Predicted Interactions Between Psychotropics and Antiretrovirals

Antiretroviral Pharmacokinetic Characteristics (summary):

	Protease Inhibitors (PIs) atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitors** Dolutegravir (Tivicay®),[14] elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[15], raltegravir (Isentress®)[16]
Metabolism	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: UGT1A1, CYP3A4 (10-15%). Elvitegravir: CYP3A, UGT1A1/3 Cobicistat: CYP3A, 2D6 (minor) Raltegravir: UGT1A1
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.[5] Ritonavir inhibits CYP2B6 in vitro,[17] but induces 2B6 in vivo.[18] Tipranavir: 2D6[19]	Efavirenz: 2C9, 2C19[10] (? Clinical significance). Etravirine[11]: CYP2C9 (weak), CYP2C19 (moderate), p-glycoprotein (weak) Delavirdine (Rescriptor®)[20]; 3A4 (potent)	Cobicistat: CYP3A, CYP2D6; also p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Dolutegravir inhibits the renal organic cation transporter, OCT2.[14] Raltegravir has no inhibitory or inductive potential in vitro.[16]
Hepatic Inducer	Nelfinavir: UGT, 2B6, 2C8, 2C9/19[21]	Efavirenz: 3A4 (potent), 2B6[22] and UGT1A1[23]	Dolutegravir does not induce CYP1A2,

	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitors
	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[9]	Etravirine[11]: 3A4 (weak) Nevirapine[12]: 3A4, 2B6 (potent) Rilpivirine: 2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak).[24] A clinically relevant effect on CYP enzyme activity is considered unlikely with the 25 mg dose.[13]	CYP2B6, or CYP3A4 in vitro.[14] Elvitegravir: CYP2C9 (modest) Raltegravir has no inhibitory or inductive potential in vitro.[16]

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Antidepressants - Tricyclic (TCA's), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and others				
Amitriptyline Elavil®	Parent: CYP2D6, 2C19, 3A> GT Metabolite: CYP2D6 (nortriptyline)	Possible ↑ TCA concentrations	Possible ↓ TCA concentrations **Etravirine:** Possible ↑ or ↓ amitriptyline concentrations.[30]	Potential for ↑ TCA concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]
Bupropion Wellbutrin® Zyban®	Parent: CYP2B6 Metabolite (active): hydroxybupropion Inhibitor: CYP2D6 (parent and active metabolite)[31]	In vitro data suggest a strong potential for **nelfinavir** and **ritonavir** to inhibit bupropion metabolism. **Indinavir, saquinavir** and **amprenavir** were only weakly inhibitory of bupropion; hence no or only minor increase in bupropion concentrations anticipated.[17] However, in vivo data suggest induction. In an open-label, 3-	In vitro data suggest a strong potential for ***efavirenz*** to inhibit bupropion metabolism.[17] However, in 13 healthy volunteers, co administration of **efavirenz 600 mg QD** and single dose bupropion 150 mg showed 55% ↓ AUC and 34% ↓ Cmax of bupropion and ↓ t1/2 of hydroxybupropion (active metabolite).[22] Monitor for therapeutic response when using	Potential for ↑ bupropion concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]

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		phase pharmacokinetic study in healthy volunteers, exposure of bupropion and its active metabolite were both significantly reduced (AUC ↓ 57% and 50%, respectively) in the presence of steady state **lopinavir/ritonavir**. No significant changes in lopinavir kinetics were observed. Mechanism is postulated to be induction of CYP2B6 and UDP-glucuronyltransferase.[32] In a pharmacokinetic study in healthy volunteers the effect of steady-state **ritonavir** at given at a high dose (600 mg BID) and low dose (100 mg BID) on single-dose **bupropion** 150 mg was studied. Bupropion AUC was decreased by 62% and 21% in each group, respectively, which demonstrates a dose-related interaction. An increase in the dose of bupropion may be required when given with ritonavir, however the authors recommend not to exceed the maximum daily bupropion dose.[33] One case series (n=11) where	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** reported no episodes of seizures.[34] ***Delavirdine*** and ***nevirapine*** were only weakly inhibitory of bupropion; hence no or only minor increase in bupropion concentrations anticipated.[17] Coadministration of **tipranavir 500/ritonavir 200 mg BID** plus bupropion 150 mg BID in healthy volunteers resulted in 49% ↓ AUC, 60% ↓ Ctrough and 44% ↓ Cmax of bupropion, as well as approximately 25% ↓ in exposure of the active metabolite hydroxybupropion. Increased ALT was observed in 6/16 subjects after 1 week of tipranavir/ritonavir, but returned to baseline by the end of the study in 5/6 subjects.[35]	

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		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.[34]		
Citalopram Celexa®	Parent: CYP2C19, 3A4>>2D6. Inhibitor (weak): CYP 2D6, 2C19; negligible effect on CYP 3A4, 1A2[36]	Possible ↑ SSRI concentrations. Use with ritonavir-boosted PIs with caution (may wish to start with ½ dose antidepressant).	Possible ↓ SSRI concentrations **Etravirine:** Possible ↑ or ↓ citalopram concentrations.[30]	No significant interaction noted when citalopram 20 mg daily was coadministered with **raltegravir** 400 mg BID in healthy volunteers. Combination may be given without dose adjustment.[37] Potential for ↑ SSRI concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]
Escitalopram Lexapro® Cipralex® (S-enantiomer of citalopram)	Parent: CYP2C19, 3A4 >> 2D6 Inhibitor (weak or negligible): CYP2D6, 1A2, 2C9, 2C19, 2E1, 3A4[38]	Possible ↑ SSRI concentrations. 18 healthy subjects received escitalopram 20mg and **ritonavir** 600 mg single dose. No significant interaction found.[39]	Possible ↓ SSRI concentrations **Etravirine:** Possible ↑ or ↓ escitalopram concentrations.[30]	Potential for ↑ SSRI concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]
Clomipramine Anafranil®	Parent: CYP2D6, 1A2, 2C19, 3A Metabolite: CYP2D6 (desmethyl)	Possible ↑ TCA concentrations	Possible ↓ TCA concentrations **Etravirine:** Possible ↑ or ↓ clomipramine concentrations.[30]	Potential for ↑ TCA concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose

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				accordingly.[15]
Desipramine Pertofrane®	Parent: CYP2D6>>UGT	No anticipated effect with unboosted PIs. **Ritonavir** (high dose): 145% ↑ desipramine AUC; consider desipramine dose reduction by 50%.[40] Lower boosting doses of ritonavir unlikely to have same degree of interaction as per lopinavir/r data. **Lopinavir/ritonavir**: no significant effect on desipramine pharmacokinetics.[41]	No anticipated effect	Desipramine 50 mg single dose administered with **elvitegravir/cobicistat:** 24% ↑ Cmax and 65% ↑ AUC of desipramine. Monitor for response and adjust antidepressant dose accordingly.[15]
Desvenlafaxine Pristiq®	UGT[42, 43] (Major active metabolite of venlafaxine) Inhibits 2D6 at high doses; does not have a clinically relevant effect on CYP2D6 metabolism at 100 mg daily. In vitro, no inhibiting/inducing effects on 3A4, no inhibiting effects on P-gp. However, in a clinical study, the AUC of single dose midazolam (a CYP3A4 substrate) was	Desvenlafaxine concentrations were ↑ 42% by ketoconazole 200 mg BID;[43] use of potent CYP3A4 inhibitors may result in ↑ concentrations of desvenlafaxine. Ritonavir also induces UGT, and may ↓ desvenlafaxine concentrations; net effect of coadministering boosted PIs is unknown. Use combination with caution. Potential for desvenlafaxine to ↓ concentrations of CYP3A4 substrates. Clinical significance with HIV protease inhibitors	Possible ↓ desvenlafaxine.	Potential for ↑ desvenlafaxine concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]

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	↓ 31% in the presence of desvenlafaxine 400 mg daily.[43] Therefore, possibility that desvenlafaxine may act as an inducer in vivo.	unclear. Monitor for HIV efficacy, consider TDM.		
Doxepin Sinequan®	Parent: hepatic metabolism (? CYPs) Metabolite (active): desmethyldoxepin	Unknown; possible ↑ doxepin concentrations	Unknown; possible ↓ doxepin concentrations	Unknown; possible ↑ doxepin concentrations with **elvitegravir/cobicistat.**
Duloxetine (Cymbalta®)	Parent:CYP1A2, 2D6; inactive metabolites Inhibitor (moderate): CYP2D6	Unboosted PIs unlikely to have a major interaction. Potential for ritonavir-boosted PIs to ↑ or ↓ duloxetine concentrations. Monitor for efficacy/toxicity. At low boosting doses, **ritonavir** does not inhibit CYP2D6 at clinically relevant concentrations, but has a more potent inhibitory effect at higher therapeutic doses.[5, 7] It may also induce CYP1A2. **Tipranavir/r** inhibits CYP2D6 and induces CYP1A2, therefore an interaction is difficult to predict.[9]	Unlikely to have a major interaction. **Rilpivirine** is a slight inducer of CYP1A2; potential for ↓ duloxetine concentrations.	Potential for ↑ duloxetine concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]
Fluoxetine Prozac®	Parent: CYP2D6 Inhibits: CYP2D6	No anticipated effect of unboosted PIs on fluoxetine.	No anticipated effect on fluoxetine or NNRTIs.	Potential for ↑ SSRI concentrations with

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	(potent) Metabolite (active): norfluoxetine	Potential for ↑ SSRI concentrations with higher doses of **ritonavir**, but unlikely with lower boosting doses of ritonavir. Kinetic study showing 19% ↑ **ritonavir** AUC.[44, 45] Post-marketing reports of cardiac and neurologic events with combination.[7] Serotonin syndrome reported in a case series of patients when **ritonavir** based HAART (200-600mg BID) was added to fluoxetine. Symptoms included mental changes (confusion, mania, agitation, 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).[46]	In a retrospective review, the pharmacokinetics of **efavirenz** did not appear to be significantly affected by concomitant use of selective serotonin reuptake inhibitors.[47] In one cohort study, fluoxetine did not significantly impact **nevirapine** clearance. However, the dose-normalized concentrations of fluoxetine and the active metabolite, norfluoxetine, were decreased by 65% and 35%, respectively. Monitor closely for the clinical response to fluoxetine; possible dose increases may be required.[48] **Delavirdine:** 50% ↑ delavirdine trough concentrations with combination. Cautious use of combination is warranted.[20]	**elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]
Fluvoxamine Luvox®	Parent:CYP2D6> 1A2 Inhibits: 1A2 (potent), 3A4, 2C (moderate), 2D6 (weak)	No major anticipated effect with unboosted PIs. Potential for ↑ SSRI concentrations with higher doses	Potential for fluvoxamine to modestly ↑ NNRTI concentrations. Clinical significance unknown, monitor for toxicity.	Potential for ↑ SSRI concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose

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		of ritonavir, but unlikely with lower boosting doses of ritonavir. Potential for fluvoxamine to modestly ↑ PI concentrations. Clinical significance unknown, monitor for toxicity.	In one cohort study, fluovoxamine inhibited the clearance of **nevirapine** by 33.7% in a dose-dependent manner; the dose-normalized concentration of fluvoxamine was not significantly altered. Close monitoring for nevirapine toxicity is warranted, particularly when high doses of fluvoxamine are used.[48] **Etravirine:** Possible ↑ etravirine concentrations.[30]	accordingly.[15]
Imipramine Tofranil®	Parent: CYP2D6, 1A2, 2C19, 3A > UGT Metabolite (active): CYP2D6 (desipramine)	Possible ↑ TCA concentrations	Possible ↓ TCA concentrations **Etravirine:** Possible ↑ or ↓ imipramine concentrations.[30]	Potential for ↑ TCA concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]
Maprotiline Ludiomil®	Parent:CYP2D6 Metabolite: UGT (hydroxyl)	Interaction unlikely with unboosted PIs. Potential ↑ maprotiline concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.	Interaction unlikely	Potential for ↑ maprotiline concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]
Milnacipran Ixel®	UGT. Not a substrate of P450 system	Interaction unlikely with unboosted atazanavir or fosamprenavir.	Potential ↓ milnacipran concentrations	Interaction unlikely.

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		Potential ↓ milnacipran concentrations via UGT induction by ritonavir or nelfinavir.		
Mirtazapine Remeron®	CYP2D6, 1A2, 3A4 Is not an enzyme inhibitor or inducer[49]	Possible ↑ mirtazapine concentrations with unboosted PIs. Possible ↑↑ mirtazapine levels with ritonavir-boosted PIs due to inhibition of 3A4 and possibly 2D6. Monitor for acute somnolence if ritonavir is added. Consider mirtazapine dosage decrease if combination is used.	Possible ↓ mirtazapine concentrations. **Etravirine:** Possible ↓ mirtazapine concentrations.[30]	Potential for ↑ mirtazapine concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]
Moclobemide Manerix®	Parent: CYP2C19>2D6 Inhibits: CYP2C19>2D6	No anticipated effect with unboosted PIs. Possible ↑ or ↓ moclobemide concentrations with ritonavir-boosted PIs.	Efavirenz and etravine are weak-moderate inhibitors of CYP2C19, and thus may possibly ↑ moclobemide concentrations. Rilpivirine is a moderate inducer of CYP2C19, and may possibly ↓ moclobemide concentrations. Monitor for efficacy & toxicity.	Potential for ↑ moclobemide concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]
Nefazodone Serzone® *(*drug discontinued in Canada in 2003)*	Parent:CYP3A Inhibits: CYP3A (potent) Metabolite: CYP2D6 (hydroxy-nefazodone)	Unboosted PIs may ↑ nefazodone concentrations; potential ↑ ↑ nefazodone concentrations with ritonavir-boosted PIs. Potential for nefazodone to ↑ PI concentrations and toxicity.	Likely ↓ nefazodone concentrations. Potential for nefazodone to ↑ NNRTI concentrations and toxicity **Etravirine:** Possible ↓ nefazodone concentrations and ↑ etravirine concentrations.[30]	Potential for ↑ nefazodone concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]

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			Potential for ↑ **rilpivirine** concentrations; AVOID co-administration.	
Nortriptyline Norventyl®	Parent: CYP2D6 Metabolite (active): 10-hydroxynortriptyline	No anticipated effect with unboosted PIs. Potential ↑ TCA concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.	No anticipated effect	Potential for ↑ TCA concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]
Paroxetine Paxil®	Parent:CYP2D6 Inhibits: CYP2D6 (potent)	Based on paroxetine metabolism potential for ↑ paroxetine concentrations exists with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir. However, interaction is complex and difficult to predict. For example, in the cases of fosamprenavir/r and darunavir/r the AUC of paroxetine was decreased by 58% and 39%, respectively (see below).[50, 51] In healthy volunteers, paroxetine 20 mg QD plus **fosamprenavir/r** 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	No anticipated effect; In a retrospective review, the pharmacokinetics of **efavirenz** did not appear to be significantly affected by concomitant use of selective serotonin reuptake inhibitors.[47] In healthy volunteers, paroxetine 20 mg QD plus **etravirine** (TMC125) 800 mg BID (old formulation) did not result in significant changes in exposures of either drug. No dosage adjustment is required.[11]	Potential for ↑ SSRI concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]

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		required.[51] Co administration of **darunavir/r** 400/100 mg BID and paroxetine 20 mg QD led to 39% ↓ paroxetine exposure; darunavir levels were not affected. Monitor for antidepressant efficacy and ↑ paroxetine dose if required.[50]		
Phenelzine Nardil®	Acetylation inhibits: CYP (weak)	Unlikely	Unlikely	Unlikely
Reboxetine Edronax®	3A4 substrate	Potential for ↑ reboxetine concentrations	Potential for ↓ reboxetine concentrations	Potential for ↑ reboxetine concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]
Selegiline (transdermal patch) EMSAM®	2B6, 1A2 substrate	Unlikely interaction with unboosted PIs. Potential for ↓ selegiline concentrations with ritonavir-boosted PIs.	Potential for ↓ selegiline concentrations	
Sertraline Zoloft®	Parent:CYP2B6 > 2C9/19, 3A4, 2D6, UGT1A1(possible)[52] Inhibits: CYP2D6 (moderate)	Potential ↑ or ↓ sertraline concentrations due to complex metabolism of sertraline. Co-administration of **darunavir/r** 400/100 mg BID and sertraline 50 mg QD led to 49% ↓ sertraline exposure; darunavir levels were not affected. Monitor for antidepressant efficacy and ↑	Potential for ↓ sertraline concentrations due to enzyme induction. Sertraline AUC↓ by 39%, **efavirenz** kinetics not affected.[10, 47] **Etravirine:** Possible ↑ or ↓ sertraline concentrations.[30]	In healthy volunteers, coadministration of single dose sertraline 50 mg in the presence of steady-state fixed-dose elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide once daily did not result in any clinically relevant changes in the

	Psychotropic Route of Metabolism[25-29]	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitors** dolutegravir (Tivicay®),[14] elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[15] raltegravir (Isentress®)[16]
		sertraline dose if required.[50]		pharmacokinetics of sertraline or any components of the antiretroviral fixed-dose tablet. No dose adjustment is required with coadministration.[53]
St. John's Wort (hypericum perforatum)	Induces CYP3A4 and P-gp	Significantly reduces **indinavir** exposure (57% ↓ AUC, 81% ↓ Cmin)[54]; similar interaction may be likely with other substrates of CYP3A4. **Avoid concomitant use of PIs and NNRTIs with St. John's wort.** **Maraviroc: Avoid concomitant use with St. John's wort.**[55]	St. John's Wort reduces **nevirapine** concentrations 35%.[56] **Avoid concomitant use of PIs and NNRTIs with St. John's wort.**	**Coadministration with elvitegravir/cobicistat is contraindicated.**[15] **Dolutegravir**: Based on modelling with clinical correlation, integrase-naïve subjects taking St. John's wort should receive dolutegravir 50mg twice daily.[57]
Tranylcypromine Parnate®	hepatic metabolism	Possible ↑ MAOI concentrations	Possible ↓ MAOI concentrations	Possible ↑ MAOI concentrations with **elvitegravir/cobicistat.**
Trazodone Desyrel®	Parent:CYP2D6> CYP3A Metabolite: CYP2D6 (m-CPP)	Possible ↑ trazodone concentrations **Indinavir:** strong inhibitor of trazodone *in vitro*. Monitor for trazodone toxicity (i.e. nausea, hypotension, syncope, somnolence, anticholinergic side-effects). **Saquinavir and nelfinavir:** weak inhibitors *in vitro*;	Possible ↓ trazodone concentrations	Potential for ↑ trazodone concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]

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		interaction is unlikely.[58] **Ritonavir:** potent inhibitor of trazodone *in vitro*.[58] 10 healthy subjects received trazodone 50 mg with RTV 4 x 200mg doses: significant increase in trazodone concentrations (52% ↓ CL, 122% ↑ T 1/2, 34% ↑ Cmax).[7] Sedation, fatigue, impaired performance, nausea, dizziness, hypotension, syncope reported.[59] **When combined with ritonavir-based regimens, use with caution and consider a lower dose of trazodone.**[7]		
Trimipramine Surmontil®	Parent: CYP2D6 Metabolite (active): Desmethytrimipramine	No anticipated effect with unboosted PIs. Potential ↑ TCA concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.	No anticipated effect	Potential for ↑ TCA concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]
Venlafaxine Effexor®	Parent: CYP2D6 > CYP3A4 (minor) Inhibits: CYP2D6 (weak) Metabolite (active): UGT (O-desmethylvenlafaxine, ODV)[60]	Possible ↑ venlafaxine concentrations with unboosted PIs; however interaction study with **indinavir** showed ↓ in indinavir concentrations (28% ↓ AUC, 36% ↓ Cmax); no change in venlafaxine concentrations.[61]	Possible ↓ venlafaxine concentrations **Etravirine:** Possible ↓ venlafaxine concentrations. [30]	Potential for ↑ venlafaxine concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[15]

	Psychotropic Route of Metabolism[25-29]	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitors** dolutegravir (Tivicay®),[14] elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[15] raltegravir (Isentress®)[16]
		CYP2D6 inhibitors may ↓ the metabolism of venlafaxine to ODV, resulting in ↑ plasma concentrations of venlafaxine and ↓ concentrations of ODV. However, as venlafaxine and ODV are both pharmacologically active, the product monograph states that no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.[60]		
Neuroleptics				
Amisulpride Solian® Special Access in Canada	Parent: 50 % renal; no clinically relevant metabolism[28]	Unlikely	Unlikely	Unlikely
Aripiprazole Abilify®	Parent: CYP 3A4, 2D6[28] Metabolite (active): dehydro-aripiprazole	Possible ↑ aripiprazole concentrations. A 43 y.o. male was on **aripiprazole** 50 mg daily and **duloxetine** 60 mg daily (CYP2D6 inhibitor) for depression/anxiety in addition to a **darunavir/ritonavir** 800/100 mg daily based regimen (CYP3A4 inhibitor). The patient developed CNS symptoms (confusion, loss of coordination) and was later hospitalized with fever, cough headache, neck	Possible ↓ aripiprazole concentrations	Potential for ↑ aripiprazole concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]

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		stiffness, back pain, and blurred vision. All investigations were negative except for lymphadenopathy. A random aripiprazole serum concentration was elevated at 1100 ng/mL (therapeutic is 100-200 ng/mL) 49 days after hospital discharge and aripiprazole was discontinued. [62] Caution is warranted when PIs and aripiprazole are coadmininstered and lower aripiprazole doses may be required.		
Asenapine Saphris®	Substrate of UGT1A4, CYP1A2>> CYP3A4, CYP2D6. Weak inhibitor of CYP2D6. Asenapine does not cause induction of CYP1A2 or CYP3A4.	Possible ↓ asenapine concentrations with boosted PIs or nelfinavir.	Possible ↓ asenapine concentrations	Possible ↑ asenapine concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]
Chlorpromazine Largactil®	Parent:CYP2D6, CYP1A2?, GT Metabolite: GT (7-OH-CPZ)	Unlikely interaction with unboosted PIs. Potential ↑ chlorpromazine concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.	Unlikely	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]
Clozapine Clozaril®	Parent: CYP1A2> 2C19, 3A4, 2D6[28] Metabolite (active): norclozapine	Possible ↑ clozapine concentrations with unboosted PIs.	Possible ↓ clozapine concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose

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		Potential for ↓ or ↑ clozapine concentrations due to ritonavir-mediated CYP1A2 induction and/or CYP3A4 inhibition. Interaction difficult to predict. **Combination no longer contraindicated in product monograph.**[7]		may be required.[15]
Flupenthixol Fluanxol®	Parent: Extensive hepatic metabolism (not well defined)	Possible ↑ flupenthixol concentrations	Possible ↓ flupenthixol concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]
Fluphenazine Modecate®	Parent: Extensive hepatic metabolism	Possible ↑ fluphenazine concentrations	Possible ↓ fluphenazine concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]
Haloperidol Haldol®	Parent: CYP2D6>3A4	Possible ↑ haloperidol concentrations	Possible ↓ haloperidol concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]
Loxapine Loxapac®	Parent: Extensive hepatic metabolism	Possible ↑ loxapine concentrations	Possible ↓ loxapine concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]
Lurasidone Latuda®	CYP3A4	Possible ↑ lurasidone concentrations. Lurasidone is contraindicated with strong	Possible ↓ lurasidone concentrations. Lurasidone is contraindicated with strong	Potential for ↑ lurasidone concentrations with **elvitegravir/cobicistat.**

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		CYP3A4 inhibitors (e.g., ketoconazole). Do not exceed 40 mg/day if coadministering with moderate CYP3A4 inhibitors.	CYP3A4 inducers (e.g., rifampin).	Lurasidone is contraindicated with strong CYP3A4 inhibitors (e.g., ketoconazole). Do not exceed 40 mg/day if coadministering with moderate CYP3A4 inhibitors.
Methotrimeprazine (levomepromazine) Nozinan®	Parent: Extensive hepatic metabolism Inhibits CYP2D6	Possible ↑ methotrimeprazine concentrations	Possible ↓ methotrimeprazine concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]
Olanzapine Zyprexa®	Parent: CYP1A2 >> 2D6; UGT1A4[28] Inhibits: CYP1A2, 2D6, 3A4 (weak)	No anticipated effect with most unboosted PIs; **nelfinavir and ritonavir** may ↓ olanzapine concentrations by inducing glucuronidation. Healthy volunteer study of olanzapine 10 mg +/- **ritonavir 500 mg BID** resulted in 53%↓ AUC of olanzapine. Higher olanzapine dosages may be necessary to maintain therapeutic effect.[63] In a healthy volunteer study, subjects received single dose olanzapine 10 mg alone or olanzapine 15 mg with steady-state **fosamprenavir 700/100 mg BID**. Olanzapine 15 mg in	No anticipated effect. Potential for olazapine to cause minor ↑ NNRTI concentrations and toxicity.	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]

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		the presence of fosamprenavir/ritonavir resulted in similar AUC and 32% ↑ Cmax as that observed with olanzapine 10 mg alone. Amprenavir pharmacokinetic parameters were similar to historical controls. Increase olanzapine dose by 50% when combining with boosted fosamprenavir.[64] Potential for olanzapine to ↑ protease concentrations and toxicity (likely not clinically significant).		
Paliperidone Invega®, Invega Sustenna®	Parent: potential for some (minimal?) involvement in P450 metabolism (59% excreted unchanged in the urine). In vitro data suggest that paliperidone is a substrate of 2D6 and 3A4, but in vivo results indicate that these isozymes play a very limited role in its metabolism. Hence, not expected to cause clinically significant interactions with P450 substrates.	Possible ↑ paliperidone concentrations. No clinically significant effect noted when paliperidone was coadministered with paroxetine, a potent 2D6 inhibitor.	Possible ↓ paliperidone concentrations. Monitor for efficacy. Co-administration of paliperidone with carbamazepine 200 mg BID (a 3A4 & P-gp inducer) caused a 37% ↓ in AUC of paliperidone.	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]

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	Substrate and inhibitor of P-gp. Paliperidone is the major active metabolite of risperidone.			
Perphenazine Trilafon®	Parent: CYP2D6 Inhibits: CYP2D6	Interaction unlikely with unboosted PIs. Potential ↑ perphenazine concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir. See "quetiapine" for case report of priapism associated with perphenazine and quetiapine with concomitant lopinavir/ritonavir.[65]	Unlikely	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]
Pimozide Orap®	Parent: CYP3A	Unboosted PIs may ↑ pimozide concentrations; **avoid** if possible. **Contraindicated with ritonavir;** potential ↑↑ pimozide concentrations.[7]	Likely ↓ pimozide concentrations	**Coadministration with Stribild® is contraindicated** due to potential for serious and/or life-threatening events such as cardiac arrhythmias.[15]
Pipotiazine Piportil L4	Parent: Extensive hepatic metabolism	Possible ↑ pipotiazine concentrations	Possible ↓ pipotiazine concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]
Quetiapine	Route of Metabolism:	Possible ↑↑ quetiapine	Possible ↓ quetiapine	Potential for ↑ neuroleptic

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Seroquel®	CYP3A4 >> 1A2 [66] Is not an enzyme inhibitor or inducer	concentrations. Report of two patients who experienced serious quetiapine adverse effects secondary to possible/probable interactions with **atazanavir/ritonavir**. One patient developed rapid and severe (50 pound) weight gain when quetiapine (titrated up to 400 mg/day) was added to his stable ARV regimen, while another patient stabilized on quetiapine 600 mg/day developed increased sedation and mental confusion shortly after initiating atazanavir/ritonavir. In both cases, symptoms resolved after discontinuation of quetiapine.[67] Another report of a deep coma, sustained hypotension, and ↑ t1/2 of quetiapine (62.4h) after an overdose of quetiapine 8000mg in a patient on **atazanavir/ritonavir**.[68] Case report of priapism lasting 42 hours with an onset of 5-6 hours after co-ingestion of perphenazine 8 mg and quetiapine 900 mg with **lopinavir/ritonavir**. Rapid	concentrations.	concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]

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		elevations in the neuroleptic concentrations were postulated as the mechanism. The symptoms were managed with intracavernous ephedrine, irrigation and aspiration.[65]		
Risperidone Risperdal®	Parent: CYP2D6, 3A4[28] Active metabolite: 9-OH risperidone (paliperidone) (renal)	Potential ↑ risperidone concentrations with ritonavir-boosted PIs. One case of extrapyramidal symptoms (dysphagia, dysphonia, difficulty breathing, and worsening tremors) with risperidone 2mg/day + **indinavir/ritonavir** (IDV/RTV) 800mg/200mg BID.[69] One case of neuroleptic malignant syndrome with risperidone 1.5mg/day + IDV 800mg/RTV 400mg daily.[70] Reversible coma reported with risperidone 3mg BID + IDV 400mg/RTV 200mg BID.[71]	Unlikely	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]
Thioridazine Mellaril®	Parent: CYP2D6 Inhibits: CYP2D6 Metabolite (active): (mesoridazine, sulforidazine)	Interaction unlikely with unboosted PIs. Potential ↑ thioridazine concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.	Unlikely	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]
Ziprasidone Geodon®, Zeldox®	Parent: CYP3A4 Is not an enzyme	Potential ↑ ziprasidone concentrations	Potential ↓ ziprasidone concentrations	Potential for ↑ neuroleptic concentrations with

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	inhibitor or inducer[72]			**elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]
Zuclopenthixol Clopixol®	Parent: Extensive hepatic metabolism	Potential ↑ zuclopenthixol concentrations	Potential ↓ zuclopenthixol concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[15]
Other				
Atomoxetine Strattera®	2D6	Possible ↑ atomoxetine concentrations.		Potential ↑ atomoxetine concentrations with **elvitegravir/cobicistat**.
Buspirone Buspar®	Parent: CYP3A4 Metabolite (active): 1-pyrimidinyl piperazine Buspirone has immunomodulating properties. A significant ↑ in CD4/CD8 ratio, and a ↓ in CD8+ T-cell counts was observed in HIV patients who were not on antiretrovirals.[73]	possible ↑ buspirone concentrations Case report of patient with Parkinson-like symptoms (ataxia, shuffling gait, cogwheel rigidity, resting tremor, and sad affect) 6 weeks after **indinavir/ritonavir** (400mg/400mg BID) were added to buspirone 40mg am/30mg pm.[74]	possible ↓ buspirone concentrations and withdrawal	Potential for ↑ buspirone concentrations with **elvitegravir/cobicistat.** A decrease in buspirone dose may be required.[15]
Dextroamphetamine Dexedrine®	Parent: hepatic metabolism (deamination and hydroxylation)	Possible ↑ dextroamphetamine concentrations	Possible ↓ dextroamphetamine concentrations	Possible ↑ dextroamphenatime concentrations with **elvitegravir/cobicistat.**
Lithium Carbolith®	None (renal)	None	None	None
Lisdexamfetamine Vyvanse®	Hydrolyzed in the blood to d-amphetamine	Possible ↑ d-amphetamine concentrations with boosted PIs.	Unlikely.	Possible ↑ d-amphenatime concentrations with

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	(active component) and L-lysine. Lisdexamfetamine is not metabolized by CYP450 enzymes. Amphetamine is oxidized to form 4-hydroxyamphetamine, alpha-hydroxy-amphetamine and norephedrine (both active). Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. In vitro, minor inhibition of CYP2D6 by amphetamine, and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites, but there are no in vivo studies of P450 enzyme inhibition.			**elvitegravir/cobicistat.**

	Psychotropic Route of Metabolism[25-29]	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitors** dolutegravir (Tivicay®),[14] elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[15] raltegravir (Isentress®)[16]
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 with **elvitegravir/cobicistat.**
Modafinil Alertec®	Parent: CYP3A Inhibits 2C19, 2C9; may induce 3A4, 1A2, 2B6	Possible ↑ modafinil concentrations, potential ↓ protease inhibitor concentrations; if possible, avoid use with CYP3A4 substrates until further data available. Antiretroviral therapeutic drug monitoring may be useful.	Possible ↓ modafinil concentrations, potential ↓ NNRTI concentrations and efficacy. If possible, avoid use with CYP3A4 substrates until further data available. Antiretroviral therapeutic drug monitoring may be useful.	Potential for ↑ modafinil concentrations and/or ↓ **elvitegravir/cobicistat** concentrations. Avoid combination if possible.

Key: CYP= Hepatic Cytochrome P450 isoenzyme; AD= Alcohol dehydrogenase; TCA= tricyclic antidepressant; MAOI= monoamine oxidase inhibitor; SSRI= selective serotonin reuptake inhibitor Substrate= route of hepatic elimination of that specific drug (specified by a specific cytochrome P450 isoenzyme); inducer = leads to more rapid clearance of substrates of a specific hepatic isoenzyme (lowers serum concentrations of the respective drug and may lead to decreased efficacy); inhibitor= leads to decreased clearance of substrates of a specific hepatic isoenzyme (increases serum concentrations of a respective drug and may lead to toxicity). Pgp= P-glycoprotein; UGT= Uridine diphosphate glucuronyltransferase.

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable

sources 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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