

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

**NB: please see “SUGGESTIONS FOR MANAGEMENT OF ANTICONVULSANT-ANTIRETROVIRAL INTERACTIONS IN HIV”  
for further discussion on anticonvulsants of choice in HIV**

	<b>Anticonvulsant Route of Metabolism<sup>1-5</sup></b>	<b>Mild-Moderate Enzyme Inhibitors</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>Potent Enzyme Inhibitors</b> Ritonavir - Norvir® <sup>13</sup> ; Lopinavir/Ritonavir – Kaletra® <sup>14</sup> Tipranavir/Ritonavir - Aptivus®/Norvir® <sup>15</sup>	<b>Enzyme Inducers</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,	Efavirenz inhibits CYP2B6 in vitro.

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			tipranavir induces CYP3A4 and UGT; when combined with ritonavir, the net effect is CYP3A4 inhibition. <sup>15</sup>	
Carbamazepine (CBZ) Tegretol®	Parent: CYP3A>> 2C8, 1A2  Induces CYP3A, 2C9, 2C19, UGT and possibly 1A2  Active metabolite: epoxide hydrolase (CBZ-10,11- epoxide)	likely ↑ CBZ levels, and ↓ protease/NNRTI levels and loss of efficacy; dosing adjustments not yet studied; <b>avoid combination as antiretroviral therapy may be significantly compromised due to enzyme induction, and carbamazepine toxicity may occur.</b> <u>Indinavir:</u> Report of antiretroviral failure with concomitant CBZ-indinavir therapy. ↓ IDV concentrations to 4-25% of mean population values. <sup>21</sup>  A 50-year-old HIV-positive male developed excessive drowsiness secondary to carbamazepine when a regimen containing <b>lopinavir/ritonavir</b> was introduced, and his CBZ serum concentration ↑ 46%. When lopinavir/ritonavir was replaced by <b>nelfinavir</b> , serum CBZ	likely ↑ CBZ levels and ↓ protease levels and loss of efficacy; <b>avoid combination as antiretroviral therapy may be significantly compromised due to enzyme induction, and carbamazepine toxicity may occur.</b> In a 20 y.o. patient, addition of <b>ritonavir (200 mg dose)</b> to CBZ and <b>zonisamide</b> resulted in 70-87% ↑ serum CBZ levels and toxicity (vomiting, vertigo). Zonisamide concentrations were unchanged. Ritonavir levels were not measured. Doses of anticonvulsants were reduced by 1/3. <sup>23</sup> Several other case reports have reported acute CBZ toxicity (ataxia, vertigo, disorientation, diplopia, drowsiness) within 2-4 days of adding RTV. <sup>24-27</sup>	likely ↓ CBZ levels and ↓ NNRTI levels and loss of efficacy; dosing adjustments not yet studied for all drugs; in general, <b>avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction.</b>  Negative dual interaction with <b>efavirenz</b> observed in a pharmacokinetic study in healthy subjects (n=36): <ul style="list-style-type: none"> <li>• Co-administration of EFV 600 mg QD with CBZ 400 mg QD at steady-state.</li> <li>• <b>EFV:</b> ↓ AUC 36%, Cmax 21%, Cmin 47%</li> <li>• <b>CBZ:</b> ↓ AUC 27%, Cmax 20%, Cmin 35%.</li> <li>• The kinetics of the active <b>CBZE</b> metabolite were unchanged.</li> </ul> Upward dosage titration of both

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		<p>concentrations ↑ 53% within 3 days, and the patient again developed excessive drowsiness and became unsteady on his feet. In both instances, ↓ CBZ dosage by 33% resulted in resolution of symptoms.<sup>22</sup></p>	<p>A 50-year-old HIV-positive male developed excessive drowsiness secondary to carbamazepine when a regimen containing <b>lopinavir/ritonavir</b> was introduced, and his CBZ serum concentration ↑ 46%. When lopinavir/ritonavir was replaced by <b>nelfinavir</b>, serum CBZ concentrations ↑ 53% within 3 days, and the patient again developed excessive drowsiness and became unsteady on his feet. In both instances, ↓ CBZ dosage by 33% resulted in resolution of symptoms.<sup>22</sup></p> <p>In an open-label, 2 phase, crossover interaction study in healthy volunteers, steady-state coadministration of <b>darunavir 600/100 mg BID</b> plus CBZ 200 mg BID resulted in 14% ↓ C<sub>min</sub>, 1.2% ↑ AUC of darunavir, 54% ↑ C<sub>min</sub>, 45% ↑ AUC of CBZ and 52% ↓ C<sub>min</sub>, 54% ↓ AUC of CBZ-epoxide compared to either</p>	<p>efavirenz and CBZ is likely required. Therapeutic drug monitoring would be useful. If possible, use alternate anticonvulsant such as vigabatrin or gabapentin.<sup>29</sup></p> <p>In a phase 1, two-period, 9 group study, a single dose of carbamazepine 400 mg given with <b>single dose nevirapine 200 mg</b> in healthy non-pregnant women significant ↓ nevirapine t<sub>1/2</sub> by 18.8 hours and ↓ time to undetectable NVP levels by 4 days compared to single-dose NVP administered alone (median t<sub>1/2</sub> with single-dose NVP alone was 53.9 hours, time to undetectable NVP was 15.5 days).<sup>30</sup></p>

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			<p>drug administered alone. Suggest monitoring for CBZ efficacy and possibly ↓ CBZ dose by 25-50% if necessary. Dosage adjustment for darunavir/ritonavir likely not required.<sup>28</sup></p> <p><b>Tipranavir/ritonavir:</b> CBZ 200mg BID with tipranavir resulted in a 23% ↑ in CBZ and CBZ-10, 11-epoxide Cmin and a 61% ↓ in tipranavir Cmin (compared to historical controls). This may compromise tipranavir efficacy. Higher doses of CBZ may lead to even larger decreases in tipranavir concentrations.<sup>15</sup> The combination should likely be avoided.</p>	
Clobazam Frisium®	Parent: CYP3A4, 2C19 Inhibits CYP2C9/19 Metabolite (active): N-desmethyl (norclobazam). <sup>31</sup>	Inhibitors of CYP450 may ↑ clobazam concentrations; monitor for toxicity and reduce dose if necessary	Inhibitors of CYP450 may ↑ clobazam concentrations; monitor for toxicity and reduce dose if necessary	potential for ↓ clobazam concentrations; monitor for efficacy and increase dose if necessary
Clonazepam	CYP3A4	potential for ↑ clonazepam	potential for ↑ clonazepam	possible ↓ clonazepam

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Rivotril®		concentrations	concentrations	concentrations and withdrawal
Ethosuximide Zarontin®	CYP3A4 (40%)>others	potential for ↑ ethosuximide concentrations; monitor for toxicity and reduce dose if necessary	potential for ↑↑ ethosuximide concentrations; monitor closely for toxicity and reduce dose if necessary	potential for ↓ ethosuximide concentrations; monitor for efficacy and increase dose if necessary
Felbamate Felbatol®	CYP3A4 Inhibits CYP2C19 Induces CYP3A4	likely ↑ felbamate levels, and ↓ protease/NNRTI levels and loss of efficacy; dosing adjustments not yet studied; <b>avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction.</b>	likely ↑ felbamate levels, and ↓ protease/NNRTI levels and loss of efficacy; dosing adjustments not yet studied; <b>avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction.</b>	likely ↓ felbamate levels and ↓ NNRTI levels and loss of efficacy; dosing adjustments not yet studied; <b>avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction.</b>
Gabapentin Neurontin®	excreted unchanged in urine	no interaction anticipated	no interaction anticipated	no interaction anticipated
Lamotrigine Lamictal®	Parent: mainly UGT Induces UGT (mild)	potential for ↓ lamotrigine concentrations due to GT induction by nelfinavir; monitor for efficacy and increase dose if necessary  <b>Raltegravir:</b> In healthy subjects, <b>raltegravir 400 mg BID</b> for five days did not affect the pharmacokinetics of single dose lamotrigine 100 mg. The mean ratio of the AUC of lamotrigine-2N-glucuronide to lamotrigine was similar when	In a pharmacokinetic study in healthy subjects, lamotrigine C <sub>min</sub> ↓ 56% when administered with <b>lopinavir/ritonavir</b> for 10 days, lopinavir concentrations unaffected. Doubling the lamotrigine dose to 200 mg BID appeared to overcome this interaction. <sup>33</sup> Monitor for lamotrigine efficacy and ↑ dose if necessary when coadministering with ritonavir-	Potential for ↓ lamotrigine concentrations due to GT induction by <b>tipranavir</b> ; monitor for efficacy and increase dose if necessary.  In healthy subjects, <b>raltegravir 400 mg BID</b> did not affect the pharmacokinetics of single-dose lamotrigine 100 mg compared to lamotrigine administered alone, and raltegravir exposures in the presence of lamotrigine were

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		lamotrigine was taken alone (0.35) or when taken with raltegravir (0.36). Raltegravir does not influence the glucuronidation of lamotrigine. <sup>32</sup>	containing regimens.  In a pharmacokinetic study in healthy volunteers of single dose lamotrigine 10 mg in the presence of steady state <b>atazanavir 400 mg QD or atazanavir 300/ritonavir 100 mg QD</b> , lamotrigine concentrations were unaffected with unboosted atazanavir, while 32% ↓ lamotrigine AUC was observed with ATV/r. Atazanavir and ritonavir concentrations were comparable to historical controls in the presence of lamotrigine. <sup>34</sup>	comparable to historical controls. <sup>32</sup>
Levetiracetam Keppra®	24% enzymatic hydrolysis (not CYP450) 66% renal unchanged	no interaction anticipated	no interaction anticipated	no interaction anticipated
Oxcarbazepine Trileptal®	Parent: Reduction via cystolic enzymes Metabolite (active): 10-mono-hydroxy which is metabolized via UGT. Inhibits CYP3A4 Induces CYP3A4 (mild), UGT	Potential for ↓ protease inhibitor concentrations. <b>Avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction.</b>	Potential for ↓ protease inhibitor concentrations. <b>Avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction.</b>	<ul style="list-style-type: none"> <li>potential ↓ NNRTI/tipranavir concentrations and efficacy. <b>Avoid combination as antiretroviral therapy will be significantly compromised due to</b></li> </ul>

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				<p align="center"><b>enzyme induction.</b></p> <p>Case report of a patient receiving an <b>efavirenz</b>-based regimen who experienced treatment failure shortly after initiating oxcarbazepine. The patient had WT virus at baseline, but showed M184V, K103N and 225H mutations at viral rebound. The patient's efavirenz levels were measured before, during, and after concomitant oxcarbazepine use, and were not changed in the presence of oxcarbazepine. At all time points, his EFV exposure was approximately in the 25th percentile, failure likely due to nonadherence.<sup>35</sup></p>
Phenobarbital (PHB)	Parent: CYP450 oxidative hydroxylation via 2C9/19  Inducer (potent): CYP3A4, 1A2, 2C9/19, UGT	potential for ↓ protease inhibitor concentrations; <b>avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction</b>	potential for ↓ ritonavir concentrations and/or ↑ PHB concentrations. <b>Avoid combination as anticonvulsant and/or antiretroviral therapy may be significantly compromised due to enzyme induction.</b>	potential for ↓ NNRTI/tipranavir concentrations

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			<p>Case report of patient started on <b>ritonavir</b> 300mg BID, <b>saquinavir</b> 400mg BID, <b>nevirapine</b> 200mg/day while on PHB 250mg/day, CBZ 400mg TID and phenytoin 500mg/day. After 2 days, CBZ toxicity was noted (99.4% ↑ CBZ concentrations); 32.7% ↓ phenytoin levels; no change in PHB levels. Ritonavir levels were not measured.<sup>25</sup></p> <p>Case report of a 49 yr old white HIV+ male on stable phenobarbital therapy (100mg daily; level 16ug/ml) for seizure prevention who seized 4 weeks after starting a new salvage ARV regimen: ABC, ddl, <b>tipranavir/ritonavir</b> (TPV/r) (500/200 mg BID), T20. Phenobarbital level was found to be reduced by ~ 50% in presence of TPV/r (level: 8.1ug/ml). Phenobarbital was ↑ 150 mg daily with subsequent plasma level increasing to 17ug/ml (similar to previous value).</p>	

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			Trough TPV concentration was 34,837 ng/mL on Phenobarbital. This was similar to a population mean value 30,760 ng/mL. Authors suggest, net effect of coadministration of TPV/r was probably induction of CYP2C9 and/or CYP2C19 leading to clinically significant decrease of phenobarbital plasma exposure. Combination of TPV/r + Phenobarbital warrants careful monitoring. <sup>36</sup>	
Phenytoin Dilantin®	Parent: CYP2C9 (70%)>2C19 (minor);  Inducer (potent): CYP3A4, 2C9/19, UGT	Potential for ↓ protease inhibitor concentrations; <b>avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction.</b> <b>Nelfinavir:</b> One healthy volunteer study of nelfinavir 1250 mg BID + phenytoin 300 mg daily x 14/7 showed ~30% reduction in phenytoin AUC; 20-34% decrease in M8 exposure. The nelfinavir Ctrough was within an acceptable range. <sup>37</sup> Also a case report of a patient	Potential for ↓ ritonavir concentrations and/or ↑ phenytoin concentrations; <b>avoid combination as antiretroviral therapy may be significantly compromised due to enzyme induction</b> Healthy volunteer kinetic study (n=24) of <b>lopinavir/ritonavir</b> 400/100 mg BID and phenytoin 300 mg daily resulted in negative 2-way interaction: lopinavir AUC ↓ 33%, Cmin ↓ 46%, ritonavir	Case report of suboptimal <b>efavirenz</b> levels in a subject receiving concomitant phenytoin 300 mg BID; when phenytoin was replaced by levetiracetam, therapeutic efavirenz levels were achieved. Elevated phenytoin levels were also noted after initiation of efavirenz. <sup>40</sup>  Case report of a 35 yr old newly diagnosed HIV+ male who experienced undetectable efavirenz levels while taking

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		<p>stable on phenytoin and phenobarbital for 17 years. One month after <b>nelfinavir</b> was started, phenytoin levels ↓ by 58%. Phenobarbital and nelfinavir levels were stable. The patient experienced seizures after 3 months on the combination.<sup>38</sup></p>	<p>AUC ↓ 28%, Cmin ↓ 47%, and phenytoin AUC ↓ 31% and Cmin ↓ 34%. Dosage adjustments of one or both drugs likely necessary.<sup>39</sup> Authors suggested a dosage increase in lopinavir/r may be necessary (i.e. 533/133 mg BID of Kaletra capsules). Since the capsules are no longer available, the dosage of Kaletra tablets that may be required is 600/150 mg BID. Therapeutic drug monitoring is recommended for both lopinavir/ritonavir and phenytoin.</p> <p>Caution with other ritonavir-boosted protease inhibitor regimens.</p>	<p>efavirenz 800mg/day and phenytoin (Dose Range 400 – 800mg/day) for partial tonic seizures. Dramatic decrease in efavirenz levels when used with phenytoin. <b>Avoid combination.</b><sup>41</sup></p> <p>In a phase 1, two-period, 9 group study, a single dose of phenytoin 184 mg for 3 or 7 days given with single dose <b>nevirapine (NVP)</b> 200 mg in healthy non-pregnant women significant ↓ NVP t<sub>1/2</sub> by 16.9-19 hours and ↓ time to undetectable NVP levels by 7-8.5 days compared to single-dose NVP administered alone (median t<sub>1/2</sub> with single-dose NVP alone was 53.9 hours, time to undetectable NVP was 15.5 days).<sup>30</sup></p> <ul style="list-style-type: none"> <li>• potential for ↓ NNRTI or tipranavir concentrations</li> <li>• <b>avoid combination as antiretroviral therapy will be significantly</b></li> </ul>

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	<b>Anticonvulsant Route of Metabolism</b> <sup>1-5</sup>	<b>Mild-Moderate Enzyme Inhibitors</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>Potent Enzyme Inhibitors</b> Ritonavir - Norvir® <sup>13</sup> ; Lopinavir/Ritonavir – Kaletra® <sup>14</sup> Tipranavir/Ritonavir - Aptivus®/Norvir® <sup>15</sup>	<b>Enzyme Inducers</b> Nevirapine - Viramune® <sup>16</sup> Efavirenz-Sustiva® <sup>**17</sup> Etravirine - Intelence® <sup>18</sup> Tipranavir (unboosted) - Aptivus® <sup>15</sup>
				<b>compromised due to enzyme induction</b>
Pregabalin Lyrica®	excreted unchanged in urine <sup>42</sup> not metabolized; no impact on hepatic enzymes	no interaction anticipated	no interaction anticipated	no interaction anticipated
Primidone Mysoline®	metabolized to phenobarbital	potential for ↓ protease inhibitor concentrations; <b>avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction</b>	potential for ↓ ritonavir concentrations and/or ↑ phenobarbital concentrations; Case report of patient started in 3TC, ddI, ritonavir 600mg BID, and saquinavir 400mg BID while stable on phenytoin 450mg/day and CBZ 600mg/day. After 2 months ongoing CBZ toxicity was seen (177% ↑ CBZ levels) . Phenytoin levels were unchanged. The CBZ was replaced with primidone 500mg/day and the patient did well in follow-up with undetectable VL. RTV levels were not measured. <sup>27</sup> Until further data are available, <b>avoid combination as antiretroviral therapy may be significantly compromised due to</b>	potential for ↓ NNRTI concentrations; <b>avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction</b>

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	<b>Anticonvulsant Route of Metabolism</b> <sup>1-5</sup>	<b>Mild-Moderate Enzyme Inhibitors</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>Potent Enzyme Inhibitors</b> Ritonavir - Norvir® <sup>13</sup> ; Lopinavir/Ritonavir – Kaletra® <sup>14</sup> Tipranavir/Ritonavir - Aptivus®/Norvir® <sup>15</sup>	<b>Enzyme Inducers</b> Nevirapine - Viramune® <sup>16</sup> Efavirenz-Sustiva® <sup>**17</sup> Etravirine - Intelence® <sup>18</sup> Tipranavir (unboosted) - Aptivus® <sup>15</sup>
			<b>enzyme induction</b>	
Tiagabine Gabitril® USA	CYP3A4 > UGT	potential for ↑ tiagabine concentrations	potential for ↑ tiagabine concentrations	potential for ↓ tiagabine concentrations
Topiramate Topamax®	CYP 450 enzymes (minor) 55-97% excreted unchanged in urine Induces 3A4 (mild) Inhibits 2C19	no major interaction anticipated; potential for small ↑ topiramate concentrations	no major interaction anticipated; potential for small ↑ topiramate concentrations	no major interaction anticipated; potential for small ↓ topiramate concentrations
Valproic Acid Epival®, Depakene®	Parent: UGT (50%), mitochondrial β-oxidation (40%), minor CYP-dependent oxidation pathway (<10%)  Inhibits: UGT, CYP2C9/19  NB: Cautious use with <b>zidovudine</b> - severe anemia has been reported secondary to increased levels of AZT (proposed mechanism is valproic acid inhibition of AZT glucuronidation). <sup>43, 44</sup>	Unlikely; possible ↓ valproate concentrations & loss of valproate efficacy with nelfinavir (induces glucuronidation).  Valproic acid may increase HIV viral replication <i>in vitro</i> , however it does not significantly affect antiretroviral drug concentrations. <sup>45-47</sup> Clinical significance is unknown, however one case series reported no impact on viral load in patients on HAART. <sup>48</sup> Caution with combination is still warranted.  In 12 HIV-infected patients on stable <b>atazanavir 300/ritonavir 100 mg QD</b> , atazanavir exposures were significantly	When combined with valproate, <b>lopinavir</b> concentrations tended to be higher (geometric mean ratio of the AUC with and without valproate was 1.38). Valproate trough not significantly changed. <sup>50</sup>  One case report of reduced valproic acid concentrations (48% ↓) 21 days after <b>lopinavir/ritonavir</b> initiated; VA dosage was doubled and levels re-stabilized. Mechanism postulated to be induction of glucuronidation by ritonavir. <sup>51</sup>  <b>Tipranavir/ritonavir:</b> ↓	In one study in HIV-positive subjects on stable <b>efavirenz</b> therapy, administration of valproic acid 250 mg BID for 7 days did not affect efavirenz exposure. <sup>50</sup>  Case report demonstrating a 50% ↓ in valproate levels when co-administered with an efavirenz-based regimen. A valproate dosage increase from 1.5 g/day to 4 g/day was required to achieve therapeutic concentrations (doubling the dose). Efavirenz-mediated UGT induction is a proposed mechanism, though not confirmed. <sup>52</sup>

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

	<b>Anticonvulsant Route of Metabolism</b> <sup>1-5</sup>	<b>Mild-Moderate Enzyme Inhibitors</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>Potent Enzyme Inhibitors</b> Ritonavir - Norvir® <sup>13</sup> ; Lopinavir/Ritonavir – Kaletra® <sup>14</sup> Tipranavir/Ritonavir - Aptivus®/Norvir® <sup>15</sup>	<b>Enzyme Inducers</b> Nevirapine - Viramune® <sup>16</sup> Efavirenz-Sustiva® <sup>**17</sup> Etravirine - Intelence® <sup>18</sup> Tipranavir (unboosted) - Aptivus® <sup>15</sup>
		reduced in the presence of valproic acid 250 mg BID and minocycline 100 mg BID for 2 weeks (ATV AUC ↓ 33%, C <sub>min</sub> ↓ 50%, C <sub>max</sub> ↓ 25% vs. ATV/rtv alone). <sup>49</sup>	valproic acid levels predicted; may require increased dose of valproic acid. <sup>15</sup>  Valproic acid may increase HIV viral replication <i>in vitro</i> , however it does not significantly affect antiretroviral drug concentrations. <sup>45-47</sup> Clinical significance is unknown, however one case series reported no impact on viral load in patients on HAART. <sup>48</sup> Caution with combination is still warranted.	Valproic acid may increase HIV viral replication <i>in vitro</i> , however it does not significantly affect antiretroviral drug concentrations. <sup>45-47</sup> Clinical significance is unknown, however one case series and a small prospective study using NNRTIs <sup>53</sup> reported no impact on viral load in patients on HAART. <sup>48</sup> Caution with combination is still warranted.  <b>Raltegravir</b> is not expected to alter the metabolism of drugs that are metabolized by UGT1A4, such as valproic acid. <sup>54</sup>
Vigabatrine Sabril®	excreted unchanged in urine	no interaction anticipated	no interaction anticipated	no interaction anticipated
Zonisamide Zonegran® USA	Parent: CYP3A4, UGT Inhibits CYP2A6, 2C9/19,	potential for ↑ zonisamide concentrations, caution is warranted.	In a 20 y.o. patient, addition of <b>ritonavir</b> (200 mg dose) to CBZ and zonisamide resulted in 70-87% ↑ serum CBZ levels and toxicity (vomiting, vertigo).	potential for ↓ zonisamide concentrations

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

	<b>Anticonvulsant Route of Metabolism</b> <sup>1-5</sup>	<b>Mild-Moderate Enzyme Inhibitors</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>Potent Enzyme Inhibitors</b> Ritonavir - Norvir® <sup>13</sup> ; Lopinavir/Ritonavir – Kaletra® <sup>14</sup> Tipranavir/Ritonavir - Aptivus®/Norvir® <sup>15</sup>	<b>Enzyme Inducers</b> Nevirapine - Viramune® <sup>16</sup> Efavirenz-Sustiva® <sup>**17</sup> Etravirine - Intelence® <sup>18</sup> Tipranavir (unboosted) - Aptivus® <sup>15</sup>
			Zonisamide concentrations were unchanged. Ritonavir levels were not measured. Doses of both anticonvulsants were reduced by 1/3. <sup>23</sup> Since potential for ↑ zonisamide concentrations exist, caution is warranted.	

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). 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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