

**Interactions Between Sedatives/Hypnotics/Anxiolytics and Protease Inhibitors /Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

	<b>Sedative Route of Metabolism</b> <sup>1, 2</sup>	<b>Mild-Moderate Enzyme Inhibitors</b> Atazanavir-Reyataz <sup>3</sup> Darunavir - Prezista <sup>4</sup> Delavirdine-Rescriptor <sup>5</sup> ; Fosamprenavir - Telzir <sup>6</sup> ; Indinavir-Crixivan <sup>7</sup> ; Nelfinavir-Viracept <sup>8</sup> ; Saquinavir-Invirase <sup>9</sup>	<b>Potent Enzyme Inhibitors</b> Ritonavir - Norvir <sup>10</sup> ; Lopinavir/Ritonavir – Kaletra <sup>11</sup> Tipranavir/Ritonavir - Aptivus <sup>12</sup> /Norvir <sup>12</sup>	<b>Enzyme Inducers</b> Nevirapine - Viramune <sup>13</sup> Efavirenz-Sustiva <sup>**14</sup> Etravirine - Intelence <sup>15</sup> Tipranavir (unboosted) - Aptivus <sup>12</sup>
<b>Hepatic Substrate</b>		Mainly CYP3A4	CYP3A4> 2D6	CYP3A4
<b>Hepatic Inducer</b>		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>12</sup>
<b>Hepatic Inhibitor</b>		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>11</sup>  Ritonavir inhibits CYP2B6 in vitro, <sup>16</sup> but induces 2B6 in vivo. <sup>17</sup>  Tipranavir: when used alone, tipranavir induces CYP3A4 and UGT; when combined with ritonavir, the net effect is CYP3A4 inhibition. <sup>12</sup>	Efavirenz inhibits CYP2B6 in vitro.
<b>Alprazolam (APZ)</b>	Parent: CYP3A Metabolite: UGT (4 & alpha)	possible ↑ alprazolam concentrations	<b>No longer contraindicated</b> in product monograph. <sup>10</sup> Short-	possible ↓ alprazolam concentrations and withdrawal

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<b>Xanax®</b>	hydroxy)		term study of 1mg APZ with 4 doses of RTV 200mg resulted in 148% ↑ APZ AUC and ↑t ½ from 13 to 30 hours. <sup>18</sup> Steady-state study of 1mg APZ with 12 days of RTV resulted in a 12% □ APZ AUC. <sup>19</sup> This likely reflects RTV early inhibitory and chronic induction effects. <b>Based on this, therapy can likely be initiated using very low APZ doses at first, and monitoring for tolerability and efficacy. After 2-3 weeks, APZ dosage may need to be increased.</b>	
<b>Bromazepam Lectopam®</b>	Parent: Hydroxylation	possible ↑ bromazepam concentrations	possible ↑ bromazepam concentrations	possible ↓ bromazepam concentrations and withdrawal
<b>Buspirone Buspar®</b>	Parent: CYP3A4 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. <sup>20</sup>	possible ↑ buspirone concentrations	possible ↑ buspirone concentrations Case report of patient with Parkinson-like symptoms (ataxia, shuffling gait, cogwheel rigidity, resting tremor, and sad affect) 6 weeks after ritonavir/indinavir (400mg/400mg BID) were added to buspirone 40mg am/30mg pm. <sup>21</sup>	possible ↓ buspirone concentrations and withdrawal
<b>Chloral hydrate (Novo, PMS)</b>	Parent: AD Metabolite: UGT (trichloroethanol)	no predicted effect	unlikely effect	no predicted effect

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<b>Clonazepam Rivotril®</b>	Parent: CYP3A4	possible ↑ clonazepam concentrations	possible ↑ clonazepam concentrations	possible ↓ clonazepam concentrations and withdrawal
<b>Clorazepate Tranxene®</b>	Parent: Acid hydrolysis Metabolites (active): nordiazepam, 2C19desmethyldiazepam	possible ↑ metabolite concentrations	<b>No longer contraindicated;</b> possible ↑ clorazepate concentrations	possible ↓ metabolite concentrations and withdrawal
<b>Diazepam Valium®</b>	Parent: CYP2C19>3A Metabolites (active): nordiazepam, N-desmethyldiazepam, temazepam	possible ↑ diazepam and nordiazepam concentrations	<b>No longer contraindicated;</b> possible ↑ diazepam and nordiazepam concentrations	possible ↓ diazepam and nordiazepam concentrations and withdrawal
<b>Estazolam Prosom®</b>	Parent: CYP3A4 <sup>22</sup>	possible ↑ estazolam concentrations	possible ↑ estazolam concentrations	possible ↓ estazolam concentrations and withdrawal
<b>Eszopiclone Lunesta®</b>	Parent: CYP3A4, 2E1 <sup>23</sup>	possible ↑ eszopiclone concentrations	possible ↑ eszopiclone concentrations	possible ↓ eszopiclone concentrations and withdrawal
<b>Flurazepam Dalmane®</b>	Parent: liver Metabolites (active): desalkyl, hydroxyethyl	possible ↑ flurazepam concentrations	<b>No longer contraindicated;</b> possible ↑ flurazepam concentrations	possible ↓ flurazepam concentrations and withdrawal
<b>Lorazepam Ativan®</b>	Parent: UGT	<b>Nelfinavir</b> may ↓ lorazepam concentrations via UGT induction; no predicted effect with other PIs.	possible ↓ lorazepam concentrations (via ritonavir-mediated UGT induction)	<b>Tipranavir</b> may ↓ lorazepam concentrations (via UGT induction); no predicted effect with the NNRTIs.
<b>Midazolam (MDZ) Versed®</b>	Parent: CYP3A Metabolite: UGT (hydroxy)	<b>Contraindicated</b> in product monographs. Possible ↑ midazolam concentrations. <u>Saquinavir:</u> case report of prolonged sedation requiring flumazenil with combination. <sup>24</sup>	<b>Contraindicated;</b> possible ↑↑ midazolam concentrations	possible ↓ midazolam concentrations and efficacy

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		Kinetic study showing 5-fold ↑ PO MDZ AUC and 2.4-fold ↑ IV MDZ AUC. <sup>25</sup>		
<b>Nitrazepam Mogadon<sup>®</sup></b>	Parent: nitro-reduction, acetylation	possible ↑ nitrazepam concentrations	possible ↑ nitrazepam concentrations	possible ↓ nitrazepam concentrations and withdrawal
<b>Oxazepam Serax<sup>®</sup></b>	Parent: UGT	<b>Nelfinavir</b> may ↓ oxazepam concentrations via UGT induction; no predicted effect with other PIs.	possible ↓ oxazepam concentrations (via ritonavir-mediated UGT induction)	<b>Tipranavir</b> may ↓ oxazepam concentrations (via UGT induction); no predicted effect with the NNRTIs.
<b>Propofol Diprivan<sup>®</sup></b>	Parent: CYP2B6 >UGT	no predicted effect	possible ↓ propofol concentrations	no predicted effect
<b>Ramelteon Rozerem<sup>®</sup></b>	Parent: CYP1A2 >2C, 3A4 <sup>26</sup>	no major predicted effect	possible ↓ ramelteon concentrations	no major predicted effect
<b>Temazepam Restoril<sup>®</sup></b>	Parent: UGT>>CYP (2B6, 2C, 3A) <sup>27</sup>	<b>Nelfinavir</b> may ↓ temazepam concentrations via UGT induction; no predicted effect with other PIs.	possible ↓ temazepam concentrations (via ritonavir-mediated UGT induction)	<b>Tipranavir</b> may ↓ temazepam concentrations via UGT induction; no predicted effect with the NNRTIs.
<b>Triazolam (TZL) Halcion<sup>®</sup></b>	Parent: CYP3A Metabolite: GT (4 & alpha hydroxy)	<b>Contraindicated</b> in product monographs. Possible ↑ triazolam concentrations.	<b>Contraindicated</b> in product monograph. <i>In vitro</i> study showed RTV is a strong inhibitor of TZL. <sup>28</sup> Short-term study of 0.125mg TZL with 4 doses of RTV 200mg resulted in □ triazolam half-life from 3.7 to 50 hours. <sup>29, 30</sup> This likely reflects RTV early inhibitory effects only, but does not account for chronic induction.	possible ↓ triazolam concentrations and withdrawal

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<b>Valerian Root</b>	May inhibit CYP3A4. <sup>31, 32</sup>	A significant interaction is unlikely.	A significant interaction is unlikely.	A significant interaction is unlikely. Potential for additive CNS toxicity when starting EFV.
<b>Zaleplon Starnoc®</b>	Aldehyde oxidase > CYP3A4 <sup>33</sup>	Possible ↑ zaleplon concentrations.	Possible ↑ zaleplon concentrations.	Possible ↓zaleplon concentrations.
<b>Zolpidem Ambien®</b>	Parent: CYP3A (61%) >> 2C9 (22%), 1A2 (14%) >> 2D6, 2C19 (<3%)	possible ↑ in zolpidem concentrations	<b>No longer contraindicated</b> in product monograph. <sup>10</sup> <i>In vitro</i> study showed RTV is a less potent inhibitor of zolpidem than triazolam. In addition, short-term study of zolpidem 5.0 mg with 4 doses of RTV 200mg resulted in an insignificant increase in t <sub>1/2</sub> from 2 to 2.4 hours. There were no clinical sequelae seen. <sup>30</sup> A 50% zolpidem dosage reduction may be warranted when used with potent enzyme inhibitors. <sup>27</sup>	Possible decrease in zolpidem concentrations and withdrawal
<b>Zopiclone Imovane®</b>	Parent: CYP3A4> 2C8, 2C9 <sup>27</sup>	possible ↑ zopiclone concentrations	possible ↑ zopiclone concentrations. A 50% zopiclone dosage reduction may be warranted when used with potent enzyme inhibitors. <sup>27</sup>	possible ↓ zopiclone concentrations and withdrawal

Key: CYP= Hepatic Cytochrome P450 isoenzyme; AD= Alcohol dehydrogenase; substrate= route of hepatic elimination of that specific drug (specified by a specific cytochrome P450 isoenzyme); inducer= leads to more rapid clearance of substrates of a specific hepatic isoenzyme (lowers levels of the respective drug and may lead to decreased efficacy); inhibitor= leads to decreased clearance of substrates of a specific hepatic isoenzyme (increases levels of a respective drug and may lead to toxicity). Protease inhibitors= saquinavir, indinavir, nelfinavir, amprenavir, ritonavir; NNRTI's= delavirdine, efavirenz, nevirapine; UGT= Uridine diphosphate glucuronyltransferase  
 \*\* Since efavirenz is both an inhibitor and inducer of CYP3A4, predictions on drug interactions are complex. Clinically, 3A4 induction predominates. Efavirenz also inhibits CYP2C9 and 2C19.

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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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