

**Predicted Interactions Between Psychotropics and Protease Inhibitors (PIs) /Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

	<b>Psychotropic Route of Metabolism<sup>1-5</sup></b>	<b><u>Mild-Moderate Enzyme Inhibitors</u></b> Atazanavir-Reyataz® <sup>6</sup> Darunavir - Prezista® <sup>7</sup> Delavirdine-Rescriptor® <sup>8</sup> ; Fosamprenavir - Telzir®; <sup>9</sup> Indinavir-Crixivan® <sup>10</sup> ; Nelfinavir-Viracept® <sup>11</sup> ; Saquinavir-Invirase® <sup>12</sup>	<b><u>Potent Enzyme Inhibitors</u></b> Ritonavir - Norvir® <sup>13</sup> ; Lopinavir/Ritonavir – Kaletra® <sup>14</sup> Tipranavir/Ritonavir - Aptivus®/Norvir® <sup>15</sup>	<b><u>Enzyme Inducers</u></b> Nevirapine - Viramune® <sup>16</sup> Efavirenz-Sustiva® <sup>**17</sup> Etravirine - Intelence® <sup>18</sup> Tipranavir (unboosted) - Aptivus® <sup>15</sup>
Hepatic Substrate		Mainly CYP3A4	CYP3A4> 2D6	CYP3A4
Hepatic Inducer		UGT, 2C9/19 (nelfinavir only)  Efavirenz: can act as both an inducer and inhibitor of CYP3A4, but induction properties prevail clinically.	UGT, CYP1A2, CYP2C9/19, 2B6	CYP3A4 Efavirenz: can act as both an inducer and inhibitor of CYP3A4, but induction properties prevail clinically. Tipranavir: when used alone, tipranavir induces CYP3A4 and UGT; when combined with ritonavir, the net effect is CYP3A4 inhibition. <sup>15</sup>
Hepatic Inhibitor		Mainly CYP3A4 (indinavir, nelfinavir, amprenavir, delavirdine, >> saquinavir)  Efavirenz also inhibits 2C9, 2C19 (? Clinical significance).  Nelfinavir inhibits 2B6 in vitro.	CYP3A4 (potent)> >2D6 >2C9 >2C19 >2A6 >1A2>2E1  At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition. <sup>14</sup>  Ritonavir inhibits CYP2B6 in vitro, <sup>19</sup> but induces 2B6 in vivo. <sup>20</sup>  Tipranavir: when used alone, tipranavir induces CYP3A4 and UGT; when combined with ritonavir, the	Efavirenz inhibits CYP2B6 in vitro.

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			net effect is CYP3A4 inhibition. <sup>15</sup>	
<b>Antidepressants - Tricyclic (TCA's), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and others.</b>				
Amitriptyline Elavil®	Parent: CYP2D6, 2C19, 3A>GT Metabolite: CYP2D6 (nortriptyline)	Possible ↑ TCA concentrations	Possible ↑ TCA concentrations	Possible ↓ TCA concentrations
Bupropion Wellbutrin® Zyban®	Parent: CYP2B6 Metabolite (active): hydroxybupropion  Inhibitor: CYP2D6 (parent and active metabolite) <sup>21</sup>	In vitro data suggest a strong potential for <b>nelfinavir</b> to inhibit bupropion metabolism. <sup>19</sup> 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. <sup>22</sup> Use combination with caution and monitor for ↑ bupropion toxicity.  <b>Indinavir, saquinavir and amprenavir</b> were only weakly inhibitory of bupropion; hence no or only minor increase in bupropion	In vitro data suggest a potential for <b>ritonavir</b> to inhibit bupropion metabolism. <sup>19</sup> However, in vivo data suggest induction. In an open-label, 3-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 <b>lopinavir/ritonavir</b> . No significant changes in lopinavir kinetics were observed. Mechanism is postulated to be induction of CYP2B6 and UDP-glucuronyltransferase. <sup>23</sup> One case series (n=11)	In vitro data suggest a strong potential for <b>efavirenz</b> to inhibit bupropion metabolism. <sup>19</sup> However, in 13 healthy volunteers, co administration of <b>efavirenz 600 mg QD</b> and single dose bupropion 150 mg showed 55% ↓ AUC and 34% ↓ Cmax of bupropion and ↓ t1/2 of hydroxybupropion (active metabolite). <sup>24</sup> Monitor for therapeutic response when using combination. 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

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		concentrations anticipated. <sup>19</sup>	where HIV-infected subjects received bupropion 150-300 mg daily for a median of 8 months in conjunction with either <b>nelfinavir, efavirenz, or ritonavir</b> 100 mg BID reported no episodes of seizures. <sup>22</sup>	reported no episodes of seizures. <sup>22</sup> <b>Delavirdine</b> and <b>nevirapine</b> were only weakly inhibitory of bupropion; hence no or only minor increase in bupropion concentrations anticipated. <sup>19</sup>  Coadministration of <b>tipranavir 500/ritonavir 200 mg BID</b> 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. <sup>25</sup>
Citalopram Celexa®	Parent: CYP2C19, 3A4>>2D6. Inhibitor (weak): CYP 2D6, 2C19; negligible effect on CYP 3A4, 1A2 <sup>26</sup>	Possible ↑ SSRI concentrations	Potential for ↑ citalopram concentrations; use combination with caution (may wish to start with ½ dose antidepressant)	Possible ↓ SSRI concentrations

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Escitalopram Lexapro® Cipralex® (S-enantiomer of citalopram)	Parent: CYP2C19, 3A4 >> 2D6 Inhibitor (weak or negligible): CYP2D6, 1A2, 2C9, 2C19, 2E1, 3A4 <sup>27</sup>	Possible ↑ SSRI concentrations	18 healthy subjects received escitalopram 20mg and <b>ritonavir</b> 600mg single dose. No significant interaction found. <sup>28</sup>	Possible ↓ SSRI concentrations
Clomipramine Anafranil®	Parent: CYP2D6, 1A2, 2C19, 3A Metabolite: CYP2D6 (desmethyl)	Possible ↑ TCA concentrations	Possible ↑ TCA concentrations	Possible ↓ TCA concentrations
Desipramine Pertofrane®	Parent: CYP2D6>>UGT	No anticipated effect	<b>Ritonavir</b> (high dose): 145% ↑ desipramine AUC; consider desipramine dose reduction by 50%. <sup>29</sup> Lower boosting doses of ritonavir unlikely to have same degree of interaction as per lopinavir/r data. <b>Lopinavir/r</b> : no significant effect on desipramine pharmacokinetics <sup>30</sup>	No anticipated effect
Doxepin Sinequan®	Parent: hepatic metabolism (? CYPs) Metabolite (active): desmethyldoxepin	Unknown ;possible ↑ doxepin concentrations	Unknown; possible ↑ doxepin concentrations	Unknown ;possible ↓ doxepin concentrations
Duloxetine (Cymbalta®)	Parent:CYP1A2, 2D6; inactive metabolites Inhibitor (moderate): CYP2D6	Unlikely to have a major interaction.	Potential for ↑ or ↓ duloxetine concentrations. Monitor for efficacy/toxicity.  At low boosting doses,	Unlikely to have a major interaction.  Rilpivirine is a slight inducer of CYP1A2; potential for ↓

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			<p><b>ritonavir</b> does not inhibit CYP2D6 at clinically relevant concentrations, but has a more potent inhibitory effect at higher therapeutic doses.<sup>13, 14</sup> It may also induce CYP1A2.</p> <p><b>Tipranavir/r</b> inhibits CYP2D6 and induces CYP1A2, therefore an interaction is difficult to predict.<sup>15</sup></p>	duloxetine concentrations.
Fluoxetine Prozac®	Parent: CYP2D6 Inhibits: CYP2D6 (potent) Metabolite (active): norfluoxetine	No anticipated effect on fluoxetine or protease inhibitors  <u>Delavirdine:</u> 50% ↑ delavirdine trough concentrations with combination. Cautious use of combination is warranted. <sup>31</sup>	Potential for ↑ SSRI concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.  Kinetic study showing 19% ↑ <b>ritonavir</b> AUC. <sup>32, 33</sup> Post-marketing reports of cardiac and neurologic events with combination. <sup>34</sup>  Serotonin syndrome reported in a case series of patients when <b>ritonavir</b> based HAART (100-600mg BID) was added to fluoxetine. Symptoms included mental changes (confusion, mania, agitation,	No anticipated effect on fluoxetine or NNRTIs  In a retrospective review, the pharmacokinetics of <b>efavirenz</b> did not appear to be significantly affected by concomitant use of selective serotonin reuptake inhibitors. <sup>36</sup>

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			paranoia, anxiety), myoclonus, fever, diarrhea, nausea, vomiting, and diaphoresis. Most symptoms resolved by discontinuation of RTV or fluoxetine, or by lowering dosages of fluoxetine by 50% and RTV to 100mg BID (if used to boost other protease inhibitors). <sup>35</sup>	
Fluvoxamine Luvox®	Parent:CYP2D6> 1A2 Inhibits: 1A2 (potent), 3A4, 2C (moderate), 2D6 (weak)	No major anticipated effect - potential for modest ↑ protease and NNRTI concentrations and toxicity	Potential for ↑ SSRI concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.  - potential for modest ↑ protease and NNRTI concentrations and toxicity	No major anticipated effect - potential for modest ↑ protease and NNRTI concentrations and toxicity
Imipramine Tofranil®	Parent: CYP2D6, 1A2, 2C19, 3A > UGT Metabolite (active): CYP2D6 (desipramine)	Possible ↑ TCA concentrations	Possible ↑ TCA concentrations	Possible ↓ TCA concentrations
Maprotiline Ludiomil®	Parent:CYP2D6 Metabolite: UGT (hydroxyl)	Interaction unlikely	Potential ↑ maprotiline concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.	Interaction unlikely

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Milnacipran Ixel®	UGT. Not a substrate of P450 system	Interaction unlikely	Potential ↓ milnacipran concentrations via UGT induction.	Potential ↓ milnacipran concentrations
Mirtazapine Remeron®	CYP2D6, 1A2, 3A4 Is not an enzyme inhibitor or inducer <sup>37</sup>	Possible ↑ mirtazapine concentrations	Possible ↑↑ mirtazapine levels due to inhibition of 3A4 and possibly 2D6. Monitor for acute somnolence if RTV is added. Consider mirtazapine dosage decrease if combination is used.	Possible ↓ mirtazapine concentrations.
Moclobemide Manerix®	Parent: CYP2C19>2D6 Inhibits: CYP2C19>2D6	No anticipated effect	Possible ↑ or ↓ moclobemide concentrations	Efavirenz and etravirine 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.
Nefazodone Serzone®	Parent:CYP3A Inhibits: CYP3A (potent) Metabolite: CYP2D6 (hydroxy-nefazodone)	Likely ↑ nefazodone concentrations -potential ↑ protease and NNRTI concentrations and toxicity	Likely ↑↑ nefazodone concentrations -potential ↑ protease concentrations and toxicity	Likely ↓ nefazodone concentrations -potential ↑ NNRTI concentrations and toxicity Potential for ↑ <b>rilpivirine</b> concentrations; AVOID co administration.

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Nortriptyline Norventyl®	Parent: CYP2D6 Metabolite (active): 10-hydroxynortriptyline	No anticipated effect	Potential ↑ TCA concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.	No anticipated effect
Paroxetine Paxil®	Parent:CYP2D6 Inhibits: CYP2D6 (potent)	In healthy volunteers, paroxetine 20 mg QD plus <b>fosamprenavir/r</b> 700/100 mg BID for 10 days resulted in ↓ 58% paroxetine AUC, while amprenavir kinetics were similar to historical controls. Mechanism unknown; monitor for efficacy and ↑ paroxetine dose if required. <sup>38</sup> Co administration of <b>darunavir/r</b> 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. <sup>39</sup>	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. <sup>38, 39</sup>	No anticipated effect; In a retrospective review, the pharmacokinetics of <b>efavirenz</b> did not appear to be significantly affected by concomitant use of selective serotonin reuptake inhibitors. <sup>36</sup>  In healthy volunteers, paroxetine 20 mg QD plus <b>etravirine</b> (TMC125) 800 mg BID (old formulation) did not result in significant changes in exposures of either drug. No dosage adjustment is required. <sup>18</sup>
Phenelzine Nardil®	Acetylation inhibits: CYP (weak)	Unlikely	Unlikely	Unlikely
Reboxetine	3A4 substrate	Potential for ↑ reboxetine	Potential for ↑ reboxetine	Potential for ↓ reboxetine

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Edronax®		concentrations	concentrations	concentrations
Selegiline (transdermal patch) EMSAM®	2B6, 1A2 substrate	Unlikely	Potential for ↓ selegiline concentrations	Potential for ↓ selegiline concentrations
Sertraline Zoloft®	Parent:CYP2B6 > 2C9/19, 3A4, 2D6, UGT1A1(possible) <sup>40</sup> Inhibits: CYP2D6 (moderate)	Co administration of <b>darunavir/r</b> 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 dose if required. <sup>39</sup>	Potential ↑ or ↓ sertraline concentrations due to complex metabolism of sertraline.	Potential for ↓ sertraline concentrations due to enzyme induction. Sertraline AUC↓ by 39%, <b>efavirenz</b> kinetics not affected. <sup>36, 41</sup>
St. John's Wort (hypericum perforatum)	Induces CYP3A4 and P-gp	Significantly reduces indinavir exposure (57% ↓ AUC, 81% ↓ Cmin) <sup>42</sup> ; similar interaction may be likely with other substrates of CYP3A4. <b>Avoid concomitant use of PIs and NNRTIs with St. John's wort.</b>	Potential for ↓ ritonavir concentrations secondary to enzyme induction. <b>Avoid concomitant administration.</b>	St. John's Wort reduces nevirapine concentrations 35%. <sup>43</sup> <b>Avoid concomitant administration.</b>
Tranlycypromine Parnate®	hepatic metabolism	Possible ↑ MAOI concentrations	Possible ↑ MAOI concentrations	Possible ↓ MAOI concentrations
Trazodone Desyrel®	Parent:CYP2D6> CYP3A Metabolite: CYP2D6 (m-CPP)	Possible ↑ trazodone concentrations <b>Indinavir:</b> strong inhibitor of trazodone <i>in vitro</i> . Monitor for trazodone toxicity (i.e. nausea, hypotension,	<b>Ritonavir:</b> potent inhibitor of trazodone <i>in vitro</i> . <sup>44</sup> 10 healthy subjects received trazodone 50 mg with RTV 4 x 200mg doses: significant increase in trazodone	Possible ↓ trazodone concentrations

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		syncope, somnolence, anticholinergic side-effects). <b>Saquinavir and nelfinavir:</b> weak inhibitors <i>in vitro</i> ; interaction is unlikely. <sup>44</sup>	concentrations (52% ↓ CL, 122% ↑ T 1/2, 34% ↑ Cmax). <sup>45</sup> Sedation, fatigue, impaired performance, nausea, dizziness, hypotension, syncope reported. <sup>46</sup> <b>When combined with ritonavir-based regimens, use with caution and consider a lower dose of trazodone.</b>	
Trimipramine Surmontil®	Parent: CYP2D6 Metabolite (active): Desmethytrimipramine	No anticipated effect	potential ↑ TCA concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.	No anticipated effect
Venlafaxine Effexor®	Parent: CYP2D6 > CYP3A4 (minor) Inhibits: CYP2D6 (weak) Metabolite (active): UGT (O-desmethylvenlafaxine, ODV) <sup>47</sup>	Possible ↑ venlafaxine concentrations; however interaction study with <b>indinavir:</b> showed a ↓ in indinavir concentrations (28% ↓ AUC, 36% ↓ Cmax); no change in venlafaxine concentrations. <sup>48</sup>	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	Possible ↓ venlafaxine

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	<b>Psychotropic Route of Metabolism<sup>1-5</sup></b>	<b><u>Mild-Moderate Enzyme Inhibitors</u></b> Atazanavir-Reyataz® <sup>6</sup> Darunavir - Prezista® <sup>7</sup> Delavirdine-Rescriptor® <sup>8</sup> ; Fosamprenavir - Telzir®; <sup>9</sup> Indinavir-Crixivan® <sup>10</sup> ; Nelfinavir-Viracept® <sup>11</sup> ; Saquinavir-Invirase® <sup>12</sup>	<b><u>Potent Enzyme Inhibitors</u></b> Ritonavir - Norvir® <sup>13</sup> ; Lopinavir/Ritonavir – Kaletra® <sup>14</sup> Tipranavir/Ritonavir - Aptivus®/Norvir® <sup>15</sup>	<b><u>Enzyme Inducers</u></b> Nevirapine - Viramune® <sup>16</sup> Efavirenz-Sustiva® <sup>**17</sup> Etravirine - Intelence® <sup>18</sup> Tipranavir (unboosted) - Aptivus® <sup>15</sup>
			coadministered with a CYP2D6 inhibitor. <sup>47</sup>	
<b>Neuroleptics</b>				
Aripiprazole Abilify®	Parent: CYP 3A4, 2D6 Metabolite (active): dehydro-aripiprazole	Possible ↑ aripiprazole concentrations	Possible ↑ aripiprazole concentrations	Possible ↓ aripiprazole concentrations
Chlorpromazine Largactil®	Parent:CYP2D6, CYP1A2?, GT Metabolite: GT (7-OH-CPZ)	Unlikely	Potential ↑ chlorpromazine concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.	Unlikely
Clozapine Clozaril®	Parent: CYP1A2, 3A4 Metabolite (active): norclozapine	Possible ↑ clozapine concentrations	Potential for ↓ or ↑ clozapine concentrations due to ritonavir-mediated CYP1A2 induction and/or CYP3A4 inhibition. Interaction difficult to predict. <b>Combination no longer contraindicated in product monograph.</b> <sup>13</sup>	Possible ↓ clozapine concentrations
Flupenthixol Fluanxol®	Parent: Extensive hepatic metabolism (not well defined)	Possible ↑ flupenthixol concentrations	Potential ↑ flupenthixol concentrations	Possible ↓ flupenthixol concentrations
Fluphenazine Modecate®	Parent: Extensive hepatic metabolism	Possible ↑ fluphenazine concentrations	Potential ↑ fluphenazine concentrations	Possible ↓ fluphenazine concentrations
Haloperidol	Parent: CYP2D6>3A4	Possible ↑ haloperidol	Potential ↑ haloperidol	Possible ↓ haloperidol

**Predicted Interactions Between Psychotropics and Protease Inhibitors (PIs) /Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

	<b>Psychotropic Route of Metabolism<sup>1-5</sup></b>	<b><u>Mild-Moderate Enzyme Inhibitors</u></b> Atazanavir-Reyataz® <sup>6</sup> Darunavir - Prezista® <sup>7</sup> Delavirdine-Rescriptor® <sup>8</sup> ; Fosamprenavir - Telzir®; <sup>9</sup> Indinavir-Crixivan® <sup>10</sup> ; Nelfinavir-Viracept® <sup>11</sup> ; Saquinavir-Invirase® <sup>12</sup>	<b><u>Potent Enzyme Inhibitors</u></b> Ritonavir - Norvir® <sup>13</sup> ; Lopinavir/Ritonavir – Kaletra® <sup>14</sup> Tipranavir/Ritonavir - Aptivus®/Norvir® <sup>15</sup>	<b><u>Enzyme Inducers</u></b> Nevirapine - Viramune® <sup>16</sup> Efavirenz-Sustiva® <sup>**17</sup> Etravirine - Intelence® <sup>18</sup> Tipranavir (unboosted) - Aptivus® <sup>15</sup>
Haldol®		concentrations	concentrations	concentrations
Loxapine Loxapac®	Parent: Extensive hepatic metabolism	Possible ↑ loxapine concentrations	Possible ↑ loxapine concentrations	Possible ↓ loxapine concentrations
Methotrimeprazine (levomepromazine) Nozinan®	Parent: Extensive hepatic metabolism Inhibits CYP2D6	Possible ↑ methotrimeprazine concentrations	Possible ↑ methotrimeprazine concentrations	Possible ↓ methotrimeprazine concentrations
Olanzapine Zyprexa®	Parent: CYP2D6, 1A2, GT Inhibits: CYP1A2, 2D6, 3A4 (weak)	No anticipated effect with most PIs & delavirdine; <b>nelfinavir</b> may ↓ olanzapine concentrations by inducing glucuronidation (clinical significant unknown). -potential minor ↑ protease/NNRTI concentrations and toxicity	Healthy volunteer study of olanzapine 10 mg +/- <b>ritonavir</b> 500 mg BID resulted in 53%↓ AUC of olanzapine. <u>Higher olanzapine dosages may be necessary to maintain therapeutic effect.</u> <sup>49</sup>  In a healthy volunteer study, subjects received single dose olanzapine 10 mg alone or olanzapine 15 mg with steady-state <b>fosamprenavir 700/100 mg BID</b> . Olanzapine <u>15 mg</u> in the presence of fosamprenavir/ritonavir resulted in similar AUC and 32% ↑ Cmax as that observed with olanzapine <u>10 mg</u> alone. Amprenavir	No anticipated effect -potential minor ↑ NNRTI concentrations and toxicity

**Predicted Interactions Between Psychotropics and Protease Inhibitors (PIs) /Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

	<b>Psychotropic Route of Metabolism<sup>1-5</sup></b>	<b><u>Mild-Moderate Enzyme Inhibitors</u></b> Atazanavir-Reyataz® <sup>6</sup> Darunavir - Prezista® <sup>7</sup> Delavirdine-Rescriptor® <sup>8</sup> ; Fosamprenavir - Telzir®; <sup>9</sup> Indinavir-Crixivan® <sup>10</sup> . Nelfinavir-Viracept® <sup>11</sup> . Saquinavir-Invirase® <sup>12</sup>	<b><u>Potent Enzyme Inhibitors</u></b> Ritonavir - Norvir® <sup>13</sup> ; Lopinavir/Ritonavir – Kaletra® <sup>14</sup> Tipranavir/Ritonavir - Aptivus®/Norvir® <sup>15</sup>	<b><u>Enzyme Inducers</u></b> Nevirapine - Viramune® <sup>16</sup> Efavirenz-Sustiva® <sup>**17</sup> Etravirine - Intelence® <sup>18</sup> Tipranavir (unboosted) - Aptivus® <sup>15</sup>
			pharmacokinetic parameters were similar to historical controls. <u>Increase olanzapine dose by 50% when combining with boosted fosamprenavir.</u> <sup>50</sup>	
Paliperidone Invega®	Parent: CYP2D6, 3A4 (in vitro- ? if this also applies in vivo). Paliperidone is the major active metabolite of risperidone.	Possible ↑ paliperidone concentrations	Possible ↑ paliperidone concentrations	Possible ↓ paliperidone concentrations
Perphenazine Trilafon®	Parent: CYP2D6 Inhibits: CYP2D6	Unlikely	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. <sup>51</sup>	Unlikely
Pimozide Orap®	Parent: CYP3A	Likely ↑ pimozide concentrations; <b>avoid</b> if possible	<b>Contraindicated</b> ; potential ↑↑ pimozide concentrations <sup>13</sup>	Likely ↓ pimozide concentrations
Pipotiazine Piportil L4	Parent: Extensive hepatic metabolism	Possible ↑ pipotiazine concentrations	Possible ↑ pipotiazine concentrations	Possible ↓ pipotiazine concentrations
Quetiapine	Route of Metabolism:	Possible ↑ quetiapine	Possible ↑↑ quetiapine	Possible ↓ quetiapine

Predicted Interactions Between Psychotropics and Protease Inhibitors (PIs) /Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

	Psychotropic Route of Metabolism <sup>1-5</sup>	<u>Mild-Moderate Enzyme Inhibitors</u> Atazanavir-Reyataz® <sup>6</sup> Darunavir - Prezista® <sup>7</sup> Delavirdine-Rescriptor® <sup>8</sup> ; Fosamprenavir - Telzir®; <sup>9</sup> Indinavir-Crixivan® <sup>10</sup> ; Nelfinavir-Viracept® <sup>11</sup> ; Saquinavir-Invirase® <sup>12</sup>	<u>Potent Enzyme Inhibitors</u> Ritonavir - Norvir® <sup>13</sup> ; Lopinavir/Ritonavir – Kaletra® <sup>14</sup> Tipranavir/Ritonavir - Aptivus®/Norvir® <sup>15</sup>	<u>Enzyme Inducers</u> Nevirapine - Viramune® <sup>16</sup> Efavirenz-Sustiva® <sup>**17</sup> Etravirine - Intelence® <sup>18</sup> Tipranavir (unboosted) - Aptivus® <sup>15</sup>
Seroquel®	CYP3A4 >> 1A2 <sup>52</sup> Is not an enzyme inhibitor or inducer	concentrations. Report of two patients who experienced serious quetiapine adverse effects secondary to possible/probable interactions with <b>atazanavir/ritonavir</b> . One patient developed rapid and severe weight gain when quetiapine was added to his stable ARV regimen, while another patient stabilized on quetiapine developed increased sedation and mental confusion shortly after initiating atazanavir/ritonavir. In both cases, symptoms resolved after discontinuation of quetiapine. <sup>53</sup> 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 <b>atazanavir/ritonavir</b> . <sup>54</sup>	concentrations.  Case report of priapism lasting 42 hours with an onset of 5-6 hours after co-ingestion of perphenazine and quetiapine with <b>lopinavir/ritonavir</b> . Rapid elevations in the neuroleptic concentrations were postulated as the mechanism. The symptoms were managed with intracavernous ephedrine, <sup>51</sup> irrigation and aspiration. <sup>51</sup>	concentrations.
Risperidone Risperdal®	Parent: CYP2D6>> 3A Active metabolite: 9-OH risperidone (paliperidone)	Unlikely. See Ritonavir for more information on boosted protease inhibitors.	Potential ↑ risperidone concentrations. One case of extrapyramidal symptoms (dysphagia, dysphonia,	Unlikely

**Predicted Interactions Between Psychotropics and Protease Inhibitors (PIs) /Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

	<b>Psychotropic Route of Metabolism<sup>1-5</sup></b>	<b><u>Mild-Moderate Enzyme Inhibitors</u></b> Atazanavir-Reyataz® <sup>6</sup> Darunavir - Prezista® <sup>7</sup> Delavirdine-Rescriptor® <sup>8</sup> ; Fosamprenavir - Telzir®; <sup>9</sup> Indinavir-Crixivan® <sup>10</sup> ; Nelfinavir-Viracept® <sup>11</sup> ; Saquinavir-Invirase® <sup>12</sup>	<b><u>Potent Enzyme Inhibitors</u></b> Ritonavir - Norvir® <sup>13</sup> ; Lopinavir/Ritonavir – Kaletra® <sup>14</sup> Tipranavir/Ritonavir - Aptivus®/Norvir® <sup>15</sup>	<b><u>Enzyme Inducers</u></b> Nevirapine - Viramune® <sup>16</sup> Efavirenz-Sustiva® <sup>**17</sup> Etravirine - Intelence® <sup>18</sup> Tipranavir (unboosted) - Aptivus® <sup>15</sup>
	(renal)		difficulty breathing, and worsening tremors) with risperidone 2mg/day + <b>indinavir/ritonavir</b> (IDV/RTV) 800mg/200mg BID. <sup>55</sup> One case of neuroleptic malignant syndrome with risperidone 1.5mg/day + IDV 800mg/RTV 400mg daily. <sup>56</sup> Reversible coma reported with risperidone 3mg BID + IDV 400mg/RTV 200mg BID. <sup>57</sup>	
Thioridazine Mellaril®	Parent: CYP2D6 Inhibits: CYP2D6 Metabolite (active): (mesoridazine, sulforidazine)	Unlikely	Potential ↑ thioridazine concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.	Unlikely
Ziprasidone Geodon®, Zeldox®	Parent: CYP3A4 Is not an enzyme inhibitor or inducer <sup>58</sup>	Potential ↑ ziprasidone concentrations	Potential ↑↑ ziprasidone concentrations	Potential ↓ ziprasidone concentrations
Zuclopenthixol Clopixol®	Parent: Extensive hepatic metabolism	Potential ↑ zuclopenthixol concentrations	Potential ↑↑ zuclopenthixol concentrations	Potential ↓ zuclopenthixol concentrations
<b>Other</b>				
Buspirone Buspar®	Parent: CYP3A4 Metabolite (active): 1-pyrimidinyl piperazine Buspirone has	possible ↑ buspirone concentrations	Case report of patient with Parkinson-like symptoms (ataxia, shuffling gait, cogwheel rigidity, resting	possible ↓ buspirone concentrations and withdrawal

**Predicted Interactions Between Psychotropics and Protease Inhibitors (PIs) /Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

	<b>Psychotropic Route of Metabolism<sup>1-5</sup></b>	<b><u>Mild-Moderate Enzyme Inhibitors</u></b> Atazanavir-Reyataz® <sup>6</sup> Darunavir - Prezista® <sup>7</sup> Delavirdine-Rescriptor® <sup>8</sup> ; Fosamprenavir - Telzir®; <sup>9</sup> Indinavir-Crixivan® <sup>10</sup> ; Nelfinavir-Viracept® <sup>11</sup> ; Saquinavir-Invirase® <sup>12</sup>	<b><u>Potent Enzyme Inhibitors</u></b> Ritonavir - Norvir® <sup>13</sup> ; Lopinavir/Ritonavir – Kaletra® <sup>14</sup> Tipranavir/Ritonavir - Aptivus®/Norvir® <sup>15</sup>	<b><u>Enzyme Inducers</u></b> Nevirapine - Viramune® <sup>16</sup> Efavirenz-Sustiva® <sup>**17</sup> Etravirine - Intelence® <sup>18</sup> Tipranavir (unboosted) - Aptivus® <sup>15</sup>
	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. <sup>59</sup>		tremor, and sad affect) 6 weeks after <b>indinavir/ritonavir</b> (400mg/400mg BID) were added to buspirone 40mg am/30mg pm. <sup>60</sup>	
Dextroamphetamine Dexedrine®	Parent: hepatic metabolism (deamination and hydroxylation)	Possible ↑ dextroamphetamine concentrations	Possible ↑ dextroamphetamine concentrations	Possible ↓ dextroamphetamine concentrations
Lithium Carbolith®	None (renal)	None	None	None
L-Tryptophan Tryptan®	Parent: metabolized via tryptophan hydroxylase Metabolite: nicotinic acid > serotonin	Unlikely	Unlikely	Unlikely
Methylphenidate Ritalin® Concerta®	Parent: hepatic and tissue nonmicrosomal hydrolytic esterases Inhibits: not well described- ?CYP3A, ?2D6, Metabolite: renal (ritalinic acid- inactive)	Possible ↑ methylphenidate concentrations	Possible ↑ methylphenidate concentrations	Possible ↓ methylphenidate concentrations
Modafinil Alertec®	Parent: CYP3A Inhibits 2C19, 2C9; may induce 3A4, 1A2, 2B6	Possible ↑ modafinil concentrations. Potential for ↓ protease inhibitor concentrations; if possible, avoid use with CYP3A4 substrates until further data	Possible ↑ modafinil concentrations, potential ↓ protease inhibitor concentrations; if possible, avoid use with CYP3A4 substrates until further data	- possible ↓ modafinil concentrations - potential ↓ NNRTI/tipranavir concentrations and efficacy - if possible, avoid use with

**Predicted Interactions Between Psychotropics and Protease Inhibitors (PIs) /Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

	<b>Psychotropic Route of Metabolism<sup>1-5</sup></b>	<b><u>Mild-Moderate Enzyme Inhibitors</u></b> Atazanavir-Reyataz® <sup>6</sup> Darunavir - Prezista® <sup>7</sup> Delavirdine-Rescriptor® <sup>8</sup> ; Fosamprenavir - Telzir®; <sup>9</sup> Indinavir-Crixivan® <sup>10</sup> ; Nelfinavir-Viracept® <sup>11</sup> ; Saquinavir-Invirase® <sup>12</sup>	<b><u>Potent Enzyme Inhibitors</u></b> Ritonavir - Norvir® <sup>13</sup> ; Lopinavir/Ritonavir – Kaletra® <sup>14</sup> Tipranavir/Ritonavir - Aptivus®/Norvir® <sup>15</sup>	<b><u>Enzyme Inducers</u></b> Nevirapine - Viramune® <sup>16</sup> Efavirenz-Sustiva® <sup>**17</sup> Etravirine - Intelence® <sup>18</sup> Tipranavir (unboosted) - Aptivus® <sup>15</sup>
		available. Antiretroviral therapeutic drug monitoring may be useful.	available. Antiretroviral therapeutic drug monitoring may be useful.	CYP3A4 substrates until further data available. Antiretroviral therapeutic drug monitoring may be useful.

**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; Protease inhibitors= saquinavir, indinavir, nelfinavir, amprenavir, ritonavir; NNRTI's= delavirdine, efavirenz, nevirapine; UGT= Uridine diphosphate glucuronyltransferase.

\*\* Since efavirenz is both an inhibitor and inducer of CYP3A4, predictions on drug interactions are difficult. Clinically, 3A4 induction predominates. Efavirenz also inhibits CYP2C9 and 2C19, however the clinical significance of this is unknown.

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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