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

	Anticonvulsant Route of Metabolism[1-5]	**Protease Inhibitors** atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	**NNRTIs** efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	**Integrase Inhibitors** dolutegravir (Tivicay®),[19] elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[20] raltegravir (Isentress®)[21] **CCR5 Inhibitor** maraviroc (Celsentri®)[22]
Hepatic Substrate		Mainly CYP3A4	Efavirenz, nevirapine: CYP3A4, 2B6 (minor) Etravirine: CYP3A4, CYP2C9, and CYP2C19. Rilpivirine: CYP3A4 (major), as well as CYP2C19, 1A2, 2C8/9/10 (minor).	Dolutegravir is primarily metabolized via UGT1A1, with some contribution from CYP3A4 (10-15%).[19] Elvitegravir is metabolized via CYP3A and UGT1A1/3. Raltegravir is primarily metabolized by glucuronidation (UGT1A1). Maraviroc is a substrate of CYP3A4 and p-glycoprotein.[22]
Hepatic Inducer		Nelfinavir: UGT, 2B6, 2C8, 2C9/19[23] Ritonavir: UGT, CYP1A2, CYP2C9/19, 2B6 Tipranavir: mixed induction/inhibition effects; often acts as inducer of CYP3A4 (potent) and UGT, even when boosted with ritonavir[14]	Efavirenz: 3A4 (potent), 2B6[24] and UGT1A1[25] Etravirine[16]: 3A4 (weak) Nevirapine[17]: 3A4, 2B6 (potent) Rilpivirine: 2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak).[26] A clinically relevant effect on CYP enzyme activity	Dolutegravir does not induce CYP1A2, CYP2B6, or CYP3A4 in vitro.[19] Elvitegravir: CYP2C9 (modest) Raltegravir has no inhibitory or inductive potential in vitro.[21]

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			is considered unlikely with the 25 mg dose.[18]	
Hepatic Inhibitor		Mainly CYP3A4 (darunavir, indinavir, nelfinavir, amprenavir >> saquinavir) Atazanavir: 3A4, UGT1A1 >>2C8 (weak) Caution when unboosted atazanavir is coadministered with drugs that are 2C8 substrates with narrow therapeutic indices (e.g., paclitaxel, repaglinide); clinically significant interactions with 2C8 substrates are not expected when atazanavir is boosted with ritonavir. Nelfinavir: 2B6 in vitro. Ritonavir: CYP3A4 (potent)> >2D6 >2C9 >2C19 >2A6 >1A2>2E1. At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition.[10] Ritonavir inhibits CYP2B6 in vitro,[27] but induces 2B6 in vivo.[28]	Efavirenz inhibits 2C9, 2C19 (? Clinical significance). Etravirine[16]: CYP2C9 (weak), CYP2C19 (moderate), p-glycoprotein (weak)	Cobicistat: CYP3A, CYP2D6; also p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3.[20] Dolutegravir inhibits the renal organic cation transporter, OCT2.[19] Raltegravir has no inhibitory or inductive potential in vitro.[21] Maraviroc is unlikely to inhibit the metabolism of co-administered drugs that aremetabolized by cytochrome P450 enzymes because it does not inhibit the seven major CYP450 isoenzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) at clinically relevant concentrations *In Vitro.* Maraviroc could inhibit P-glycoprotein in the gut and may thus affect bioavailability of certain drugs; systemic effects

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		Tipranavir: 2D6[29]		of P-glycoprotein inhibition are unlikely to be of relevance.[22]
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 inhibitor levels and loss of efficacy; **avoid combination as antiretroviral therapy may be significantly compromised due to enzyme induction, and carbamazepine toxicity may occur**. In a 20 y.o. patient, addition of **ritonavir (200 mg dose)** to CBZ and **zonisamide** 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.[30] Several other case reports have reported acute CBZ toxicity (ataxia, vertigo, disorientation, diplopia, drowsiness) within 2-4 days of adding RTV.[31-34] In an open-label, 2 phase,	likely ↓ CBZ levels and ↓ NNRTI levels and loss of efficacy; dosing adjustments not yet studied for all drugs; in general, **avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction**. Negative dual interaction with **efavirenz** observed in a pharmacokinetic study in healthy subjects (n=36). Co-administration of EFV 600 mg QD with CBZ 400 mg QD at steady-state. • EFV:↓ AUC 36%, Cmax 21%, Cmin 47% • CBZ: ↓ AUC 27%, Cmax 20%, Cmin 35%. The kinetics of the active CBZE metabolite were unchanged. Upward dosage titration of both efavirenz and CBZ is likely required. Therapeutic drug	**Dolutegravir**: In an open-label, single sequence study, healthy adult subjects received dolutegravir 50 mg daily for 5 days, then carbamazepine 100mg q12h for 3 days, then 200mg q12h for 3 days, then 300mg q12h for 10 days, followed by dolutegravir 50 mg daily plus carbamazepine 300 mg q12h for 5 days. There were no washout intervals between treatments. Dolutegravir exposures were significantly reduced in the presence of carbamazepine (49% decrease AUC, 33% decrease Cmax, 73% decrease Ctrough). Integrase-naïve subjects taking carbamazepine should receive dolutegravir 50mg twice daily.[43] **Elvitegravir/cobicistat:** Healthy subjects (n=14) received the following

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		crossover interaction study in healthy volunteers, steady-state coadministration of **darunavir 600/100 mg BID** plus CBZ 200 mg BID resulted in 14% ↓ Cmin, 1.2% ↑ AUC of darunavir, 54% ↑ Cmin, 45% ↑ AUC of CBZ and 52% ↓ Cmin, 54% ↓ AUC of CBZ-epoxide compared to either 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.[35] A 39 y.o. African male experienced CBZ central nervous system toxicity one week after starting on **lopinavir/ritonavir 600/150 mg BID** with CBZ 400 mg BID. The dose of CBZ was decreased by 25%, while the lopinavir/ritonavir dose (50% increase) was maintained to compensate for the inductive interaction.[36] A 50-year-old HIV-positive male	monitoring would be useful. If possible, use alternate anticonvulsant such as vigabatrin or gabapentin .[40] In a phase 1, two-period, 9 group study, a single dose of carbamazepine 400 mg given with **single dose nevirapine 200 mg** in healthy non-pregnant women significant ↓ nevirapine $t_{1/2}$ by 18.8 hours and ↓ time to undetectable NVP levels by 4 days compared to single-dose NVP administered alone (median t1/2 with single-dose NVP alone was 53.9 hours, time to undetectable NVP was 15.5 days).[41] In a 1:1 randomized study, HIV-infected ARV-naïve pregnant women were given single-dose **nevirapine** 200 mg vs.single dose nevirapine 200 mg + CBZ 400mg at delivery in an attempt to increase nevirapine clearance and decrease	treatments sequentially over 41 days: elvitegravir/cobicistat 150/150 mg daily for 10 days, carbamazepine 100 mg BID for 3 days then carbamazepine 200 mg BID for 18 days, followed by elvitegravir/cobicistat 150/150 mg daily plus carbamazepine 200 mg BID for 10 days. With coadministration, elvitegravir and cobicistat exposures were decreased significantly (AUC decreased 69%, Cmax decreased 45%, Ctau decreased 97%, and AUC decreased 84%, Cmax decreased 72%, Ctau decreased 91%, respectively). Of note, elvitegravir Ctau was below the protein binding adjusted IC95 (45 ng/mL) in 11 of 12 subjects. Carbamazepine AUC increased 43%, Cmax increased 40% and Ctau increased 51% while exposures of the carbamazepine epoxide

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		developed excessive drowsiness secondary to carbamazepine when a regimen containing **lopinavir/ritonavir** was introduced, and his CBZ serum concentration ↑ 46%. When lopinavir/ritonavir was replaced by **nelfinavir,** 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.[37] Report of antiretroviral failure with concomitant CBZ-**indinavir** therapy. ↓ IDV concentrations to 4-25% of mean population values.[38] **Tipranavir/ritonavir:** 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).	resistance. One week post-dose, the nevirapine concentrations were 36% lower in the CBZ group with a trend toward fewer resistance mutations at 6 weeks (21% vs. 11%).[42] **Rilpivirine:** CBZ is contraindicated due to potential for decreased rilpivirine AUC and virologic failure/resistance.[18] **Etravirine:** Avoid use with CBZ due to potential for decreased etravirine AUC and virologic failure/resistance.[16]	metabolite were modestly decreased (35% decrease AUC) in the presence of elvitegravir/cobicistat. **Combination is contraindicated**.[44] **Raltegravir**: The impact on UGT1A1 is unknown. Use with caution.[21] Increase **maraviroc** dose to 600 mg BID if using concomitant potent CYP3A4 inducer.[22]

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		This may compromise tipranavir efficacy. Higher doses of CBZ may lead to even larger decreases in tipranavir concentrations.[39] The combination should likely be avoided.		
Clobazam Frisium®	Parent: CYP3A4, 2C19 Inhibits CYP2C9/19 Metabolite (active): N-desmethyl (norclobazam).[45]	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 **Etravirine** induces CYP3A4 and induces 2C9/2C19. One case report of increased clobazam concentrations and onset of neurotoxic symptoms after etravirine was added to an HIV patient's regimen. Drug concentrations returned to baseline and symptoms resolved after clobazam dose was reduced by 50%.[46]	**Elvitegravir/cobicistat:** potential for ↑ clobazam concentrations; monitor for toxicity and reduce dose if necessary.
Clonazepam Rivotril®	CYP3A4	potential for ↑ clonazepam concentrations	possible ↓ clonazepam concentrations and withdrawal	**Elvitegravir/cobicistat:** potential for ↑ clonazepam concentrations.[20]
Ethosuximide Zarontin®	CYP3A4 (40%)>others	potential for ↑ ethosuximide concentrations; monitor for	potential for ↓ ethosuximide concentrations; monitor for	**Elvitegravir/cobicistat:** potential for ↑ ethosuximide

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		toxicity and reduce dose if necessary	efficacy and increase dose if necessary	concentrations.[20]
Felbamate Felbatol®	CYP3A4 Inhibits CYP2C19 Induces CYP3A4	likely ↑ felbamate levels, and ↓ protease levels and loss of efficacy; dosing adjustments not yet studied. **Avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction**.	likely ↓ felbamate levels and ↓ NNRTI levels and loss of efficacy; dosing adjustments not yet studied; **avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction**.	**Elvitegravir/cobicistat:** potential for ↑ felbamate and/or ↓ elvitegravir/cobicistat concentrations; **avoid combination if possible**. Potential for ↓ **maraviroc** concentrations. Avoid combination if possible.
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 In a pharmacokinetic study in healthy subjects, lamotrigine Cmin ↓ 56% when administered with **lopinavir/ritonavir** for 10 days, lopinavir concentrations unaffected. Doubling the lamotrigine dose to 200 mg BID appeared to overcome this interaction.[47] Monitor for lamotrigine efficacy and ↑ dose if necessary when	Potential for ↓ lamotrigine concentrations due to GT induction by efavirenz; monitor for efficacy and increase dose if necessary.	In healthy subjects, **raltegravir 400 mg BID** 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 lamotrigine was taken alone (0.35) or when taken with raltegravir (0.36). Raltegravir does not influence the glucuronidation of lamotrigine.[49]

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		coadministering with ritonavir-containing regimens.[10] In a pharmacokinetic study in healthy volunteers of single dose lamotrigine 10 mg in the presence of steady state **atazanavir 400 mg QD or atazanavir 300/ritonavir 100 mg QD**, 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.[48] Therefore, no dose adjustment of lamotrigine is required when co-administering with unboosted atazanavir. With concomitant use of atazanavir/ritonavir, dose adjustment of lamotrigine may be required.[6] Potential for ↓ lamotrigine concentrations due to GT induction by **tipranavir**; monitor for efficacy and increase dose if		

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		necessary.		
Levetiracetam Keppra®	24% enzymatic hydrolysis (not CYP450) 66% renal unchanged	no interaction anticipated In a 22 y.o. female with advanced HIV, low albumin and a **lopinavir/ritonavir**-based regimen, **phenytoin** 300 mg daily yielded toxic concentrations when corrected for the low albumin and increased seizure frequency. To simplify therapy, phenytoin was changed to **levetiracetam** and the patient stabilized. Virologic data was not presented.[50]	no interaction anticipated	no interaction anticipated
Oxcarbazepine Trileptal®	Parent: Reduction via cystolic enzymes Metabolite (active): 10-mono-hydroxy which is metabolized via UGT. Inhibits CYPC19 Induces CYP3A4 (mild), UGT	Potential for ↓ protease inhibitor concentrations. **Avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction**.	Potential ↓ NNRTI concentrations and efficacy. **Avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction**. Case report of a patient receiving an **efavirenz**-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	**Dolutegravir**: Oxcarbamazepine is predicted to decrease dolutegravir Cmin by 32% but this is not considered clinically significant; therefore, no dose adjustment of dolutegravir is recommended with coadministration.[43] Potential for significant ↓ in **elvitegravir and cobicistat** concentrations. Consider alternate anticonvulsants.[20] **Raltegravir**: The impact on

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			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.[51] **Rilpivirine:** oxcarbazepine is contraindicated due to potential for decreased rilpivirine AUC and virologic failure/resistance.[18]	UGT1A1 is unknown. Use with caution.[21] Potential for ↓ **maraviroc** concentrations. Avoid combination if possible.
Phenobarbital (PHB)	Parent: CYP450 oxidative hydroxylation via 2C9/19 Inducer (potent): CYP3A4, 1A2, 2C9/19, UGT	Potential for ↓ protease inhibitor concentrations **Avoid combination as anticonvulsant and/or antiretroviral therapy may be significantly compromised due to enzyme induction.** Case report of patient started on **ritonavir** 300mg BID, **saquinavir** 400mg BID, **nevirapine** 200mg/day while on PHB	Potential for ↓ NNRTI concentrations. **Nevirapine:** After PHB 200 mg single dose, there was no significant change in the mean half-life of nevirapine.[53] **Rilpivirine:** PHB is contraindicated due to potential for decreased rilpivirine AUC and virologic	**Dolutegravir**: Based on modelling with clinical correlation, integrase-naïve subjects taking phenobarbital should receive dolutegravir 50mg twice daily.[43] Potential for significant ↓ in **elvitegravir and cobicistat** concentrations. Consider alternate anticonvulsants.[20]

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		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.[32] Atazanavir: do not coadminister phenobarbital with **unboosted atazanavir** due to risk of ↓ atazanavir concentrations. With **atazanavir/ritonavir**, there is potential for ↓ Phenobarbital exposures, and dose adjustment of phenobarbital may be required.[6] 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, ddI, **tipranavir/ritonavir** (TPV/r) (500/200 mg BID), T20. Phenobarbital level was found to be reduced by ~ 50% in presence	failure/resistance.[18] **Etravirine:** Avoid use with PHB due to potential for decreased etravirine AUC and virologic failure/resistance.[16]	**Raltegravir**: The impact on UGT1A1 is unknown. Use with caution.[21] Increase **maraviroc** dose to 600 mg BID if using concomitant potent CYP3A4 inducer.[22]

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		of TPV/r (level: 8.1ug/ml). Phenobarbital was ↑ 150 mg daily with subsequent plasma level increasing to 17ug/ml (similar to previous value). 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.[52]		
Phenytoin Dilantin®	Parent: CYP2C9 (70%)>2C19 (minor); Inducer (potent): CYP3A4, 2C9/19, UGT	Potential for ↓ protease inhibitor concentrations and/or ↑ phenytoin concentrations; **avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction**. Healthy volunteer kinetic study (n=24) of **lopinavir/ritonavir** 400/100 mg BID and phenytoin	Potential for ↓ NNRTI concentrations. **Avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction.** Case report of suboptimal **efavirenz** levels in a subject receiving concomitant phenytoin 300 mg BID; when	**Dolutegravir**: Based on modelling with clinical correlation, integrase-naïve subjects taking phenytoin should receive dolutegravir 50mg twice daily.[43] Potential for significant ↓ in **elvitegravir and cobicistat** concentrations. Consider

	Anticonvulsant Route of Metabolism[1-5]	**Protease Inhibitors** atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	**NNRTIs** efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	**Integrase Inhibitors** dolutegravir (Tivicay®),[19] elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[20] raltegravir (Isentress®)[21] **CCR5 Inhibitor** maraviroc (Celsentri®)[22]
		300 mg daily resulted in negative 2-way interaction: lopinavir AUC ↓ 33%, Cmin ↓ 46%, ritonavir AUC ↓ 28%, Cmin ↓ 47%, and phenytoin AUC ↓ 31% and Cmin ↓ 34%. Dosage adjustments of one or both drugs likely necessary.[54] 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. Two cases describe the safe and effective use of **lopinavir/ritonavir** with phenytoin. In both cases a 50% increase in the dose of lopinavir/ritonavir (600/150 mg BID) was empirically used to compensate for the potential interaction. The dose of phenytoin required a 12 to 20%	phenytoin was replaced by levetiracetam, therapeutic efavirenz levels were achieved. Elevated phenytoin levels were also noted after initiation of efavirenz.[57] Case report of a 35 yr old newly diagnosed HIV+ male who experienced undetectable efavirenz levels while taking efavirenz 800mg/day and phenytoin (Dose Range 400 – 800mg/day) for partial tonic seizures. Dramatic decrease in efavirenz levels when used with phenytoin. **Avoid combination**.[58] 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 **nevirapine (NVP)** 200 mg in healthy non-pregnant women significant ↓ NVP $t_{1/2}$ by 16.9-19 hours and ↓ time to undetectable NVP levels by 7-	alternate anticonvulsants.[20] **Raltegravir**: The impact on UGT1A1 is unknown. Use with caution.[21] Increase **maraviroc** dose to 600 mg BID if using concomitant potent CYP3A4 inducer.[22]

	Anticonvulsant Route of Metabolism[1-5]	**Protease Inhibitors** atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	**NNRTIs** efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	**Integrase Inhibitors** dolutegravir (Tivicay®),[19] elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[20] raltegravir (Isentress®)[21] **CCR5 Inhibitor** maraviroc (Celsentri®)[22]
		increase from baseline. Another case reported a low darunavir Cmin when **darunavir/ritonavir** 900/100 mg daily was given with phenytoin 450 mg daily. The darunavir Cmin was therapeutic when the dose was changed to 600/100 mg BID. The dose of phenytoin remained stable. In all cases, the patients remained virologically suppressed.[36] In a 22 y.o. female with advanced HIV, low albumin and a **lopinavir/ritonavir**-based regimen, **phenytoin** 300 mg daily yielded toxic concentrations when corrected for the low albumin and increased seizure frequency. To simplify therapy, phenytoin was changed to **levetiracetam** and the patient stabilized. Virologic data was not presented.[50] Caution with other ritonavir-boosted protease inhibitor regimens. Atazanavir: do not coadminister	8.5 days compared to single-dose NVP administered alone (median t1/2 with single-dose NVP alone was 53.9 hours, time to undetectable NVP was 15.5 days).[41] **Rilpivirine:** Phenytoin is contraindicated due to potential for decreased rilpivirine AUC and virologic failure/resistance[18]. **Etravirine:** Avoid use with phenytoin due to potential for decreased etravirine AUC and virologic failure/resistance.[16]	

	Anticonvulsant Route of Metabolism[1-5]	**Protease Inhibitors** atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	**NNRTIs** efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	**Integrase Inhibitors** dolutegravir (Tivicay®),[19] elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[20] raltegravir (Isentress®)[21] **CCR5 Inhibitor** maraviroc (Celsentri®)[22]
		phenytoin with **unboosted atazanavir** due to risk of ↓ atazanavir concentrations. With **atazanavir/ritonavir**, there is potential for ↓ phenytoin exposures, and dose adjustment of phenytoin may be required.[6] 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.[55] Also a case report of a patient stable on phenytoin and phenobarbital for 17 years. One month after **nelfinavir** was started, phenytoin levels ↓ by 58%. Phenobarbital and nelfinavir levels were stable. The patient experienced seizures after 3 months on the combination.[56]		
Pregabalin Lyrica®	excreted unchanged in urine[59] not metabolized; no impact on hepatic	no interaction anticipated	no interaction anticipated	No interaction anticipated

	Anticonvulsant Route of Metabolism[1-5]	**Protease Inhibitors** atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	**NNRTIs** efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	**Integrase Inhibitors** dolutegravir (Tivicay®),[19] elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[20] raltegravir (Isentress®)[21] **CCR5 Inhibitor** maraviroc (Celsentri®)[22]
	enzymes			
Primidone Mysoline®	metabolized to phenobarbital	Potential for ↓ protease inhibitor concentrations and/or ↑ phenobarbital concentrations. **Avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction.** 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.[34] Until further data are available, **avoid combination as antiretroviral therapy may be significantly compromised due to enzyme induction**	Potential for ↓ NNRTI concentrations; **avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction**	**Dolutegravir**: potential for ↓ dolutegravir concentrations. Avoid combination if possible. Potential for significant ↓ in **elvitegravir and cobicistat** concentrations. Consider alternate anticonvulsants. **Raltegravir**: The impact on UGT1A1 is unknown. Use with caution.[21] Potential for ↓ **maraviroc** concentrations. Avoid combination if possible.
Tiagabine	CYP3A4 > UGT	potential for ↑ tiagabine	potential for ↓ tiagabine	Potential for ↑ tiagabine

	Anticonvulsant Route of Metabolism[1-5]	**Protease Inhibitors** atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	**NNRTIs** efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	**Integrase Inhibitors** dolutegravir (Tivicay®),[19] elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[20] raltegravir (Isentress®)[21] **CCR5 Inhibitor** maraviroc (Celsentri®)[22]
Gabitril® USA		concentrations	concentrations	concentrations with **elvitegravir/cobicistat**. No interaction anticipated with **raltegravir or maraviroc**.
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	**Elvitegravir/cobicistat**: potential for small ↑ topiramate concentrations and/or ↓ in elvitegravir/cobicistat concentrations. Potential for ↓ **maraviroc** concentrations (clinical significance unknown). Avoid combination if possible.
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 **zidovudine**- severe anemia has been	Unlikely; possible ↓ valproate concentrations & loss of valproate efficacy with **nelfinavir or lopinavir/ritonavir**[10] (induces glucuronidation). Valproic acid may increase HIV viral replication *in vitro*, however it does not significantly affect antiretroviral drug concentrations.[62-64] Clinical significance is unknown, however one case series reported no impact on viral	In one study in HIV-positive subjects on stable **efavirenz** therapy, administration of valproic acid 250 mg BID for 7 days did not affect efavirenz exposure.[68] 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	**Raltegravir** is not expected to alter the metabolism of drugs that are metabolized by UGT1A4, such as valproic acid.[72]

	Anticonvulsant Route of Metabolism[1-5]	**Protease Inhibitors** atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	**NNRTIs** efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	**Integrase Inhibitors** dolutegravir (Tivicay®),[19] elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[20] raltegravir (Isentress®)[21] **CCR5 Inhibitor** maraviroc (Celsentri®)[22]
	reported secondary to increased levels of AZT (proposed mechanism is valproic acid inhibition of AZT glucuronidation).[60, 61]	load in patients on HAART.[65] These findings are also confirmed by a larger study assessing the cumulative impact of anticonvulsant therapy on HIV proliferation.[66] Caution with combination is still warranted. In 12 HIV-infected patients on stable **atazanavir 300/ritonavir 100 mg QD**, atazanavir exposures were significantly reduced in the presence of valproic acid 250 mg BID and minocycline 100 mg BID for 2 weeks (ATV AUC ↓ 33%, Cmin ↓ 50%, Cmax ↓ 25% vs. ATV/rtv alone).[67] When combined with valproate, **lopinavir** concentrations tended to be higher (geometric mean ratio of the AUC with and without valproate was 1.38). Valproate trough not significantly changed.[68] One case report of reduced valproic acid concentrations	required to achieve therapeutic concentrations (doubling the dose). Efavirenz-mediated UGT induction is a proposed mechanism, though not confirmed.[70] Valproic acid may increase HIV viral replication *in vitro*, however it does not significantly affect antiretroviral drug concentrations.[62-64] Clinical significance is unknown, however one case series and a small prospective study using NNRTIs[71] reported no impact on viral load in patients on HAART.[65] These findings are also confirmed by a larger study assessing the cumulative impact of anticonvulsant therapy on HIV proliferation.[66] Caution with combination is still warranted.	

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		(48% ↓) 21 days after **lopinavir/ritonavir** initiated; VA dosage was doubled and levels re-stabilized. Mechanism postulated to be induction of glucuronidation by ritonavir.[69] A dose increase of valproic acid may be required.[10] **Tipranavir/ritonavir:** ↓ valproic acid levels predicted; may require increased dose of valproic acid.[39]		
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 **ritonavir** (200 mg dose) to CBZ and zonisamide resulted in 70-87% ↑ serum CBZ levels and toxicity (vomiting, vertigo). Zonisamide concentrations were unchanged. Ritonavir levels were not measured. Doses of both anticonvulsants were reduced by 1/3.[30] Since potential for ↑ zonisamide concentrations exist,	potential for ↓ zonisamide concentrations	**Elvitegravir/cobicistat:** potential for ↑ zonisamide concentrations, caution is warranted. No interaction anticipated with raltegravir or maraviroc.

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		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); 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 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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