

**Interactions Between Opioids and Protease Inhibitors /Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI's)**

	<b>Narcotic Route of Metabolism<sup>1</sup></b>	<b><u>Mild-Moderate Enzyme Inhibitors</u></b> Atazanavir-Reyataz <sup>®2</sup> ; Delavirdine-Rescriptor <sup>®3</sup> ; Fosamprenavir-Telzir <sup>®4</sup> ; Indinavir-Crixivan <sup>®5</sup> ; Nelfinavir-Viracept <sup>®6</sup> ; Saquinavir-Invirase <sup>®7</sup> ; Efavirenz-Sustiva <sup>®**8</sup>	<b><u>Potent Enzyme Inhibitors</u></b> Ritonavir - Norvir <sup>®9</sup> ; Lopinavir/Ritonavir – Kaletra <sup>®10</sup>	<b><u>Enzyme Inducers</u></b> Nevirapine - Viramune <sup>®11</sup> Efavirenz-Sustiva <sup>®**8</sup> Tipranavir-Aptivus <sup>®12</sup>
<b>Hepatic Substrate</b>		Mainly CYP3A4	CYP3A4> 2D6	CYP3A4
<b>Hepatic Inducer</b>		GT, 2C9/19 (nelfinavir only) CYP3A4 (efavirenz only)	GT, CYP1A2, CYP2C9/19	CYP3A4 (NB: Efavirenz can act as both an inducer and inhibitor of CYP3A4, but induction properties prevail clinically). GT (tipranavir)
<b>Hepatic Inhibitor</b>		Mainly CYP3A4 (indinavir, nelfinavir, amprenavir, delavirdine, >> saquinavir) Efavirenz also inhibits 2C9, 2C19 (? Clinical significance). Nelfinavir inhibits 2B6 in vitro.	CYP3A4 >2D6 >2C9 >2C19 >2A6 >1A2>2E1 (potent). Ritonavir inhibits CYP2B6 in vitro.	Efavirenz inhibits CYP2B6 in vitro.
<b>Alfentanil Alfenta<sup>®</sup></b>	Parent: CYP3A	potential ↑ narcotic concentration	potential >3 fold ↑ narcotic concentration	potential ↓ narcotic concentration
<b>Buprenorphine Subutex<sup>®</sup> USA Partial agonist</b>	Parent: CYP3A4, 2C8 Metabolite: norbuprenorphine inhibits: CYP3A4, 2D6 (this inhibition is not likely to lead to clinically significant interactions); <sup>13</sup> buprenorphine and norbuprenorphine undergo glucuronidation. <sup>14</sup>	potential ↑ narcotic concentration.  Case report of 3 subjects on <b>atazanavir 300/ritonavir 100 mg</b> who experienced symptoms of opiate excess when initiated on buprenorphine 8-14 mg/day. In all cases, symptoms improved	potential ↑ narcotic concentration  Case report of 3 subjects on <b>atazanavir 300/ritonavir 100 mg</b> who experienced symptoms of opiate excess when initiated on buprenorphine 8-14 mg/day. In all cases,	potential ↓ narcotic concentration  In a study of HIV-negative opioid-dependent patients receiving chronic buprenorphine/naloxone, the addition of <b>efavirenz 600 mg per day</b> for 15

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		<p>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.<sup>15</sup></p> <p>A prospective, open-label, multiple dose study assessed the kinetics of buprenorphine (BUP) + <b>ATV 400 mg or ATV/r 300mg/100mg daily</b> 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:</p> <ul style="list-style-type: none"> <li>• BUP treatment did not significantly alter ATV or RTV concentrations (~31% ↓ in AUC and ~33% ↓ in</li> </ul>	<p>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.<sup>15</sup></p> <p>In a study of 10 HIV-negative opioid-dependent patients receiving chronic buprenorphine/naloxone, the addition of <b>lopinavir/ritonavir 400/100 mg BID</b> 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</p>	<p>days resulted in a 50% ↓ in the AUC of buprenorphine and 71% ↓ AUC of norbuprenorphine.<sup>16</sup> Despite these significant decreases in the presence of efavirenz, no participants showed evidence of opiate withdrawal symptoms. Efavirenz kinetics were not affected by buprenorphine.</p>

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		<p>Cmin of ATV when BUP was given concomitantly).</p> <ul style="list-style-type: none"> <li>The coadministration of ATV +/- RTV with BUP for 5 days significantly ↑ BUP and BUP metabolite levels.                             <ul style="list-style-type: none"> <li>ATV + BUP: BUP AUC ↑ 1.9 fold; BUP Cmax ↑ 1.6 fold; BUP Cmin ↑ 2 fold</li> <li>ATV/r + BUP: BUP AUC ↑ 1.7 fold; BUP Cmax ↑ 1.37 fold; BUP Cmin ↑ 1.7 fold</li> </ul> </li> </ul> <p>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.  <b>[McCance-Katz, 2007 #1448]</b></p>	<p>buprenorphine, not likely clinically significant.<sup>17</sup></p> <p>In the same study, the addition of <b>ritonavir</b> 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.<sup>17</sup></p>	

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		<p>In a study of HIV-negative opioid-dependent patients receiving chronic buprenorphine/naloxone, the addition of <b>delavirdine</b> 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.<sup>16</sup> A significant increase in the reporting of drowsiness was observed. Delavirdine kinetics were not affected by buprenorphine.</p> <p>In a study of 10 HIV-negative opioid-dependent patients receiving chronic buprenorphine/naloxone, the addition of <b>nelfinavir</b> 1250 mg BID for 5 days did not affect buprenorphine or norbuprenorphine AUC (Cmax ↓ norbuprenorphine). No participants showed evidence of opiate withdrawal symptoms</p>		

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		Nelfinavir AUC was not affected by buprenorphine. <sup>17</sup>		
<b>Codeine</b>	Parent: GT> CYP2D6>CYP3A Metabolite: GT (morphine)	unlikely - nelfinavir may ↓ narcotic concentration	potential ↓ narcotic concentration	unlikely
<b>Diphenoxylate Lomotil<sup>®</sup></b>	Parent: ester hydrolysis Metabolite: GT (difenoquine)	no anticipated effect - nelfinavir may ↓ metabolite concentration	possible ↓ metabolite concentration	no anticipated effect with NNRTIs; tipranavir may ↓ metabolite concentration
<b>Fentanyl Duragesic<sup>®</sup></b>	Parent: CYP3A	potential ↑ narcotic concentration	174% ↑ fentanyl AUC with ritonavir 900 mg/day. Consider dose reduction with continuous IV or transdermal fentanyl. Monitor for respiratory and CNS depression. <sup>18</sup> Impact of coadministering lower ritonavir doses with fentanyl are unclear; monitor for side effects and reduce fentanyl dose if necessary.	potential ↓ narcotic concentration
<b>Heroin</b>	<b>Heroin</b> (diacetylmorphine) undergoes deacetylation to 6-monoacetylase morphine and morphine. Morphine undergoes glucuronidation to morphine-6-glucuronide.  Parent: Deacetylase	no anticipated effect  <b>Nelfinavir:</b> via induction of GT, nelfinavir may facilitate the conversion of morphine to the active metabolite morphine-6-glucuronide; clinical significance is unknown. <sup>19</sup>	<b>Ritonavir:</b> via induction of GT, ritonavir may facilitate 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	no anticipated effect with NNRTIs; <b>tipranavir</b> may facilitate the conversion of morphine to the active metabolite morphine-6-glucuronide via induction of GT; clinical significance is unknown

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	Metabolite: GT (6-monoacetylase morphine) Morphine and morphine-6-glucuronide are also P-glycoprotein substrates.		the effects of opiates in the CNS. <sup>19</sup>	
<b>Hydrocodone Hycodan<sup>®</sup></b>	Parent: CYP2D6, 3A Metabolite: GT (hydromorphone)	potential ↑ narcotic concentration - nelfinavir may ↓ metabolite concentration	potential 1.5-3 fold ↑ narcotic concentration - may ↓ metabolite concentration	potential ↓ narcotic concentration
<b>Hydromorphone Dilaudid<sup>®</sup></b>	Parent: GT> ketoreductase	no anticipated effect - nelfinavir may ↓ hydromorphone concentration	possible ↓ hydromorphone concentration	no anticipated effect with NNRTIs; tipranavir may ↓ hydromorphone concentration
<b>Levomethadyl (LAAM; levo-alpha-acetyl methadol) Orlaam<sup>®</sup> USA</b>  <b>Note: product D/C due to severe cardiac events (April 2004)</b>	Parent: CYP4503A4 Metabolites: norLAAM, dinorLAAM <sup>20</sup>	<u>Nelfinavir</u> : ↓ LAAM & dinorLAAM concentrations; ↑ norLAAM concentrations. No change in nelfinavir concentrations. <sup>21</sup> 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. <sup>22</sup>	potential ↓ narcotic concentration
<b>Loperamide Imodium<sup>®</sup></b>	Parent: GT> CYP, Pgp	no anticipated effect - nelfinavir may ↓ loperamide concentration	In healthy subjects, loperamide 16 mg plus ritonavir 200 mg BID for 5.5 days led to ↑ AUC of both loperamide and its	no anticipated effect with NNRTIs;  In healthy subjects, loperamide 16 mg plus

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			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. <sup>23</sup>	tipranavir 750 mg BID for 5.5 days or <b>tipranavir 750 mg/ritonavir 200 mg BID</b> 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. <sup>23</sup>
<b>Meperidine Demerol®</b>	Parent: CYP?>> GT Metabolite: normeperidine	potential ↑ narcotic concentration	<b>Contraindicated</b> in Norvir product monograph, however single dose study showed a 67% ↓ meperidine AUC, and 47% ↑ normeperidine AUC. <sup>24</sup> <b>Based on this, therapy</b>	potential ↓ narcotic concentration.  Combination of <b>tipranavir/rtv</b> and meperidine not studied; potential for ↓ meperidine

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			<b>can likely be cautiously initiated; however, potential for normeperidine toxicity (i.e. seizures) with prolonged or high-dose therapy. Therefore, close monitoring is still suggested.</b>	and ↑ normeperidine. Monograph states that dosage ↑ and long-term use of meperidine not recommended due to ↑ metabolite concentrations which has both analgesic activity and CNS stimulant activity (e.g., seizures). <sup>12</sup>
<b>Methadone</b>	Parent: CYP3A>>GT Inhibits: CYP2D6 (weak)  In vitro, methadone can increase HIV activation and replication. The clinical significance of this is unclear. <sup>25</sup>	<b>(refer to separate chart on Methadone-Antiretroviral Drug Interactions)<sup>22-37</sup></b>		
<b>Morphine</b>	Parent: GT Metabolite: morphine-6-glucuronide (renal)	no anticipated effect - nelfinavir may ↓ narcotic concentration	possible ↓ narcotic concentration	no anticipated effect
<b>Naloxone Narcan<sup>®</sup> Opioid antagonist</b>	Parent: GT	no anticipated effect - nelfinavir may ↓ naloxone concentration	possible ↓ naloxone concentration	no anticipated effect with NNRTIs, tipranavir may ↓ naloxone concentration
<b>Naltrexone ReVia<sup>®</sup> Opioid antagonist</b>	Parent: ketoreductase>GT Metabolite: GT (6-naltrexol)	unlikely	possible ↓ naltrexone concentration	unlikely

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<b>Oxycodone Supeudol<sup>®</sup></b>	Parent: CYP2D6, 3A, ketoreductase	potential ↑ narcotic concentration	potential 1.5-3 fold ↑ narcotic concentration	potential ↓ narcotic concentration
<b>Propoxyphene Darvon-N<sup>®</sup></b>	Parent: CYP? Inhibits: CYP2D6 Metabolite: norpropoxyphene	potential ↑ narcotic concentration	potential for ↑ narcotic concentration; use with caution, propoxyphene dose ↓ may be necessary	potential ↓ narcotic concentration
<b>Tramadol Ultram<sup>®</sup> USA</b>  <b>Non-opioid analgesic</b>	Parent: CYP2D6 Metabolite: mono-O-desmethyl tramadol <sup>26</sup>	unlikely	1.5-3 fold ↑ tramadol concentration	unlikely

Key: CYP= Hepatic Cytochrome P450 isoenzyme; GT= Glucuronyl transferase; 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  
\*\* 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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