### Antiretroviral Pharmacokinetic Characteristics (summary):

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Hepatic Inhibitor</th>
<th>Integrate Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mainly CYP3A4</td>
<td>Mainly CYP3A4 (darunavir, indinavir, nelfinavir, amprenavir &gt;&gt; saquinavir)</td>
<td>Dolutegravir: UGT1A1, CYP3A4 (10-15%).</td>
</tr>
<tr>
<td>Rilpivirine: CYP3A4 (major), as well as CYP2C19, 1A2, 2C8/9/10 (minor).</td>
<td>Raltegravir: UGT1A1</td>
<td>Raltegravir inhibits the renal organic cation transporter, OCT2.</td>
</tr>
<tr>
<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>
<td>At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition. Ritonavir inhibits CYP2B6 in vitro, but induces 2B6 in vivo.</td>
<td>Raltegravir has no inhibitory or inductive potential in vitro.</td>
</tr>
<tr>
<td>Nelfinavir: 2B6 in vitro.</td>
<td>Tipranavir: 2D6</td>
<td>Dolutegravir does not induce CYP1A2,</td>
</tr>
</tbody>
</table>

### Protease Inhibitors (PIS)

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

### Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

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

### Integrate Inhibitors

- Dolutegravir (Tivicay®)
- elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)
- raltegravir (Isentress®)
**Predicted Interactions Between Psychotropics and Antiretrovirals**

<table>
<thead>
<tr>
<th><strong>Protease Inhibitors (PIs)</strong></th>
<th><strong>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</strong></th>
<th><strong>Integrase Inhibitors</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir: UGT, CYP1A2, CYP2C9/19, 2B6</td>
<td>Etravirine&lt;sup&gt;11&lt;/sup&gt;: 3A4 (weak)</td>
<td>CYP2B6, or CYP3A4 in vitro.&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tipranavir: mixed induction/inhibition effects; often acts as inducer of CYP3A4 (potent) and UGT, even when boosted with ritonavir&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Nevirapine&lt;sup&gt;12&lt;/sup&gt;: 3A4, 2B6 (potent)</td>
<td>Elvitegravir: CYP2C9 (modest)</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine: 2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak)&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Raltegravir has no inhibitory or inductive potential in vitro.&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Psychotropic Route of Metabolism<sup>28-29</sup>

#### **Protease Inhibitors**
- atazanavir (Reyataz®)<sup>1</sup>,
- darunavir (Prezista®)<sup>2</sup>,
- fosamprenavir (Telzir®)<sup>3</sup>,
- indinavir (Crixivan®)<sup>4</sup>,
- lopinavir/ritonavir (Kaletra®)<sup>5</sup>,
- nelfinavir (Viracept®)<sup>6</sup>,
- ritonavir (Norvir®)<sup>7</sup>,
- saquinavir (Invirase®)<sup>8</sup>,
- tipranavir (Aptivus®)<sup>9</sup>

#### **NNRTIs**
- efavirenz (Sustiva®)<sup>10</sup>,
- etravirine (Intence®)<sup>11</sup>,
- nevirapine (Viramune®)<sup>12</sup>,
- rilpivirine (Edurant®)<sup>13</sup>

#### **Integrase Inhibitors**
- dolutegravir (Tivicay®),
- elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)<sup>15</sup>.
- raltegravir (Isentress®)<sup>16</sup>

### Antidepressants - Tricyclic (TCA's), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and others

| Amitriptyline Elavil® | Parent: CYP2D6, 2C19, 3A> GT | Possible ↑ TCA concentrations | Possible ↓ TCA concentrations
<table>
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<tr>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Metabolite: CYP2D6 (nortriptyline)</td>
<td>Etravirine: Possible ↑ or ↓ amitriptyline concentrations.&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Potential for ↑ TCA concentrations with elvitegravir/cobicistat. Monitor for response and adjust antidepressant dose accordingly.&lt;sup&gt;16&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

| Bupropion Wellbutrin® Zyban® | Parent: CYP2B6 | In vitro data suggest a strong potential for nelfinavir and ritonavir to inhibit bupropion metabolism. Indinavir, saquinavir and amprenavir were only weakly inhibitory of bupropion; hence no or only minor increase in bupropion concentrations anticipated.<sup>17</sup> | In vitro data suggest a strong potential for efavirenz to inhibit bupropion metabolism.<sup>17</sup> However, in 13 healthy volunteers, co-administration of efavirenz 600 mg QD and single dose bupropion 150 mg showed 55% ↓ AUC and 34% ↓ Cmax of bupropion and ↓ t1/2 of hydroxybupropion (active metabolite).<sup>22</sup> Monitor for therapeutic response when using |
| Metabolite (active): hydroxybupropion | In vivo data suggest induction. In an open-label, 3- | Potential for ↑ bupropion concentrations with elvitegravir/cobicistat. Monitor for response and adjust antidepressant dose accordingly.<sup>15</sup> |
| Inhibitor: CYP2D6 (parent and active metabolite)<sup>31</sup> | |

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<sup>1-29</sup> Academic copyright. Prepared by: Michelle Foisy, Pharm.D., Northern Alberta Program, Edmonton, Alberta. Updated by Michelle Foisy, Pharm.D. & Alice Tseng, Pharm.D., Toronto General Hospital, June 2015

[www.hivclinic.ca](http://www.hivclinic.ca)
# Predicted Interactions Between Psychotropics and Antiretrovirals

<table>
<thead>
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<th>NNRTIs</th>
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<tr>
<td>Metabolism</td>
<td>atazanavir (Reyataz®)&lt;sup&gt;1&lt;/sup&gt;, darunavir (Prezista®)&lt;sup&gt;2&lt;/sup&gt;, fosamprenavir (Telzir®)&lt;sup&gt;3&lt;/sup&gt;, indinavir (Crixivan®)&lt;sup&gt;4&lt;/sup&gt;, lopinavir/ritonavir (Kaltra®)&lt;sup&gt;5&lt;/sup&gt;, nelfinavir (Viracept®)&lt;sup&gt;6&lt;/sup&gt;, ritonavir (Norvir®)&lt;sup&gt;7&lt;/sup&gt;, saquinavir (Invirase®)&lt;sup&gt;8&lt;/sup&gt;, tipranavir (Aptivus®)&lt;sup&gt;9&lt;/sup&gt;</td>
<td>efavirenz (Sustiva®)&lt;sup&gt;10&lt;/sup&gt;, etravirine (Intelence®)&lt;sup&gt;11&lt;/sup&gt;, nevirapine (Viramune®)&lt;sup&gt;12&lt;/sup&gt;, rilpivirine (Edurant®)&lt;sup&gt;13&lt;/sup&gt;</td>
<td>dolutegravir (Tivicay®)&lt;sup&gt;14&lt;/sup&gt;, elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)&lt;sup&gt;15&lt;/sup&gt;, raltegravir (Isentress®)&lt;sup&gt;16&lt;/sup&gt;</td>
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### Protease Inhibitors

- **Phase pharmacokinetic study in healthy volunteers, exposure of bupropion and its active metabolite were both significantly reduced (AUC ↓ 57% and 50%, respectively) in the presence of steady state lopinavir/ritonavir. No significant changes in lopinavir kinetics were observed. Mechanism is postulated to be induction of CYP2B6 and UDP-glucuronyltransferase.**

  In a pharmacokinetic study in healthy volunteers the effect of steady-state ritonavir at given at a high dose (600 mg BID) and low dose (100 mg BID) on single-dose bupropion 150 mg was studied. Bupropion AUC was decreased by 62% and 21% in each group, respectively, which demonstrates a dose-related interaction. An increase in the dose of bupropion may be required when given with ritonavir, however the authors recommend not to exceed the maximum daily bupropion dose.

  One case series (n=11) where HIV-infected subjects received bupropion 150-300 mg daily for a median of 8 months in conjunction with either nelfinavir, efavirenz, or ritonavir 100 mg BID reported no episodes of seizures.

  Delavirdine and nevirapine were only weakly inhibitory of bupropion; hence no or only minor increase in bupropion concentrations anticipated.

  Coadministration of tipranavir 500/ritonavir 200 mg BID plus bupropion 150 mg BID in healthy volunteers resulted in 49% ↓ AUC, 60% ↓ Ctrough and 44% ↓ Cmax of bupropion, as well as approximately 25% ↓ in exposure of the active metabolite hydroxybupropion. Increased ALT was observed in 6/16 subjects after 1 week of tipranavir/ritonavir, but returned to baseline by the end of the study in 5/6 subjects.
### Predicted Interactions Between Psychotropics and Antiretrovirals

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<tr>
<td>Citalopram Celexa®</td>
<td>atazanavir (Reyataz®), darunavir (Prezista®) fosamprenavir (Telzir®), indinavir (Crixivan®), lopinavir/ritonavir (Kaletra®), nelfinavir (Virapect®), ritonavir (Norvir®), saquinavir (Invirase®), tipranavir (Aptivus®)</td>
<td>efavirenz (Sustiva®), etravirine (Intence®), nevirapine (Viramune®), rilpivirine (Edurant®)</td>
<td>dolutegravir (Tivicay®), elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine), raltegravir (Isentress®)</td>
</tr>
<tr>
<td>Escitalopram Lexapro® Cipralex® (S-enantiomer of citalopram)</td>
<td>Parent: CYP2C19, 3A4&gt;&gt;2D6. Inhibitor (weak): CYP 2D6, 2C19; negligible effect on CYP 3A4, 1A2</td>
<td>Possible ↑ SSRI concentrations. Use with ritonavir-boosted PIs with caution (may wish to start with ½ dose antidepressant).</td>
<td>Possible ↓ SSRI concentrations. Etravirine: Possible ↑ or ↓ citalopram concentrations.</td>
</tr>
<tr>
<td>Clomipramine Anafranil®</td>
<td>Parent: CYP2D6, 1A2, 2C19, 3A Metabolite: CYP2D6 (desmethyl)</td>
<td>Possible ↑ TCA concentrations</td>
<td>Possible ↓ TCA concentrations. Etravirine: Possible ↑ or ↓ clomipramine concentrations.</td>
</tr>
</tbody>
</table>
### Predicted Interactions Between Psychotropics and Antiretrovirals

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<tr>
<td>Desipramine Pertofrane® (Pristiq®)</td>
<td>Parent: CYP2D6&gt;&gt;UGT</td>
<td>No anticipated effect with unboosted PIs.</td>
<td>No anticipated effect</td>
<td>Desipramine 50 mg single dose administered with elvitegravir/cobicistat: 24% ↑ Cmax and 65% ↑ AUC of desipramine. Monitor for response and adjust antidepressant dose accordingly.</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>UGT (Major active metabolite of venlafaxine)</td>
<td>Desvenlafaxine concentrations were ↑ 42% by ketoconazole 200 mg BID; use of potent CYP3A4 inhibitors may result in ↑ concentrations of desvenlafaxine. Ritonavir also induces UGT, and may ↓ desvenlafaxine concentrations; net effect of coadministering boosted PIs is unknown. Use combination with caution. Potential for desvenlafaxine to ↓ concentrations of CYP3A4 substrates. Clinical significance with HIV protease inhibitors</td>
<td>Possible ↓ desvenlafaxine.</td>
<td>Potential for ↑ desvenlafaxine concentrations with elvitegravir/cobicistat. Monitor for response and adjust antidepressant dose accordingly.</td>
</tr>
</tbody>
</table>

1. atazanavir (Reyataz®)
2. darunavir (Prezista®)
3. fosamprenavir (Telzir®)
4. indinavir (Crixivan®)
5. lopinavir/ritonavir (Kaletra®)
6. nelfinavir (Viracept®)
7. ritonavir (Norvir®)
8. saquinavir (Invirase®)
9. tipranavir (Aptivus®)
10. efavirenz (Sustiva®)
11. etravirine (Intelence®)
12. nevirapine (Viramune®)
13. rilpivirine (Edurant®)
14. dolutegravir (Tivicay®)
15. elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)
16. raltegravir (Isentress®)
17. dolutegravir (Tivicay®),
18. elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)
19. raltegravir (Isentress®)
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<tr>
<td>25-29</td>
<td>atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Telzir®), indinavir (Crixivan®), lopinavir/ritonavir (Kaletra®), nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Invirase®), tipranavir (Aptivus®)</td>
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<td>dolutegravir (Tivicay®), elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine), raltegravir (Isentress®)</td>
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<tr>
<th>Psychotropics</th>
<th>Metabolism</th>
<th>Interactions</th>
</tr>
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<tbody>
<tr>
<td>Doxepin (Sinequan®)</td>
<td>Parent: hepatic metabolism (? CYPs) Metabolite (active): desmethyldoxepin</td>
<td>↓ 31% in the presence of desvenlafaxine 400 mg daily. Therefore, possibility that desvenlafaxine may act as an inducer in vivo.</td>
</tr>
</tbody>
</table>

| Duloxetine (Cymbalta®) | Parent: CYP1A2, 2D6; inactive metabolites Inhibitor (moderate): CYP2D6 | Unboosted PIs unlikely to have a major interaction. Potential for ritonavir-boosted PIs to ↑ or ↓ duloxetine concentrations. Monitor for efficacy/toxicity. At low boosting doses, ritonavir does not inhibit CYP2D6 at clinically relevant concentrations, but has a more potent inhibitory effect at higher therapeutic doses. It may also induce CYP1A2. Tipranavir inhibits CYP2D6 and induces CYP1A2, therefore an interaction is difficult to predict. | Potential for ↑ duloxetine concentrations with elvitegravir/cobicistat. Rilpivirine is a slight inducer of CYP1A2; potential for ↓ duloxetine concentrations. Monitor for response and adjust antidepressant dose accordingly. |

| Fluoxetine (Prozac®) | Parent: CYP2D6 Inhibits: CYP2D6 | No anticipated effect of unboosted PIs on fluoxetine. No anticipated effect on fluoxetine or NNRTIs. | Potential for ↑ SSRI concentrations with |
# Predicted Interactions Between Psychotropics and Antiretrovirals

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<tbody>
<tr>
<td>(potent) Metabolite (active): norfluoxetine</td>
<td>atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Telzir®), indinavir (Crixivan®), lopinavir/ritonavir (Kaletra®), nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Invirase®), tipranavir (Aptivus®)</td>
<td>efavirenz (Sustiva®), etravirine (Intelence®), nevirapine (Viramune®), rilpivirine (Edurant®)</td>
<td>dolutegravir (Tivicay®), elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine), raltegravir (Isentress®)</td>
</tr>
<tr>
<td></td>
<td>Potential for ↑ SSRI concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir. Kinetic study showing 19% ↑ ritonavir AUC. Post-marketing reports of cardiac and neurologic events with combination.</td>
<td>In a retrospective review, the pharmacokinetics of efavirenz did not appear to be significantly affected by concomitant use of selective serotonin reuptake inhibitors. In one cohort study, fluoxetine did not significantly impact nevirapine clearance. However, the dose-normalized concentrations of fluoxetine and the active metabolite, norfluoxetine, were decreased by 65% and 35%, respectively. Monitor closely for the clinical response to fluoxetine; possible dose increases may be required. Delavirdine: 50% ↑ delavirdine trough concentrations with combination. Cautious use of combination is warranted.</td>
<td>elvitegravir/cobicistat. Monitor for response and adjust antidepressant dose accordingly.</td>
</tr>
<tr>
<td>Fluvoxamine Luvox®</td>
<td>No major anticipated effect with unboosted PIs. Potential for ↑ SSRI concentrations with higher doses</td>
<td>Potential for fluvoxamine to modestly ↑ NNRTI concentrations. Clinical significance unknown, monitor for toxicity.</td>
<td>Potential for ↑ SSRI concentrations with elvitegravir/cobicistat.</td>
</tr>
</tbody>
</table>

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**Parent:** CYP2D6 > 1A2
**Inhibits:** 1A2 (potent), 3A4, 2C (moderate), 2D6 (weak)
## Predicted Interactions Between Psychotropics and Antiretrovirals

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<td>efavirenz (Sustiva®)$^{10}$, etravirine (Intencence®)$^{11}$, nevirapine (Viramune®)$^{12}$, rilpivirine (Edurant®)$^{13}$</td>
<td>dolutegravir (Tivicay®)$^{14}$, elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)$^{15}$, raltegravir (Isentress®)$^{16}$</td>
<td></td>
</tr>
<tr>
<td>of ritonavir, but unlikely with lower boosting doses of ritonavir. Potential for fluvoxamine to modestly ↑ PI concentrations. Clinical significance unknown, monitor for toxicity.</td>
<td>In one cohort study, fluvoxamine inhibited the clearance of nevirapine by 33.7% in a dose-dependent manner; the dose-normalized concentration of fluvoxamine was not significantly altered. Close monitoring for nevirapine toxicity is warranted, particularly when high doses of fluvoxamine are used.$^{48}$</td>
<td>accordingly.$^{16}$</td>
<td></td>
</tr>
</tbody>
</table>

### Imipramine Tofranil®

**Parent:** CYP2D6, 1A2, 2C19, 3A > UGT  
**Metabolite (active):** CYP2D6 (desipramine)  
**Possible ↑ TCA concentrations**  
**Possible ↓ TCA concentrations**  
**Etravirine:** Possible ↑ etravirine concentrations.$^{30}$  

### Maprotiline Ludiomil®

**Parent:** CYP2D6  
**Metabolite:** UGT (hydroxyl)  
**Interaction unlikely with unboosted PIs.**  
**Interaction unlikely**  
**Potential ↑ maprotiline concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.**  
**Potential for ↑ TCA concentrations with elvitegravir/cobicistat.**  
**Monitor for response and adjust antidepressant dose accordingly.$^{15}$**  

### Milnacipran Ixel®

**UGT. Not a substrate of P450 system**  
**Interaction unlikely with unboosted atazanavir or fosamprenavir.**  
**Potential ↓ milnacipran concentrations**  
**Interaction unlikely.**
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#### Potential

- **Mirtazapine** (Remeron®)
  - CYP2D6, 1A2, 3A4
  - Is not an enzyme inhibitor or inducer
  - Potential ↓ milnacipran concentrations via UGT induction by ritonavir or nelfinavir.
  - Possible ↑ mirtazapine concentrations with unboosted PIs.
  - Possible ↑↑ mirtazapine levels with ritonavir-boosted PIs due to inhibition of 3A4 and possibly 2D6. Monitor for acute somnolence if ritonavir is added. Consider mirtazapine dosage decrease if combination is used.
  - Possible ↓ mirtazapine concentrations.
  - Etravirine: Possible ↓ mirtazapine concentrations.
  - Potential for ↑ mirtazapine concentrations with elvitegravir/cobicistat. Monitor for response and adjust antidepressant dose accordingly.

- **Moclobemide** (Manerix®)
  - Parent: CYP2C19>2D6
  - Inhibits: CYP2C19>2D6
  - No anticipated effect with unboosted PIs.
  - Possible ↑ or ↓ moclobemide concentrations with ritonavir-boosted PIs.
  - Efavirenz and etravire are weak-moderate inhibitors of CYP2C19, and thus may possibly ↑ moclobemide concentrations. Rilpivirine is a moderate inducer of CYP2C19, and may possibly ↓ moclobemide concentrations. Monitor for efficacy & toxicity.
  - Potential for ↑ moclobemide concentrations with elvitegravir/cobicistat. Monitor for response and adjust antidepressant dose accordingly.

- **Nefazodone** (Serzone®)
  - (*drug discontinued in Canada in 2003*)
  - Parent: CYP3A
  - Inhibits: CYP3A (potent)
  - Metabolite: CYP2D6 (hydroxy-nefazodone)
  - Unboosted PIs may ↑ nefazodone concentrations; potential ↑↑ nefazodone concentrations with ritonavir-boosted PIs.
  - Potential for nefazodone to ↑ PI concentrations and toxicity.
  - Likely ↓ nefazodone concentrations. Potential for nefazodone to ↑ NNRTI concentrations and toxicity
  - Etravirine: Possible ↓ nefazodone concentrations and ↑ etravirine concentrations.
  - Potential for ↑ nefazodone concentrations with elvitegravir/cobicistat. Monitor for response and adjust antidepressant dose accordingly.
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<td>atazanavir (Reyataz®)&lt;sup&gt;1&lt;/sup&gt;, darunavir (Prezista®)&lt;sup&gt;2&lt;/sup&gt;, fosamprenavir (Tezir®)&lt;sup&gt;3&lt;/sup&gt;, indinavir (Crixivan®)&lt;sup&gt;4&lt;/sup&gt;, lopinavir/ritonavir (Kaletra®)&lt;sup&gt;5&lt;/sup&gt;, nelfinavir (Viracept®)&lt;sup&gt;6&lt;/sup&gt;, ritonavir (Norvir®)&lt;sup&gt;7&lt;/sup&gt;, saquinavir (Invirase®)&lt;sup&gt;8&lt;/sup&gt;, tipranavir (Aptivus®)&lt;sup&gt;9&lt;/sup&gt;</td>
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<td>dolutegravir (Tivicay®)&lt;sup&gt;14&lt;/sup&gt;, elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)&lt;sup&gt;15&lt;/sup&gt;, raltegravir (Isentress®)&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Potential for ↑ rilpivirine concentrations; AVOID co-administration.

Nortriptyline Norventyl®

Parent: CYP2D6
Metabolite (active): 10-hydroxynortriptyline

No anticipated effect with unboosted PIs.
Potential ↑ TCA concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.

No anticipated effect

Potential for ↑ TCA concentrations with elvitegravir/cobicistat. Monitor for response and adjust antidepressant dose accordingly.

Paroxetine Paxil®

Parent: CYP2D6
Inhibits: CYP2D6 (potent)

Based on paroxetine metabolism potential for ↑ paroxetine concentrations exists with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir. However, interaction is complex and difficult to predict. For example, in the cases of fosamprenavir/r and darunavir/r the AUC of paroxetine was decreased by 58% and 39%, respectively (see below).

No anticipated effect;
In a retrospective review, the pharmacokinetics of efavirenz did not appear to be significantly affected by concomitant use of selective serotonin reuptake inhibitors.<sup>47</sup>

In healthy volunteers, paroxetine 20 mg QD plus etravirine (TMC125) 800 mg BID (old formulation) did not result in significant changes in exposures of either drug. No dosage adjustment is required.<sup>11</sup>

Potential for ↑ SSRI concentrations with elvitegravir/cobicistat. Monitor for response and adjust antidepressant dose accordingly.<sup>15</sup>
## Predicted Interactions Between Psychotropics and Antiretrovirals

<table>
<thead>
<tr>
<th>Psychotropic Route of Metabolism</th>
<th>Protease Inhibitors</th>
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<tr>
<td>25-29</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 (Intelence®)(^11), nevirapine (Viramune®)(^12), rilpivirine (Edurant®)(^13)</td>
<td>dolutegravir (Tivicay®)(^14), elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)(^15), raltegravir (Isentress®)(^16)</td>
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</table>

**Phenelzine Nardil®**
- Acetylation inhibits: CYP (weak)
- Likely interaction required.\(^31\)
- Co administration of darunavir/r 400/100 mg BID and paroxetine 20 mg QD led to 39%↓ paroxetine exposure; darunavir levels were not affected. Monitor for antidepressant efficacy and ↑ paroxetine dose if required.\(^50\)

**Reboxetine Edronax®**
- 3A4 substrate
- Potential for ↑ reboxetine concentrations
- Potential for ↓ reboxetine concentrations
- Potential for ↑ reboxetine concentrations with elvitegravir/cobicistat. Monitor for response and adjust antidepressant dose accordingly.\(^15\)

**Selegiline (transdermal patch) EMSAM®**
- 2B6, 1A2 substrate
- Unlikely interaction with unboosted PIs.
- Potential for ↓ selegiline concentrations with ritonavir-boosted PIs.
- Potential for ↓ selegiline concentrations

**Sertraline Zoloft®**
- Parent: CYP2B6 > 2C9/19, 3A4, 2D6, UGT1A1(possible)\(^52\)
- Inhibits: CYP2D6 (moderate)
- Potential ↑ or ↓ sertraline concentrations due to complex metabolism of sertraline.
- Co-administration of darunavir/r 400/100 mg BID and sertraline 50 mg QD led to 49%↓ sertraline exposure; darunavir levels were not affected. Monitor for antidepressant efficacy and ↑ sertraline concentrations.\(^50\)
- Potential for ↓ sertraline concentrations due to enzyme induction.
- Sertraline AUC↓ by 39%, efavirenz kinetics not affected.\(^10\),\(^47\)
- Etravirine: Possible ↑ or ↓ sertraline concentrations.\(^30\)
- In healthy volunteers, coadministration of single dose sertraline 50 mg in the presence of steady-state fixed-dose elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide once daily did not result in any clinically relevant changes in the
<table>
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</thead>
</table>
| **St. John’s Wort**  
(hypericum perforatum) | atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Telzir®), indinavir (Crixivan®), lopinavir/ritonavir (Kalaztra®), nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Invirase®), tipranavir (Aptivus®) | efavirenz (Sustiva®), etravirine (Intelence®), nevirapine (Viramune®), rilpivirine (Edurant®) | dolutegravir (Tivicay®), elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine) |
| **Tranylcypromine**  
Parnate® | Induces CYP3A4 and P-gp | Significantly reduces indinavir exposure (57% ↓ AUC, 81% ↓ Cmin); similar interaction may be likely with other substrates of CYP3A4.  

Avoid concomitant use of PIs and NNRTIs with St. John’s wort.  

Maraviroc: Avoid concomitant use with St. John’s wort. | St. John’s Wort reduces nevirapine concentrations 35%.  
Avert concomitant use of PIs and NNRTIs with St. John’s wort. | Coadministration with elvitegravir/cobicistat is contraindicated.  

Dolutegravir: Based on modelling with clinical correlation, integrase-naïve subjects taking St. John’s wort should receive dolutegravir 50mg twice daily. |
| **Trazodone**  
Desyrel® | hepatic metabolism | Possible ↑ MAOI concentrations | Possible ↓ MAOI concentrations |

| Parent: CYP2D6> CYP3A  
Metabolite: CYP2D6 (m-CPP) | Possible ↑ trazodone concentrations  
Indinavir: strong inhibitor of trazodone in vitro. Monitor for trazodone toxicity (i.e. nausea, hypotension, syncope, somnolence, anticholinergic side-effects).  

Monitor for response and adjust antidepressant dose accordingly. |

sertraline dose if required.  

pharmacokinetics of sertraline or any components of the antiretroviral fixed-dose tablet. No dose adjustment is required with coadministration.  

St. John’s Wort reduces nevirapine concentrations 35%.  
Avert concomitant use of PIs and NNRTIs with St. John’s wort.  

Co-administration with elvitegravir/cobicistat is contraindicated.  

Dolutegravir: Based on modelling with clinical correlation, integrase-naïve subjects taking St. John’s wort should receive dolutegravir 50mg twice daily. |

Potentially ↑ trazodone concentrations with elvitegravir/cobicistat.  
Monitor for response and adjust antidepressant dose accordingly. |
### Predicted Interactions Between Psychotropics and Antiretrovirals

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<td><img src="path" alt="Psychotropic Route of Metabolism" /></td>
<td>atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Telzir®), indinavir (Crixivan®), lopinavir/ritonavir (Kaletra®), saquinavir (Invirase®), tipranavir (Aptivus®)</td>
<td>efavirenz (Sustiva®), etravirine (Intelence®), nevirapine (Viramune®), rilpivirine (Edurant®)</td>
<td>dolutegravir (Tivicay®), elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine), raltegravir (Isentress®)</td>
</tr>
<tr>
<td><img src="path" alt="Protease Inhibitors" /></td>
<td>Interaction is unlikely. 58</td>
<td>Ritonavir: potent inhibitor of trazodone in vitro. 58 10 healthy subjects received trazodone 50 mg with RTV 4 x 200mg doses: significant increase in trazodone concentrations (52% ↓ CL, 122% ↑ T 1/2, 34% ↑ Cmax). 7 Sedation, fatigue, impaired performance, nausea, dizziness, hypotension, syncope reported. When combined with ritonavir-based regimens, use with caution and consider a lower dose of trazodone. 7</td>
<td>Trimipramine Surmontil® Parent: CYP2D6 Metabolite (active): Desmethytrimipramine No anticipated effect with unboosted PIs. Potential ↑ TCA concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir. No anticipated effect</td>
</tr>
<tr>
<td><img src="path" alt="NNRTIs" /></td>
<td>Venlafaxine Effexor® Parent: CYP2D6 &gt; CYP3A4 (minor) Inhibits: CYP2D6 (weak) Metabolite (active): UGT (O-desmethylvenlafaxine, ODV)</td>
<td>Possible ↑ venlafaxine concentrations with unboosted PIs; however interaction study with indinavir showed ↓ in indinavir concentrations (28% ↓ AUC, 36% ↓ Cmax); no change in venlafaxine concentrations. Etravirine: Possible ↓ venlafaxine concentrations. 30</td>
<td>Potential for ↑ venlafaxine concentrations with elvitegravir/cobicistat. Monitor for response and adjust antidepressant dose accordingly. 15</td>
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<td>efavirenz (Sustiva®)¹⁰</td>
<td>dolutegravir (Tivicay®)¹⁴</td>
</tr>
<tr>
<td></td>
<td>darunavir (Prezista®)²</td>
<td>etravirine (Intelence®)¹¹</td>
<td>elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)¹⁵</td>
</tr>
<tr>
<td></td>
<td>fosamprenavir (Telzir®)³</td>
<td>nevirapine (Viramune®)¹²</td>
<td>raltegravir (Isentress®)¹⁶</td>
</tr>
<tr>
<td></td>
<td>indinavir (Crixivan®)⁴</td>
<td>rilpivirine (Edurant®)¹³</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lopinavir/ritonavir (Kaletra®)⁵</td>
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<tr>
<td></td>
<td>saquinavir (Invirase®)⁸</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>tipranavir (Aptivus®)⁹</td>
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</tbody>
</table>

CYP2D6 inhibitors may ↓ the metabolism of venlafaxine to ODV, resulting in ↑ plasma concentrations of venlafaxine and ↓ concentrations of ODV. However, as venlafaxine and ODV are both pharmacologically active, the product monograph states that no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.⁶⁵

### Neuroleptics

<table>
<thead>
<tr>
<th>Amisulpride Solian®</th>
<th>Parent: 50 % renal; no clinically relevant metabolism²⁸</th>
<th>Unlikely</th>
<th>Unlikely</th>
<th>Unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Special Access in Canada</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Aripiprazole Abilify®

Parent: CYP 3A4, 2D6⁶ Metabolite (active): dehydro-aripiprazole

Possible ↑ aripiprazole concentrations.

A 43 y.o. male was on aripiprazole 50 mg daily and duloxetine 80 mg daily (CYP2D6 inhibitor) for depression/anxiety in addition to darunavir/ritonavir 800/100 mg daily based regimen (CYP3A4 inhibitor). The patient developed CNS symptoms (confusion, loss of coordination) and was later hospitalized with fever, cough, headache, neck pain. A decrease in neuroleptic dose may be required.¹⁵
<table>
<thead>
<tr>
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<td><strong>Psychotropic Route of Metabolism</strong>&lt;sup&gt;25-29&lt;/sup&gt;</td>
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<td>efavirenz (Sustiva®)&lt;sup&gt;10&lt;/sup&gt;, etravirine (Intelence®)&lt;sup&gt;11&lt;/sup&gt;, nevirapine (Viramune®)&lt;sup&gt;12&lt;/sup&gt;, rilpivirine (Edurant®)&lt;sup&gt;13&lt;/sup&gt;</td>
<td>dolutegravir (Tivicay®)&lt;sup&gt;14&lt;/sup&gt;, elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)&lt;sup&gt;15&lt;/sup&gt; raltegravir (Isentress®)&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Stiffness, back pain, and blurred vision. All investigations were negative except for lymphadenopathy. A random aripiprazole serum concentration was elevated at 1100 ng/mL (therapeutic is 100-200 ng/mL) 49 days after hospital discharge and aripiprazole was discontinued.</strong>&lt;sup&gt;62&lt;/sup&gt; Caution is warranted when PIs and aripiprazole are coadministered and lower aripiprazole doses may be required.</td>
<td><strong>Possible ↓ asenapine concentrations with boosted PIs or nelfinavir.</strong></td>
<td><strong>Possible ↓ asenapine concentrations</strong></td>
<td><strong>Possible ↑ asenapine concentrations with elvitegravir/cobicistat. A decrease in neuroleptic dose may be required.</strong>&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Chlorpromazine Largactil®</strong></td>
<td>Parent: CYP2D6, CYP1A2, GT Metabolite: GT (7-OH-CPZ)</td>
<td><strong>Unlikely interaction with unboosted PIs.</strong> Potential ↑ chlorpromazine concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.</td>
<td><strong>Unlikely</strong></td>
</tr>
<tr>
<td><strong>Clozapine Clozaril®</strong></td>
<td>Parent: CYP1A2&gt; 2C19, 3A4, 2D6&lt;sup&gt;28&lt;/sup&gt; Metabolite (active): norclozapine</td>
<td><strong>Possible ↑ clozapine concentrations with unboosted PIs.</strong></td>
<td><strong>Possible ↓ clozapine concentrations</strong></td>
</tr>
</tbody>
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</tr>
<tr>
<td>Fluphenazine Modecate®</td>
<td>Parent: Extensive hepatic metabolism (not well defined)</td>
<td>Possible ↑ fluphenazine concentrations</td>
<td>Possible ↓ fluphenazine concentrations</td>
</tr>
<tr>
<td>Haloperidol Haldol®</td>
<td>Parent: CYP2D6&gt;3A4</td>
<td>Possible ↑ haloperidol concentrations</td>
<td>Possible ↓ haloperidol concentrations</td>
</tr>
<tr>
<td>Loxapine Loxapac®</td>
<td>Parent: Extensive hepatic metabolism</td>
<td>Possible ↑ loxapine concentrations</td>
<td>Possible ↓ loxapine concentrations</td>
</tr>
<tr>
<td>Lurasidone Latuda®</td>
<td>CYP3A4</td>
<td>Possible ↑ lurasidone concentrations. Lurasidone is contraindicated with strong</td>
<td>Possible ↓ lurasidone concentrations. Lurasidone is contraindicated with strong</td>
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<td>CYP3A4 inhibitors (e.g., ketoconazole). Do not exceed 40 mg/day if coadministering with moderate CYP3A4 inhibitors.</td>
<td>CYP3A4 inducers (e.g., rifampin).</td>
<td>Lurasidone is contraindicated with strong CYP3A4 inhibitors (e.g., ketoconazole). Do not exceed 40 mg/day if coadministering with moderate CYP3A4 inhibitors.</td>
<td></td>
</tr>
</tbody>
</table>

### Methotrimeprazine (levomepromazine) Nozinan®

- Parent: Extensive hepatic metabolism
- Inhibits CYP2D6
- Possible ↑ methotrimeprazine concentrations
- Possible ↓ methotrimeprazine concentrations
- Potential for ↑ neuroleptic concentrations with elvitegravir/cobicistat. A decrease in neuroleptic dose may be required.¹⁵

### Olanzapine Zyprexa®

- Parent: CYP1A2 >> 2D6; UGT1A4
- Inhibits CYP1A2, 2D6, 3A4 (weak)
- No anticipated effect with most unboosted PIs; **nelfinavir and ritonavir** may ↓ olanzapine concentrations by inducing glucuronidation.
  - Healthy volunteer study of olanzapine 10 mg +/- **ritonavir 500 mg BID** resulted in 53%↓ AUC of olanzapine. Higher olanzapine dosages may be necessary to maintain therapeutic effect.⁶³
  - In a healthy volunteer study, subjects received single dose olanzapine 10 mg alone or olanzapine 15 mg with steady-state **fosamprenavir 700/100 mg BID**. Olanzapine 15 mg in
- No anticipated effect.
- Potential for olanzapine to cause minor ↑ NNRTI concentrations and toxicity.
- Potential for ↑ neuroleptic concentrations with elvitegravir/cobicistat. A decrease in neuroleptic dose may be required.¹⁵
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<td>efavirenz (Sustiva®)¹⁰, etravirine (Intelence®)¹¹, nevirapine (Viramune®)¹², rilpivirine (Edurant®)¹³</td>
<td>dolutegravir (Tivicay®)¹⁴, elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)¹⁵, raltegravir (Isentress®)¹⁶</td>
</tr>
<tr>
<td></td>
<td>The presence of fosamprenavir/ritonavir resulted in similar AUC and 32% ↑ Cmax as that observed with olanzapine 10 mg alone. Amprenavir pharmacokinetic parameters were similar to historical controls. Increase olanzapine dose by 50% when combining with boosted fosamprenavir. Potential for olanzapine to ↑ protease concentrations and toxicity (likely not clinically significant).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paliperidone Invega®, Invega Sustenna®</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parent: potential for some (minimal?) involvement in P450 metabolism (59% excreted unchanged in the urine). In vitro data suggest that paliperidone is a substrate of 2D6 and 3A4, but in vivo results indicate that these isozymes play a very limited role in its metabolism. Hence, not expected to cause clinically significant interactions with P450 substrates. Possible ↑ paliperidone concentrations. No clinically significant effect noted when paliperidone was coadministered with paroxetine, a potent 2D6 inhibitor.</td>
<td>Possible ↓ paliperidone concentrations. Monitor for efficacy. Co-administration of paliperidone with carbamazepine 200 mg BID (a 3A4 &amp; P-gp inducer) caused a 37% ↓ in AUC of paliperidone.</td>
<td>Potential for ↑ neuroleptic concentrations with elvitegravir/cobicistat. A decrease in neuroleptic dose may be required.¹⁵</td>
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<td>Perphenazine Trilafon®</td>
<td>Interaction unlikely with unboosted PIs. Potential ↑ perphenazine concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir. See “quetiapine” for case report of priapism associated with perphenazine and quetiapine with concomitant lopinavir/ritonavir.</td>
<td>Potentially ↑ neuroleptic concentrations with elvitegravir/cobicistat. A decrease in neuroleptic dose may be required.</td>
<td>Coadministration with Stribild® is contraindicated due to potential for serious and/or life-threatening events such as cardiac arrhythmias.</td>
</tr>
<tr>
<td>Pimozide Orap®</td>
<td>Unboosted PIs may ↑ pimozide concentrations; avoid if possible. Contraindicated with ritonavir; potential ↑↑ pimozide concentrations.</td>
<td>Likely ↓ pimozide concentrations</td>
<td>Coadministration with Stribild® is contraindicated due to potential for serious and/or life-threatening events such as cardiac arrhythmias.</td>
</tr>
<tr>
<td>Pipotiazine Piportil L4</td>
<td>Possible ↑ pipotiazine concentrations</td>
<td>Possible ↓ pipotiazine concentrations</td>
<td>Potential for ↑ neuroleptic concentrations with elvitegravir/cobicistat. A decrease in neuroleptic dose may be required.</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Possible ↑↑ quetiapine</td>
<td>Possible ↓ quetiapine</td>
<td>Potential for ↑ neuroleptic</td>
</tr>
</tbody>
</table>

**Psychotropic Route of Metabolism**

- Substrate and inhibitor of P-gp.
- Paliperidone is the major active metabolite of risperidone.

**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 Inhibitors**

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

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1. Paliperidone is the major active metabolite of risperidone.
2. The route of metabolism varies among different psychotropics.
3. Interactions with protease inhibitors can affect the concentration of psychotropics.
4. NNRTIs can also interact with various psychotropics, potentially altering their effectiveness.
5. Integrase inhibitors can further complicate these interactions, necessitating careful monitoring.

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**Note:** Updates and cautions may vary depending on the specific drug interactions and current guidelines.
### Predicted Interactions Between Psychotropics and Antiretrovirals

<table>
<thead>
<tr>
<th>Psychotropic Route of Metabolism</th>
<th>Protease Inhibitors</th>
<th>NNRTIs</th>
<th>Integrase Inhibitors</th>
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</thead>
</table>
| CYP3A4 >> 1A2 | atazanavir (Reyataz®)
| darunavir (Prezista®)
| fosamprenavir (Telzir®)
| indinavir (Crixivan®)
| lopinavir/ritonavir (Kaletra®)
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| tipranavir (Aptivus®) | efavirenz (Sustiva®)
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| elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine) | raltegravir (Isentress®) |

- **Seroquel®**
  - CYP3A4 >> 1A2
  - Is not an enzyme inhibitor or inducer

- Report of two patients who experienced serious quetiapine adverse effects secondary to possible/probable interactions with atazanavir/ritonavir. One patient developed rapid and severe (50 pound) weight gain when quetiapine (titrated up to 400 mg/day) was added to his stable ARV regimen, while another patient stabilized on quetiapine 600 mg/day developed increased sedation and mental confusion shortly after initiating atazanavir/ritonavir. In both cases, symptoms resolved after discontinuation of quetiapine.

- Another report of a deep coma, sustained hypotension, and ↑ t1/2 of quetiapine (62.4h) after an overdose of quetiapine 8000mg in a patient on atazanavir/ritonavir.

- Case report of priapism lasting 42 hours with an onset of 5-6 hours after co-ingestion of perphenazine 8 mg and quetiapine 900 mg with lopinavir/ritonavir. Rapid concentrations. **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.
<table>
<thead>
<tr>
<th>Psychotropic Route of Metabolism</th>
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<tr>
<td>25-29</td>
<td>atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Telzir®), indinavir (Crixivan®), lopinavir/ritonavir (Kaletra®), nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Invirase®), tipranavir (Aptivus®)</td>
<td>efavirenz (Sustiva®), etravirine (Intecence®), nevirapine (Viramune®), rilpivirine (Edurant®)</td>
<td>dolutegravir (Tivicay®), elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine), raltegravir (Isentress®)</td>
</tr>
<tr>
<td></td>
<td>elevations in the neuroleptic concentrations were postulated as the mechanism. The symptoms were managed with intracavernous ephedrine, irrigation and aspiration.</td>
<td></td>
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</tr>
<tr>
<td>Risperidone Risperdal®</td>
<td>Parent: CYP2D6, 3A4; Active metabolite: 9-OH risperidone (paliperidone) (renal)</td>
<td>Potential ↑ risperidone concentrations with ritonavir-boosted PIs. One case of extrapyramidal symptoms (dysphagia, dysphonia, difficulty breathing, and worsening tremors) with risperidone 2mg/day + indinavir/ritonavir (IDV/RTV) 800mg/200mg BID. One case of neuroleptic malignant syndrome with risperidone 1.5mg/day + IDV 800mg/RTV 400mg daily. Reversible coma reported with risperidone 3mg BID + IDV 400mg/RTV 200mg BID.</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Thioridazine Mellaril®</td>
<td>Parent: CYP2D6; Inhibits: CYP2D6 Metabolite (active): (mesoridazine, sulforidazine)</td>
<td>Interaction unlikely with unboosted PIs. Potential ↑ thioridazine concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Ziprasidone Geodon®, Zeldox®</td>
<td>Parent: CYP3A4; Is not an enzyme</td>
<td>Potential ↑ ziprasidone concentrations</td>
<td>Potential ↓ ziprasidone concentrations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Potential for ↑ neuroleptic concentrations with elvitegravir/cobicistat. A decrease in neuroleptic dose may be required.</td>
</tr>
</tbody>
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## Predicted Interactions Between Psychotropics and Antiretrovirals

### Psychotropic Route of Metabolism

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<td>inhibitor or inducer</td>
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### Protease Inhibitors

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<td></td>
<td>atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Telzir®), indinavir (Crixivan®), lopinavir/ritonavir (Kaletra®), nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Invirase®), tipranavir (Aptivus®)</td>
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### NNRTIs

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<td>efavirenz (Sustiva®), etravirine (Intelence®), nevirapine (Viramune®), rilpivirine (Edurant®)</td>
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### Integrase Inhibitors

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<td>dolutegravir (Tivicay®), elvitegravir/cobicistat, (Stribild®, single-tablet regimen with tenofovir/emtricitabine), raltegravir (Isentress®)</td>
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### Other

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<tbody>
<tr>
<td>Atomoxetine</td>
<td>Atomoxetine Strattera®, 2D6, Possible ↑ atomoxetine concentrations</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Buspirone Buspar®, Parent: CYP3A4 Metabolite (active): 1-pyrimidinyl piperazine Buspirone has immunomodulating properties. A significant ↑ in CD4/CD8 ratio, and a ↓ in CD8+ T-cell counts was observed in HIV patients who were not on antiretrovirals.</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>Dextroamphetamine Dexedrine®, Parent: hepatic metabolism (deamination and hydroxylation)</td>
</tr>
<tr>
<td>Lithium</td>
<td>Lithium Carbolith®, None (renal) None None None</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>Lisdexamfetamine Vyvanse®, Hydrolyzed in the blood to d-amphetamine</td>
</tr>
</tbody>
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Predicted Interactions Between Psychotropics and Antiretrovirals

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<tr>
<td>(active component) and L-lysine. Lisdexamfetamine is not metabolized by CYP450 enzymes. Amphetamine is oxidized to form 4-hydroxyamphetamine, alpha-hydroxy-amphetamine and norephedrine (both active). Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. In vitro, minor inhibition of CYP2D6 by amphetamine, and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites, but there are no in vivo studies of P450 enzyme inhibition.</td>
<td>atazanavir (Reyataz®)&lt;sup&gt;1&lt;/sup&gt;, darunavir (Prezista®)&lt;sup&gt;2&lt;/sup&gt;, fosamprenavir (Telzir®)&lt;sup&gt;3&lt;/sup&gt;, indinavir (Crixivan®)&lt;sup&gt;4&lt;/sup&gt;, lopinavir/ritonavir (Kaletra®)&lt;sup&gt;5&lt;/sup&gt;, nelfinavir (Viracept®)&lt;sup&gt;6&lt;/sup&gt;, ritonavir (Norvir®)&lt;sup&gt;7&lt;/sup&gt;, saquinavir (Invirese®)&lt;sup&gt;8&lt;/sup&gt;, tipranavir (Aptivus®)&lt;sup&gt;9&lt;/sup&gt;</td>
<td>efavirenz (Sustiva®)&lt;sup&gt;10&lt;/sup&gt;, etravirine (Intelence®)&lt;sup&gt;11&lt;/sup&gt;, nevirapine (Viramune®)&lt;sup&gt;12&lt;/sup&gt;, rilpivirine (Edurant®)&lt;sup&gt;13&lt;/sup&gt;</td>
<td>dolutegravir (Tivicay®)&lt;sup&gt;14&lt;/sup&gt;, elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)&lt;sup&gt;15&lt;/sup&gt;, raltegravir (Isentress®)&lt;sup&gt;16&lt;/sup&gt;</td>
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<sup>1</sup> atazanavir (Reyataz®)<sup>1</sup>, darunavir (Prezista®)<sup>2</sup>, fosamprenavir (Telzir®)<sup>3</sup>, indinavir (Crixivan®)<sup>4</sup>, lopinavir/ritonavir (Kaletra®)<sup>5</sup>, nelfinavir (Viracept®)<sup>6</sup>, ritonavir (Norvir®)<sup>7</sup>, saquinavir (Invirese®)<sup>8</sup>, tipranavir (Aptivus®)<sup>9</sup> |
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<tr>
<td><strong>I-Tryptophan</strong></td>
<td>Parent: metabolized via tryptophan hydroxylase</td>
<td>atazanavir (Reyataz®)(^1), darunavir (Prezista®)(^2), fosamprenavir (Telzir®)(^3), indinavir (Crixivan®)(^4), lopinavir/ritonavir (Kalentra®)(^5), nelfinavir (Viracept®)(^6), ritonavir (Norvir®)(^7), saquinavir (Invirase®)(^8), tipranavir (Aptivus®)(^9)</td>
<td>efavirenz (Sustiva®)(^10), etravirine (Intelence®)(^11), nevirapine (Viramune®)(^12), rilpivirine (Edurant®)(^13)</td>
</tr>
<tr>
<td><strong>Methylphenidate</strong></td>
<td>Parent: hepatic and tissue nonmicrosomal hydrolytic esterases Inhibits: not well described- ?CYP3A, ?2D6, Metabolite: renal (ritalinic acid- inactive)</td>
<td>Possible ↑ methylphenidate concentrations</td>
<td>Possible ↓ methylphenidate concentrations</td>
</tr>
<tr>
<td><strong>Modafinil</strong></td>
<td>Parent: CYP3A Inhibits 2C19, 2C9; may induce 3A4, 1A2, 2B6</td>
<td>Possible ↑ modafinil concentrations, potential ↓ protease inhibitor concentrations; if possible, avoid use with CYP3A4 substrates until further data available. Antiretroviral therapeutic drug monitoring may be useful.</td>
<td>Possible ↓ modafinil concentrations, potential ↓ NNRTI concentrations and efficacy. If possible, avoid use with CYP3A4 substrates until further data available. Antiretroviral therapeutic drug monitoring may be useful.</td>
</tr>
</tbody>
</table>

Key: CYP= Hepatic Cytochrome P450 isoenzyme; AD= Alcohol dehydrogenase; TCA= tricyclic antidepressant; MAOI= monoamine oxidase inhibitor; SSRI= selective serotonin reuptake inhibitor 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 serum concentrations of the respective drug and may lead to decreased efficacy); inhibitor= leads to decreased clearance of substrates of a specific hepatic isoenzyme (increases serum concentrations of a respective drug and may lead to toxicity). Pgp= P-glycoprotein; 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.
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