Actual and Predicted Pharmacokinetic Interactions Between Antihypertensives 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] Ritonavir: UGT, CYP1A2, CYP2C9/19, 2B6 Tipranavir: mixed induction/inhibition effects; often	Efavirenz: 3A4 (potent), 2B6[22] and UGT1A1[23] Etravirine[11]: 3A4 (weak)	Dolutegravir does not induce CYP1A2, CYP2B6, or CYP3A4 in vitro.[14] Elvitegravir: CYP2C9 (modest)

	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitors
	acts as inducer of CYP3A4 (potent) and UGT, even when boosted with ritonavir[9]	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]	Raltegravir has no inhibitory or inductive potential in vitro.[16]

Drug	Usual Dose (essential hypertension)	Metabolism[25]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitor (**i.e.,elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS					
Benazepril (Lotensin®) Captopril (Capoten®) Cilazapril (Inhibace®) Enalapril (Vasotec®) Fosinopril (Monopril®) Lisinopril (Prinvil®, Zestril®) Perindopril (Coversyl®) Quinapril (Accupril®) Ramipril (Altace®) Trandolapril (Mavik®, Tarka®)		Other than captopril and lisinopril, ACE inhibitors are prodrug esters that must be converted in the liver and/or GI tract to active metabolites. Elimination of unchanged drug or metabolites may be renal or fecal.	no predicted effect	no predicted effect	no predicted effect
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)					
Candesartan (Atacand®)	8-32 mg once daily	2C9 (minor), biliary excretion	Possible ↓ ARB (nelfinavir, ritonavir), may not be clinically significant.	Possible ↑ ARB (efavirenz, etravirine), may not be clinically significant.	Possible ↓ ARV, may not be clinically significant.

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Drug	Usual Dose (essential hypertension)	Metabolism[25]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	**<u>Integrase Inhibitor</u>** (**i.e.,elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
Eprosartan (Teveten®)	600 mg once daily (max 800 mg once daily or 400 mg BID)	Biliary excretion	no predicted effect	no predicted effect	no predicted effect
Irbesartan (Avapro®)	150 mg once daily (max 300 mg)	2C9, biliary excretion	Possible ↓ ARB (nelfinavir, ritonavir), may not be clinically significant.	Possible ↑ ARB (efavirenz, etravirine), may not be clinically significant.	Possible ↓ ARV, may not be clinically significant.
Losartan (Cozaar®)	50-100 mg once daily	2C9>>3A4 to active metabolite, E-3174	Possible ↓ in active metabolite formation and ↓ efficacy	Possible ↑ in active metabolite formation and ↑ effect	Net effect difficult to predict.
Olmesartan (Olmetec®)	20-40 mg once daily	Biliary excretion	no predicted effect	no predicted effect	no predicted effect
Telmisartan (Micardis®)	80 mg once daily (40 mg in hepatic impairment)	Biliary excretion	no predicted effect	no predicted effect	no predicted effect
Valsartan (Diovan®)	Starting dose 80 mg, max 320 mg once daily	Biliary excretion	no predicted effect	no predicted effect	no predicted effect
BETA-BLOCKERS					
Acebutolol (Monitan®)	100 mg BID (max 400 mg BID)	2D6	Possible ↑ beta-blocker with ritonavir	no predicted effect	Possible ↑ beta-blocker; monitor for effect and decrease beta-blocker dose if necessary.[15]
Atenolol (Tenormin®, Tenoretic® - atenolol-	50 mg once daily (max 100 mg)	Renal	no predicted effect **Atazanavir** 400 mg daily plus atenolol 50 mg daily for 5 days did not cause a substantial	no predicted effect	no predicted effect

Drug	Usual Dose (essential hypertension)	Metabolism[25]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	<u>Integrase Inhibitor</u> (**i.e.,elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
chlorthalidone)			increase in the PR interval. Also, minimal changes in atenolol (34% ↑ C_{max}, 25% ↑ AUC, 2% ↑ C_{min}) and atazanavir levels (7% ↓ AUC and 26% ↓ C_{min}). No dose adjustment needed.[26] **Lopinavir/ritonavir** and drugs that prolong the PR have not been studied. Caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval (such as beta-blockers).[5] Cardiac events, have been reported with patients on **ritonavir** and beta blockers.[7] PR prolongation may occur and caution is warranted.		
Carvedilol (Coreg®)	6.25 mg BID (max 25 mg BID)	2D6, 2C9>1A2, 2E1, 3A4	Possible ↑ beta-blocker **Lopinavir/ritonavir** and drugs that prolong the PR have not been studied. Caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval (such as beta-blockers).[5] Cardiac events, have been	Possible ↓ beta-blocker	Possible ↑/↓ beta-blocker; monitor for effect and adjust beta-blocker dose if necessary.[15]

Drug	Usual Dose (essential hypertension)	Metabolism[25]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitor (i.e.,elvitegravir/cobicistat; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
			reported with patients on **ritonavir** and beta blockers.[7] PR prolongation may occur and caution is warranted.		
Labetalol (Trandate®)	Starting dose 100 mg BID after food, range 200-400 mg BID (max 600 mg BID)	2D6	Possible ↑ beta-blocker with ritonavir. Cardiac events, have been reported with patients on **ritonavir** and beta blockers.[7] PR prolongation may occur and caution is warranted. **Lopinavir/ritonavir** and drugs that prolong the PR have not been studied. Caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval (such as beta-blockers).[5]	no predicted effect	Possible ↑ beta-blocker; monitor for effect and decrease beta-blocker dose if necessary.[15]
Metoprolol (Betaloc®, Lopresor®)	50-100 mg BID (max 200 mg BID)	2D6	Possible ↑ beta-blocker with ritonavir. Cardiac events, have been reported with patients on **ritonavir** and beta blockers.[7] PR prolongation may occur and caution is warranted. Extreme bradycardia (20-25 bpm) with complete AV block and severe hypotension (BP 50/20 mmHg) occurred in a patient on stable therapy including lacidipine and metoprolol; symptoms	no predicted effect	Possible ↑ beta-blocker; monitor for effect and decrease beta-blocker dose if necessary.[15]

Drug	Usual Dose (essential hypertension)	Metabolism[25]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitor (i.e.,elvitegravir/cobicistat; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
			developed 48 hours after starting tenofovir, emtricitabine, and **lopinavir/ritonavir** for post-exposure prophylaxis. An interaction between lopinavir/ritonavir and metoprolol and lacidipine was hypothesized to be the cause of this adverse event.[27]		
Nadolol (Corgard®)	Starting dose 40-80 mg once daily, usual dose 320 mg daily (max 640 mg per day)	Renal	no predicted effect **Lopinavir/ritonavir** and drugs that prolong the PR have not been studied. Caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval (such as beta-blockers).[5] Cardiac events, have been reported with patients on **ritonavir** and beta blockers.[7] PR prolongation may occur and caution is warranted.	no predicted effect	no predicted effect
Pindolol (Visken®)	Starting dose 5 mg BID with meals, usual dose 15-45 mg daily	2D6	Possible ↑ beta-blocker with ritonavir. Cardiac events, have been reported with patients on **ritonavir** and beta blockers.[7] PR prolongation may occur and caution is warranted. **Lopinavir/ritonavir** and drugs	no predicted effect	Possible ↑ beta-blocker; monitor for effect and decrease beta-blocker dose if necessary.[15]

Drug	Usual Dose (essential hypertension)	Metabolism[25]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitor (i.e.,elvitegravir/cobicistat; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
			that prolong the PR have not been studied. Caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval (such as beta-blockers).[5]		
Propranolol (Inderal LA®)	Starting dose 80 mg once daily, usual dose 160-320 mg once daily	2D6, 3A4, 2C19	Possible ↑ beta-blocker. **Lopinavir/ritonavir** and drugs that prolong the PR have not been studied. Caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval (such as beta-blockers).[5] Cardiac events, have been reported with patients on **ritonavir** and beta blockers.[7] PR prolongation may occur and caution is warranted.	Possible ↓ beta-blocker	Possible ↑ beta-blocker; monitor for effect and decrease beta-blocker dose if necessary.[15]
CALCIUM CHANNEL BLOCKERS (CCB)					
Amlodipine (Norvasc®)	5 mg once daily (max 10 mg)	CYP3A	In healthy subjects on **indinavir 800/ritonavir 100 mg BID**, steady-state amlodipine AUC ↑ 90%.[28] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side	Possible ↓ CCB concentrations; titrate to response with careful monitoring	Possible ↑ CCB; monitor for effect and decrease CCB dose if necessary.[15]

Drug	Usual Dose (essential hypertension)	Metabolism[25]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitor (i.e.,elvitegravir/cobicistat; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
			effects. PR prolongation may occur with the combination of CCBs and **ritonavir-based regimens**; caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval such as CCBs.[7]		
Diltiazem (Cardizem CD®, Tiazac®)	180-240 mg once daily (max 360 mg)	CYP3A, plasma and tissue esterases, sulfation and glucuridonation. Active metabolite 25 to 50% as potent as diltiazem. 2 to 4% unchanged in the urine[29]	In healthy subjects on **indinavir 800/ritonavir 100 mg BID**, steady-state diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[28] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects. **Atazanavir 400 mg daily** with diltiazem 180 mg daily increased diltiazem plasma concentrations, C_{min}, and AUC by approx. 2-fold (n=28). There was also an additive PR effect. There was no significant change in the pharmacokinetics of atazanavir (n=30). A dose reduction of diltiazem by 50% should be	Possible ↓ CCB concentrations; titrate to response with careful monitoring. Coadministration of **efavirenz** (600 mg for 14 days) resulted in ↓ 60% C_{max}, ↓ 69% AUC and ↓ 63% C_{min} of diltiazem. Higher doses of diltiazem may be required. No dose adjustment of efavirenz is necessary.[31] Potential drug interaction between **nevirapine** and diltiazem, which may cause decreased diltiazem plasma concentrations.[32] Higher doses of diltiazem may be required.	Possible ↑ CCB; monitor for effect and decrease CCB dose if necessary.[15]

Drug	Usual Dose (essential hypertension)	Metabolism[25]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitor (i.e.,elvitegravir/cobicistat; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
			considered. Coadministration of atazanavir/ritonavir with diltiazem has not been studied, however similar recommendations would apply.[26] Coadministration with **tipranavir/ritonavir** has not been studied; the net effect on dilitiazem is difficult to predict given the conflicting effect of tipranavir and ritonavir on substrates of both CYP3A and P-gp. Caution is warranted.[30] PR prolongation may occur with the combination of CCBs and **ritonavir-based regimens**; caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval such as CCBs.[7]		
Felodipine (Plendil®, Renedil®)	5 mg once daily (range 2.5-10 mg daily)	CYP3A	↑ CCB concentrations; initiate therapy at low doses, with careful titration to response and side effects. Case report of patient on stable fixed dose combination of felodipine 5 mg and metoprolol 50 mg daily who	Possible ↓ CCB concentrations; titrate to response with careful monitoring	Possible ↑ CCB; monitor for effect and decrease CCB dose if necessary.[15]

Drug	Usual Dose (essential hypertension)	Metabolism[25]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitor (i.e.,elvitegravir/cobicistat; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
			was started on **nelfinavir** 2000 mg daily, with zidovudine and lamivudine for post-exposure prophylaxis (PEP). After 3 days, the patient experienced edema, dizziness, fatigue and orthostatic hypotension. The authors concluded that the patient developed side effects due to an increase in felodipine concentrations mediated due to nelfinavir-mediated CYP3A4 inhibition.[33] PR prolongation may occur with the combination of CCBs and **ritonavir-based regimens**; caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval such as CCBs.[7]		
Ladicipine (not currently available in Canada)	2 mg once daily (max 6 mg)	CYP3A4, possible P-gp	↑ CCB concentrations; initiate therapy at low doses, with careful titration to response and side effects. Extreme bradycardia (20-25 bpm) with complete AV block and severe hypotension (BP 50/20 mmHg) occurred in a patient on stable therapy including lacidipine and	Possible ↓ CCB concentrations; titrate to response with careful monitoring	Possible ↑ CCB; monitor for effect and decrease CCB dose if necessary.[15]

Drug	Usual Dose (essential hypertension)	Metabolism[25]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitor (i.e.,elvitegravir/cobicistat; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
			metoprolol; symptoms developed 48 hours after starting tenofovir, emtricitabine, and **lopinavir/ritonavir** for post-exposure prophylaxis. An interaction between lopinavir/ritonavir and metoprolol and lacidipine was hypothesized to be the cause of this adverse event.[27] PR prolongation may occur with the combination of CCBs and **ritonavir-based regimens**; caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval such as CCBs.[7]		
Nifedipine (Adalat XL®)	20-30 mg once daily (max 90 mg)	CYP3A (major), 1A2, 2A6	↑ CCB concentrations; initiate therapy at low doses, with careful titration to response and side effects. A severe interaction resulting in acute renal insufficiency, hypotension and edema was noted when a regimen containing **lopinavir/ritonavir** was started in a patient receiving nifedipine 30 mg twice a day; the symptoms	Possible ↓ CCB concentrations; titrate to response with careful monitoring	Possible ↑ CCB; monitor for effect and decrease CCB dose if necessary.[15]

Drug	Usual Dose (essential hypertension)	Metabolism[25]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	**<u>Integrase Inhibitor</u>** (**i.e.,elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
			resolved upon discontinuation of the HAART regimen, and re-emerged after lopinavir/ritonavir was re-introduced.[34] A 51-year-old man with HIV infection who was receiving extended-release nifedipine (60 mg/day) developed symptomatic orthostasis and heart block after starting antiretroviral therapy that included **nelfinavir** 1250 mg twice daily. Medication was changed, however, the patient developed orthostatic symptoms after restarting nelfinavir. Subsequent administration of antiretroviral therapy containing indinavir/ritonavir with extended-release nifedipine resulted in recurrence of his orthostatic symptoms.[35] PR prolongation may occur with the combination of CCBs and **ritonavir-based regimens**; caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval such as CCBs.[7]		

Actual and Predicted Pharmacokinetic Interactions Between <u>Antihypertensives</u> and Antiretrovirals

Drug	Usual Dose (essential hypertension)	Metabolism[25]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	<u>Integrase Inhibitor</u> (**i.e.,elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
Verapamil (Isoptin SR®, Lovera-HS®)	180-240 mg once daily (max 480 mg)	CYP3A (major), 1A2, 2C9, 2C19. Active metabolite norverapamil has 20% activity of verapamil.	↑ CCB concentrations; initiate therapy at low doses, with careful titration to response and side effects. PR prolongation may occur with the combination of CCBs and **ritonavir-based regimens**; caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval such as CCBs.[7]	Possible ↓ CCB concentrations; titrate to response with careful monitoring	Possible ↑ CCB; monitor for effect and decrease CCB dose if necessary.[15]
DIURETICS					
Chlorthalidone (Hygroton®; Tenoretic® - atenolol-chlorthalidone)	12.5-50 mg once daily	Negligible hepatic metabolism 30-65% renal excretion as unchanged drug[36]	no predicted effect	no predicted effect	no predicted effect
Furosemide (Lasix®)	20-40 mg BID	Renal (90%); hepatic metabolism mainly glucuronidation. Proportion of hepatic clearance increases substantially (4x) in severe renal	no predicted effect	no predicted effect	no predicted effect

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Drug	Usual Dose (essential hypertension)	Metabolism[25]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	**<u>Integrase Inhibitor</u>** (**i.e.,elvitegravir/cobicistat**; generally no predicted interactions with dolutegravir or raltegravir based on pharmacokinetic properties)
		failure.[37]			
Hydrochloro-thiazide	12.5-50 mg once daily	Renal	no predicted effect	no predicted effect	no predicted effect
Indapamide (Lozide®)	1.25 mg once daily in the morning (max 2.5 mg once daily)	2C9, 2D6, 3A4	Possible ↑ indapamide	Possible ↓ indapamide	Possible ↑/↓ indapamide concentrations; monitor for effect and adjust indapamide dose if necessary.
Metolazone (Zaroxolyn®)	2.5-5 mg once daily (max 10 mg)	Renal	no predicted effect	no predicted effect	no predicted effect
Spironolactone (Aldactone®)	50-100 mg daily (max 200 mg daily)	Renal	no predicted effect	no predicted effect	no predicted effect

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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