Interactions Between Opioids and Antiretrovirals

Antiretroviral Pharmacokinetic Characteristics (summary):

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Mainly CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic Inhibitor</td>
<td>Mainly CYP3A4 (darunavir, indinavir, nevirapine, amprenavir &gt;&gt; saquinavir)</td>
</tr>
<tr>
<td><strong>Atazanavir</strong>: 3A4, UGT1A1 &gt;&gt; 2C8 (weak)</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Nelfinavir</strong>: 2B6 in vitro.</td>
<td></td>
</tr>
<tr>
<td><strong>Ritonavir</strong>: CYP3A4 (potent) &gt; 2D6 &gt; 2C9 &gt; 2C19 &gt; 2A6 &gt; 1A2 &gt; 2E1.</td>
<td>At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition. Ritonavir inhibits CYP2B6 in vitro, but induces 2B6 in vivo.</td>
</tr>
<tr>
<td><strong>Tipranavir</strong>: 2D6</td>
<td></td>
</tr>
<tr>
<td>Hepatic Inducer</td>
<td>Nelfinavir: UGT, 2B6, 2C8, 2C9/19</td>
</tr>
<tr>
<td>Nelfinavir: UGT, 2B6, 2C8, 2C9/19</td>
<td>Efavirenz: 3A4 (potent), 2B6 and UGT1A1</td>
</tr>
</tbody>
</table>

| Integrase Inhibitors | dolutegravir (Tivicay®), elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine), raltegravir (Isentress®) |

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<tr>
<th>Protease Inhibitors (PIs)</th>
<th>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</th>
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<tr>
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<td>efavirenz (Sustiva®), etravirine (Intecelence®), nevirapine (Viramune®), rilpivirine (Edurant®)</td>
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Hepatic Inhibitor: Mainly CYP3A4 (darunavir, indinavir, nevirapine, 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. 


Ritonavir: CYP3A4 (potent) > 2D6 > 2C9 > 2C19 > 2A6 > 1A2 > 2E1. 

At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition. Ritonavir inhibits CYP2B6 in vitro, but induces 2B6 in vivo. 

Tipranavir: 2D6

Hepatic Inducer: Nelfinavir: UGT, 2B6, 2C8, 2C9/19 

Ritonavir: UGT, CYP1A2, CYP2C9/19, 2B6 

Efavirenz: 3A4 (potent), 2B6 and UGT1A1 

Etravirine: 3A4 (weak) 

Dolutegravir does not induce CYP1A2, CYP2B6, or CYP3A4 in vitro.


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<td>Tipranavir: mixed induction/inhibition effects; often acts as inducer of CYP3A4 (potent) and UGT, even when boosted with ritonavir</td>
<td>Nevirapine: 3A4, 2B6 (potent)</td>
<td>Elvitegravir: CYP2C9 (modest)</td>
</tr>
<tr>
<td>Rilpivirine: 2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak). A clinically relevant effect on CYP enzyme activity is considered unlikely with the 25 mg dose.</td>
<td>Raltegravir has no inhibitory or inductive potential in vitro.</td>
<td></td>
</tr>
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### Narcotic Route of Metabolism

**Parent:** CYP3A<br>
**Potential ↑ alfentanil concentration**

**Nortrenorphine (active): norbuprenorphine inhibits CYP3A4, 2D6 (this inhibition is not likely to lead to clinically significant interactions):**

- Buprenorphine and norbuprenorphine undergo glucuronidation. Potential mechanism may be due to CYP3A4 inhibition by buprenorphine at reduced doses and titrate slowly.

**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.**

- 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.

- 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. 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...
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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.\textsuperscript{31}

A prospective cohort study did not observe hepatic pharmacodynamic changes 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.\textsuperscript{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.\textsuperscript{42}
### Interactions Between Opioids and Antiretrovirals

**Narcotic Route of Metabolism**

25, 26, 27

**Protease Inhibitors**

- atazanavir (Reyataz®)
- darunavir (Prezista®)
- fosamprenavir (Telzir®)
- indinavir (Crixivan®)
- lopinavir/ritonavir (Kaletra®)
- nelfinavir (Viracept®)
- ritonavir (Norvir®)
- saquinavir (Invirase®)
- tipranavir (Aptivus®)

**NNRTIs**

- efavirenz (Sustiva®)
- etravirine (Intelence®)
- nevirapine (Viramune®)
- rilpivirine (Edurant®)

**Integrase Inhibitor**

(i.e. elvitegravir/cobicistat; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)

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**Interactions** (i.e. significant elevations in liver transaminases) in patients on buprenorphine/naloxone with atazanavir ± ritonavir.

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 ↑ norbuprenorphine exposure is unknown, close monitoring is recommended with this combination.

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.

buprenorphine (or buprenorphine/naloxone) maintenance therapy may need to be adjusted in some patients.

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. 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.

Prepared by: Michelle Foisy, Pharm.D., Northern Alberta Program, Edmonton, Alberta. Updated by Michelle Foisy, Pharm.D., Alice Tseng, Pharm.D., Toronto General Hospital. September 2014

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|                              | indinavir (Crixivan®)
|                              | lopinavir/ritonavir (Kaletra®)
|                              | nevirapine (Viramune®)
|                              | raltegravir (Edurant®) |
|                              | efavirenz (Sustiva®)
|                              | etravirine (Intelence®)
|                              | rilpivirine (Edurant®) |

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.

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.

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...
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<td>efavirenz (Sustiva®)^10, etravirine (Intelence®)^11, nevirapine (Viramune®)^12, rilpivirine (Edurant®)^13</td>
<td>(i.e. elvitegravir/cobicistat; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)</td>
<td></td>
</tr>
<tr>
<td>historical controls. Therefore, this combination may be coadministered without dose adjustment.¹⁶</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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, but tipranavir may be less effective due to decreased tipranavir plasma concentrations; coadminister...
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<td>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</td>
<td>efavirenz (Sustiva®)¹⁰, etravirine (Intence®)¹¹, nevirapine (Viramune®)¹², rilpivirine (Edurant®)¹³</td>
<td>combination with caution.³⁷</td>
</tr>
<tr>
<td>Butorphanol Apo®-Butorphanol Agonist/ Antagonist</td>
<td>Parent: Extensive liver metabolism via oxidation and conjugation to inactive metabolites</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>Codeine</td>
<td>Parent: UGT (to codeine-6-glucuronide); &gt;CYP2D6 (to morphine-active) &gt;CYP3A (to norcodeine-active) Rapid metabolizers of codeine via 2D6 may lead to high levels of morphine and toxicity.</td>
<td>Unlikely with unboosted PIs. Net effect unknown with ritonavir, as ritonavir may induce UGT and inhibit CYP3A.</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Diphenoxylate Lomotil®</td>
<td>Parent: ester hydrolysis Metabolite (active): difenoxine (UGT)</td>
<td>No anticipated effect with unboosted atazanavir or fosamprenavir. Nelfinavir or ritonavir-boosted PIs may ↓ metabolite concentration via UGT induction.</td>
<td>no anticipated effect</td>
</tr>
<tr>
<td>Fentanyl Duragesic®</td>
<td>Parent: CYP3A</td>
<td>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</td>
<td>potential ↓ narcotic concentration</td>
</tr>
<tr>
<td>Heroin</td>
<td>Heroin (diacetylmorphine)</td>
<td>No anticipated effect with unboosted atazanavir or fosamprenavir.</td>
<td>Potential ↑ opiate.</td>
</tr>
</tbody>
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**Notes:**
- Combination with caution:³⁷
- Unlikely: Unlikely with unboosted PIs. Net effect unknown with ritonavir, as ritonavir may induce UGT and inhibit CYP3A.
- Potentially ↑ narcotic concentration: Potential ↑ opiate.

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| **Hydrocodone**             | **Hycodan®**        |        | potential ↑ hydrocodone concentration
| Parent: CYP2D6, 3A          | Metabolite (active): hydromorphone via 2D6 | potential ↓ hydrocodone concentration
| Metabolites: norLAAM, dinorLAAM | Poor metabolizers of 2D6 will not produce hydromorphone and derive little/no analgesic benefit | potential ↓ hydromorphone concentration
| Ritonavir may ↓ metabolite concentration (hydromorphone), clinical significance unclear. | Cobicistat may ↓ metabolite concentration (hydromorphone), clinical significance unclear. |

| **Hydromorphone**           | **Dilaudid®**       |        | No anticipated effect with unboosted atazanavir or fosamprenavir. |
| Parent: UGT> ketoreductase  | Metabolite: norLAAM, dinorLAAM | no anticipated effect | no anticipated effect |

| **Levomethadyl**            | **(LAAM; levo-alpha-acetyl)** |        | potential ↑ narcotic concentration
| Parent: CYP3A4               | Metabolites: norLAAM, dinorLAAM | potential ↓ narcotic concentration | potential ↑ narcotic concentration |

### Narcotic Route of Metabolism

Narcotic Route of Metabolism: A process in which narcotics undergo deacetylation to 6-monoacetyl morphine and morphine. Morphine undergoes glucuronidation (UGT) to morphine-6-glucuronide.

Parent: Deacetylase
Metabolite: UGT (6-monoacetyl morphine)
Morphine and morphine-6-glucuronide are also P-glycoprotein substrates.

### Protease Inhibitors

- **atazanavir (Reyataz®)**
- **darunavir (Prezista®)**
- **fosamprenavir (Telzir®)**
- **indinavir (Crixivan®)**
- **lopinavir/ritonavir (Kaletra®)**
- **nelfinavir (Viracept®)**
- **ritonavir (Norvir®)**
- **saquinavir (Invirase®)**
- **tipranavir (Aptivus®)**

### NNRTIs

- **efavirenz (Sustiva®)**
- **etravirine (Intelence®)**
- **nevirapine (Viramune®)**
- **rilpivirine (Edurant®)**

### Integrase Inhibitor

(i.e. elvitegravir/cobicistat; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
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<td>methadol) Orlaam® USA Note: product D/C due to severe cardiac events (April 2004)</td>
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**Loperamide Imodium®** Parent: CYP 2C8, 3A4, UGT, Pgp

In healthy subjects, loperamide 16 mg plus **ritonavir 200 mg BID** for 5.5 days resulted in **46.3% ↓** saquinavir C\(\text{max}\) 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.

In healthy subjects, loperamide 16 mg and **saquinavir 600mg** resulted in a 46.3% ↓ saquinavir C\(\text{max}\) 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.

In healthy subjects, loperamide 16 mg plus **tipranavir 750 mg BID** for 5.5 days or **tipranavir 750 mg/ritonavir**

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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.

### Meperidine (Demerol®)

- Parent: CYP2B6>>3A4>2C19
- Metabolite: normeperidine\(^90\)

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.

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<tr>
<th><strong>Narcotic Route of Metabolism</strong></th>
<th><strong>Protease Inhibitors</strong></th>
<th><strong>NNRTIs</strong></th>
<th><strong>Integrase Inhibitor</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methadone</strong></td>
<td></td>
<td></td>
<td>(i.e. elvitegravir/cobicistat; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)</td>
</tr>
<tr>
<td>Parent: CYP3A, 2B6 (S isomer), 2C19 (R* isomer), 2D6</td>
<td>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</td>
<td>efavirenz (Sustiva®)¹⁰, etravirine (Intence®)¹¹, nevirapine (Viramune®)¹², rilpivirine (Edurant®)¹³</td>
<td>term co-administration is not recommended. Tipranavir/rtv: ↓ meperidine and ↑ normeperidine.⁹</td>
</tr>
<tr>
<td><strong>Morphine</strong></td>
<td>Parent: UGT Metabolite (active): morphine-6-glucuronide (renal)</td>
<td>No anticipated effect with unboosted atazanavir and fosamprenavir.</td>
<td>no anticipated effect</td>
</tr>
<tr>
<td><strong>Nalbuphine</strong></td>
<td>Parent: liver metabolism to inactive metabolites</td>
<td>Nelfinavir and ritonavir may ↓ morphine concentration and ↑ active metabolite concentration.</td>
<td>no anticipated effect</td>
</tr>
<tr>
<td><strong>Naloxone</strong></td>
<td>Parent: UGT</td>
<td>No anticipated effect with unboosted atazanavir and fosamprenavir.</td>
<td>no anticipated effect</td>
</tr>
<tr>
<td><strong>Suboxone®</strong></td>
<td>Parent: liver metabolism to inactive metabolites</td>
<td>Nelfinavir and ritonavir may ↓ naloxone concentration. Also see entries under “Buprenorphine” for interaction data with buprenorphine/naloxone.</td>
<td>In 18 subjects on stable buprenorphine/naloxone who received elvitegravir 150 mg/cobicistat 150 mg daily for 10 days, buprenorphine AUC ↑ 35%, Cmax ↑ 12%, Ctaph ↓ 66%, norbuprenorphine AUC ↑ 42%, Cmax ↑ 24%, Ctaph ↑ 57%, while naloxone AUC and Cmax ↓ 28%. These changes were not considered clinically significant, and no dose adjustments are needed.</td>
</tr>
<tr>
<td><strong>Targin®</strong></td>
<td>Parent: liver metabolism to inactive metabolites</td>
<td>unknown</td>
<td>unknown</td>
</tr>
</tbody>
</table>

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**Interactions Between Opioids and Antiretrovirals**

Prepared by: Michelle Foisy, Pharm.D., Northern Alberta Program, Edmonton, Alberta. Updated by Michelle Foisy, Pharm.D., Alice Tseng, Pharm.D., Toronto General Hospital. September 2014

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<th>Integrase Inhibitor</th>
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<tbody>
<tr>
<td><strong>Narcotic Route of Metabolism</strong></td>
<td>atazanavir (Reyataz®)¹, darunavir (Prezista®)², fosamprenavir (Telzir®)³, indinavir (Crixivan®)⁴, lopinavir/ritonavir (Kaltra®)⁵, nelfinavir (Viracept®)⁶, ritonavir (Norvir®)⁷, saquinavir (Invirase®)⁸, tipranavir (Aptivus®)⁹</td>
<td>efavirenz (Sustiva®)¹⁰, etravirine (Intenence®)¹¹, nevirapine (Viramune®)¹², rilpivirine (Edurant®)¹³</td>
<td>(i.e. elvitegravir/cobicistat; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)</td>
</tr>
<tr>
<td><strong>Naltrexone</strong></td>
<td></td>
<td></td>
<td>required when coadministering with elvitegravir/cobicistat.¹²</td>
</tr>
<tr>
<td><strong>Opioid antagonist</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ReVia®</strong></td>
<td>Parent: Not via CYP450; metabolized via dihydrodiol dehydrogenase</td>
<td>unlikely</td>
<td>unlikely</td>
</tr>
<tr>
<td><strong>Metabolite (active): 6-B-naltrexol</strong></td>
<td>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</td>
<td>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</td>
<td>unlikely</td>
</tr>
<tr>
<td><strong>Oxycodone</strong></td>
<td>Parent: CYP2D6, 3A4</td>
<td>potential ↑ oxycodone concentration</td>
<td>potential ↓ oxycodone concentration</td>
</tr>
<tr>
<td><strong>OxyContin®</strong></td>
<td>Metabolites (active): oxymorphone via 2D6; noroxycodone via 3A4. Poor 2D6 metabolizers will not get analgesic effect.</td>
<td>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 &lt;0.001) and 2.6-fold (range 1.9- to 3.3-fold, P &lt;0.001), respectively. Both ritonavir (P &lt;0.001) and lopinavir/ritonavir (P &lt;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</td>
<td>potential ↑ oxycodone concentration</td>
</tr>
<tr>
<td><strong>OxyNEO®</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Supeudol®</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endocet®</strong></td>
<td>Parent: extensive liver metabolism with</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td><strong>Percocet®</strong> (acetaminophen/oxycodone)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Targin®</strong> (naloxone/oxycodone)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pentazocine</strong></td>
<td>Parent: extensive liver metabolism with</td>
<td>unknown</td>
<td>unknown</td>
</tr>
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<th>NNRTIs: efavirenz (Sustiva®)¹⁰, etravirine (Intelence®)¹¹, nevirapine (Viramune®)¹², rilpivirine (Edurant®)¹³</th>
<th>Integrate Inhibitor: (i.e. elvitegravir/cobicistat; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agonist/ antagonist</td>
<td>inactive glucuronide metabolite</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>Talwin®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propoxyphene Darvon-N® (discontinued in 2010 due to risk of QT prolongation)</td>
<td>Parent: extensive liver metabolism</td>
<td>metabolite (active): norpropoxyphene</td>
<td>unknown</td>
</tr>
<tr>
<td></td>
<td>Tramadol</td>
<td>Parent: CYP 3A4, 2B6, CYP2D6</td>
<td>Metabolite (active): O-desmethyl tramadol via 2D6⁵⁺</td>
</tr>
<tr>
<td></td>
<td>Ralivia®, Tridural®, Ultram®, Zytram XL®, Tramacet® (acetaminophen/tramadol)</td>
<td>Inhibition of 2D6 may lead to ↓ therapeutic response</td>
<td></td>
</tr>
</tbody>
</table>

Key: CYP= Hepatic Cytochrome P450 isoenzyme; AD= Alcohol dehydrogenase; AUC= area under the concentration-time curve. Substrate= route of hepatic elimination of a 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 glucuronosyltransferase

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


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