraindicated** in product monograph. Single dose study with with meperidine 50mg and ritonavir 500mg BID x 10 days showed a 67% ↓ meperidine AUC, and 47% ↑ normeperidine AUC.[39] **Therapy can likely be cautiously initiated for short**	potential ↓ narcotic concentration. Combination of **tipranavir/rtv** (see ritonavir)** ↓ meperidine and ↑ normeperidine.[13]

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			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-term co-administration is not recommended.	
Methadone	Parent: CYP3A, 2B6 (*S* isomer), 2C19 (*R** isomer), 2D6 Inhibits: CYP2D6 (weak) * The *R* isomer is active - In vitro, methadone can increase HIV activation and replication. The clinical significance of this is unclear.[40]	**(refer to separate chart on Methadone-Antiretroviral Drug Interactions)**		
Morphine	Parent: UGT Metabolite (active): morphine-6-glucuronide (renal)	no anticipated effect - nelfinavir may ↓ morphine concentration and ↑ active metabolite concentration	possible ↓ morphine concentration and ↑ active metabolite concentration	no anticipated effect; tipranavir may ↓ morphine concentration and ↑ active metabolite concentration
Nalbuphine Nubain® Agonist/ antagonist	Parent: liver metabolism to inactive metabolites	unknown	unknown	unknown
Naloxone Narcan® Opioid antagonist	Parent: UGT	no anticipated effect • nelfinavir may ↓ naloxone concentration	possible ↓ naloxone concentration In 12 HIV-negative subjects on stable	no anticipated effect with NNRTIs, tipranavir may ↓ naloxone concentration

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		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.[41]	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 historical controls. Therefore, this combination may be coadministered without dose adjustment.[28]	
Naltrexone ReVia® Opioid antagonist	Parent: Not via CYP450; metabolized via dihydrodiol dehydrogenase Metabolite (active): 6-B-naltrexol	unlikely	unlikely	unlikely
Oxycodone Supeudol®	Parent: CYP2D6, 3A4 Metabolites (active): oxymorphone via 2D6; noroxycodone via 3A4. Poor 2D6 metabolizers will not get analgesic effect.	potential ↑ oxycodone concentration	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	potential ↓ oxycodone concentration

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			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.[42]	
Pentazocine **Talwin®** **Agonist/ antagonist**	Parent: extensive liver metabolism with inactive glucuronide metabolite	unknown	unknown	unknown
Propoxyphene **Darvon-N®**	Parent: extensive liver metabolism Metabolite (active): norpropoxyphene	unknown	unknown	unknown
Tramadol **USA: Ultram®** **Canada: Ralivia®, Zytram®, Tridural®**	Parent: CYP 3A4, 2B6, CYP2D6 Metabolite (active): O-desmethyl tramadol via 2D6[43] 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). Protease inhibitors= saquinavir, indinavir, nelfinavir, amprenavir, ritonavir; NNRTI's= delavirdine, efavirenz, nevirapine; UGT= Uridine diphosphate glucuronyltransferase
** Since efavirenz is both an inhibitor and inducer of CYP3A4, predictions on drug interactions are difficult. Clinically, 3A4 induction predominates. Efavirenz also inhibits CYP2C9 and 2C19.

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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