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Review

Getting to the Heart of the Matter: A Review of Drug Interactions Between HIV Antiretrovirals and Cardiology Medications

Pierre Giguère, BPharm, MSc,[a] Salin Nhean, Pharm D,[b] Alice L. Tseng, Pharm D,[c] Christine A. Hughes, Pharm D,[d] and Jonathan B. Angel, MD, FRCPC[e]

[a] Department of Pharmacy, The Ottawa Hospital, The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

[b] University Health Network, Toronto, Ontario, and McGill University Health Centre, Montréal, Quebec, Canada

[c] University of Health Network, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

[d] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada

[e] Faculty of Medicine, University of Ottawa, The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

ABSTRACT

The past 20 years have seen remarkable advances in the treatment of HIV such that most people diagnosed with HIV today can live long, healthy lives by taking antiretrovirals which are usually life-long. Advancements in antiretroviral therapy include the availability of well tolerated, single tablet regimens that are associated with a lower risk of drug-drug interactions. Despite this, many people living with HIV infection might be taking antiretroviral agents that are associated with significant drug-drug interactions. Because HIV infection itself is associated with cardiovascular complications and this population is living longer, concomitant use of antiretrovirals and medications to treat cardiovascular-related diseases is often required. For this reason, it is imperative that clinicians are aware of the potential for clinically significant drug-drug interactions between antiretroviral agents and cardiac medications as well as the useful HIV drug interaction resources that

RÉSUMÉ

Les 20 dernières années ont vu des progrès remarquables dans le traitement du VIH de sorte que la plupart des gens qui découvrent être porteurs du VIH aujourd'hui peuvent vivre une vie longue et en bonne santé grâce aux agents antirétroviraux qu'ils prendront habituellement pour toute la vie. Les progrès réalisés en matière de traitement antirétroviral ont permis d'offrir des schémas thérapeutiques à comprimés uniques bien tolérés qui sont associés à un risque réduit d'interactions médicament-médicament. Malgré tout, de nombreuses personnes vivant avec le VIH peuvent prendre des agents antirétroviraux qui sont associés à des interactions médicament-médicament importantes. Étant donné que l'infection par le VIH est elle-même associée à des complications cardiovasculaires et que les personnes atteintes vivent plus longtemps qu'avant, celles-ci doivent souvent prendre en concomitance des agents antirétroviraux et des médicaments pour les

Treatment of HIV has evolved considerably since the early days of combination antiretroviral therapy. The availability of potent and well tolerated single-tablet regimens has led to unprecedented rates of treatment success with sustained suppression of viral replication and patient acceptability. With early initiation of HIV treatment, life expectancy of treated individuals is nearing that of the general population.[1,2]

Several observational cohorts have shown increased rates of comorbidities such as cardiovascular, bone, and renal disease in the HIV population compared with the general population, a finding that persists in patients who have achieved viral suppression. With respect to cardiovascular disease, people living with HIV have a 1.5- to twofold increase in the risk of acute myocardial infarction or coronary artery disease.[3,4] Although traditional risk factors partly explain this phenomenon, recent studies are highlighting the interplay between immune activation and inflammatory markers.[5]

Improvements in the treatment of HIV infection include the fact that the many current first-line regimens are comprised of drugs that have very few drug-drug interactions. "Unboosted" integrase inhibitors (raltegravir, dolutegravir, and bictegravir) are a component of preferred regimens in most treatment guidelines and are frequently prescribed for treatment-naive patients. Although the use of medications with fewer drug-drug interactions makes the treatment of HIV and comorbidities easier, many antiretrovirals commonly used in practice are associated with important drug-drug interactions via involvement of the cytochrome (CYP) P450 system and/or drug transporters. Because polypharmacy is already common in the management of heart failure,

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Corresponding author: Dr Pierre Giguère, Pharmacy department, The Ottawa Hospital, 501 Smyth Rd, Ottawa, Ontario K1H 8L6, Canada. Tel.: +1-613-737-8922; fax: +1-617-737-8009.

E-mail: pgiguere@toh.ca

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might provide guidance. Available data on significant interactions are summarized and suggested guidance regarding management is discussed.

maladies cardiovasculaires. C'est pourquoi il est impératif que les cliniciens connaissent la possibilité d'interactions médicament-médicament importantes sur le plan clinique entre les agents antirétroviraux et les médicaments contre les troubles cardiaques, ainsi que les ressources utiles sur les interactions avec les médicaments contre le VIH qui peuvent les aider. Les données dont on dispose sur les interactions d'importance sont résumées, et des propositions d'orientations relatives à la prise en charge sont abordées.

hypertension, and coronary heart disease,[6,7] managing these conditions is even more challenging in people living with HIV.

This article provides an overview of drug-drug interactions between antiretrovirals and medications frequently used in the treatment of arrhythmia, heart failure, and coronary heart disease, including mechanisms as well as guidance on management.

Pharmacology of Antiretrovirals and Mechanism of Drug-Drug Interactions

HIV treatment is usually comprised of 3 active agents from a minimum of 2 drug classes. From a pharmacology perspective, many antiretrovirals are metabolized through CYP450 and/or uridine diphosphate-glucuronosyltransferase (UGT) enzymes. Some antiretrovirals can also induce or inhibit these enzymes, which can affect the serum concentration and effect of coadministered drugs (Fig. 1).[8] The efficacy or toxicity associated with antiretrovirals can also be affected by coadministered drugs that induce or inhibit CYP450 enzymes. In addition to metabolism, changes in the disposition of drugs might be secondary to drug transporters such as p-glycoprotein (P-gp), breast cancer-related protein (BCRP), organic anion transporting polypeptide (OATP), or organic anion transporter (OAT). In simple terms, drug-drug interactions are a bidirectional process that might affect the concentrations of either drug and compromise their efficacy or safety.

A very common example of this concept is seen with the pharmacokinetic enhancers, ritonavir and cobicistat. These drugs, commonly called "boosters," are used to optimize drug exposure of protease inhibitors and the integrase inhibitor, elvitegravir. They can be prescribed separately (eg, ritonavir) or coformulated with cobicistat (eg, Stribild [Gilead Sciences Canada Inc, Mississauga, ON], Genvoya [Gilead Sciences Canada Inc], Prezcobix [Janssen Inc, Toronto, ON], Symtuza [Janssen Inc]). The inhibition of select CYP450 enzymes and drug transporters by ritonavir and cobicistat increases drug exposure of substrates of these enzymes or transporters. Other antiretrovirals such as the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz, etravirine, and nevirapine might induce CYP450 enzymes, and therefore have the opposite effect. Drug-drug interactions can be managed either by selecting an agent (antiretroviral or coadministered drug) that does not interfere with the other, or by adjusting the dose and/or close monitoring when the interaction cannot be avoided. Collaboration and good communication between cardiologists, HIV practitioners, and pharmacists are key elements for optimal management of these clinical scenarios. Drug-drug interactions between antiretrovirals and cardiovascular medications are summarized in the text that follows, as well as in Figures 2-5.

Diuretics

Loop diuretics and thiazides

A clinically significant pharmacokinetic interaction between antiretrovirals and most diuretics is unlikely on the basis of metabolism and clearance. In theory, hydrochlorothiazide could interact with tenofovir disoproxyl fumarate (TDF) via renal transporter OAT1, but in vitro data demonstrate that OAT1 inhibition by hydrochlorothiazide is negligible.[9] Therefore, hydrochlorothiazide is unlikely to affect the renal elimination of TDF.[10] Unlike TDF, tenofovir alafenamide is not a substrate for OAT1 and is also not expected to interact with hydrochlorothiazide.[11] Interactions between antiretrovirals and metolazone, furosemide, bumetanide, and chlorthalidone are not anticipated, because these diuretics are primarily excreted unchanged renally.[12-15]

In contrast, indapamide is extensively metabolized by CYP3A4 and CYP2C19.[16] Coadministration with protease inhibitors, cobicistat or NNRTIs might lead to increased or decreased indapamide concentrations, requiring additional monitoring for clinical effect.

Mineralocorticoid receptor antagonists

Spironolactone is not expected to interact with antiretrovirals on the basis of its metabolism and clearance.[17] However, eplerenone is predominantly metabolized by CYP3A4, and its area under the plasma drug concentration-time curve (AUC) was increased fourfold with potent CYP3A4 inhibitor coadministration.[18] Eplerenone is contraindicated with protease inhibitors and cobicistat because of risk of increased exposures and serious toxicities, including hyperkalemia.[8] In contrast, concurrent administration of eplerenone with the CYP3A4 inducers efavirenz, nevirapine, and etravirine could reduce the efficacy of eplerenone by reducing its concentration.

Vasoactive Agents

α-Adrenoceptor antagonists

Prazosin and terazosin are extensively metabolized, but the exact pathway is unknown.[19,20] In contrast, doxazosin's metabolic pathway is well characterized, depending primarily on CYP3A4 for its clearance. When coadministered with protease inhibitors or cobicistat, doxazosin and terazosin exposures are expected to be increased.[21,22] Pharmacokinetic

Generic name	Trade name	Substrate	Effect on metabolizing pathways		Potential for interaction with cardiac comedications
			Inhibitor	Inducer	
Integrase inhibitors					
Bictegravir	Bictarvy*	CYP3A4 UGT1A1	OCT2		Low
Dolutegravir	Tivicay Triumeq* Juluca*	CYP3A4 UGT1A1 P-gp substrate	OCT2		Low
Elvitegravir/c	Stribild* Genvoya*	CYP3A4 UGT1A1	3A4>2D6 P-gp	CYP2C9 (weak)	**High**
Raltegravir	Isentress	UGT1A1			Low
Non-nucleoside reverse transcriptase inhibitors					
Doravirine	Pifeltro Delstrigo*	CYP3A4			Low
Efavirenz	Sustiva Atripla*	CYP2B6>3A4		CYP3A4, 2B6, 2C19	Intermediate
Etravirine	Intelence	CYP3A4, 2C9, 2C19	CYP2C9, 2C19	CYP3A4	Intermediate
Nevirapine	Viramune	CYP3A4, 2B6		CYP3A4, 2B6	Intermediate
Rilpivirine	Edurant Complera* Odefsey* Juluca*	CYP3A4			Low
Protease inhibitors					
Atazanavir/r	Reyataz	CYP3A4	CYP3A4>2D6, OATP, P-gp, UGT1A1	CYP1A2, 2B6, 2C8, 2C9, 2C19	**High**
Atazanavir/c	Evotaz	CYP3A4	CYP3A4>2D6, OATP, P-gp, UGT1A1		**High**
Darunavir/r	Prezista	CYP3A4	CYP3A4>2D6, OATP, P-gp	CYP1A2, 2B6, 2C8, 2C9, 2C19	**High**
Darunavir/c	Prezcobix Symtuza*	CYP3A4	CYP3A4>2D6, OATP, P-gp	CYP2C9	**High**
Nucleoside reverse transcriptase inhibitors					
Abacavir/ lamivudine	Kivexa				Low
Emtricitabine /tenofovir DF	Truvada	P-gp			Low
Emtricitabine/ tenofovir alafenamide	Descovy	P-gp			Low

Figure 1. Mechanisms of antiretroviral-associated drug interactions. Biktarvy, Complera, Descovy, Genvoya Odefsey, Stribild, Truvada from Gilead Sciences Canada Inc (Mississauga, ON); Atripla, Evotaz, Reyataz, Sustiva from Bristol-Myers Squibb Canada (Montreal, QC); Intelence, Prezcobix, Prezista, Symtuza from Janssen Inc (Toronto, ON) Viramune from Boehringer Ingelheim (Canada) Ltd (Burlington, ON); Juluca, Kivexa, Tivicay, Triumeq from ViiV Healthcare Canada (Laval, QC); Delstrigo, Isentress, Pifeltro from Merck Canada Inc (Kirkland, QC). c, cobicistat; CYP, cytochrome P450; P-gp, p-glycoprotein; OCT2, organic cation transporter 2; OATP, organic anion-transporting polypeptide; r, ritonavir; UGT, Uridine 5′-diphospho-glucuronosyltransferase. *Single-tablet regimen, which includes a combination of agents to treat HIV.

extrapolations from studies with other CYP3A4 inhibitors showed a 10% increase in doxazosin AUC when it was coadministered with cimetidine[21] and a 24% increase in terazosin AUC when it was given together with verapamil.[22] Doxazosin and terazosin should be started at a low dose and increased as tolerated when used with cobicistat or ritonavir. Prazosin is also a substrate of the drug transporter BCRP.[23] Although in theory prazosin serum concentrations could be increased by ritonavir or cobicistat, to our knowledge, no reports of adverse reactions have been published. However, blood pressure should be monitored frequently, because of the potential for interactions at the metabolic and drug transporter levels.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors are not involved in significant CYP450-mediated interactions with other agents.[24-33] Thus, drug interactions with antiretrovirals are not expected.

	CV agent	Antiretroviral with potential DDIs	Effect	Management
Diuretics and mineralocorticoid receptor antagonists				
Diuretics	Bumetanide chlorthalidone, furosemide, HCTZ, metolazone	None	N/A	Use standard doses with all antiretrovirals
	Indapamide	PI/r, PI/c, EVG/c	Possible ↑ indapamide	Monitor clinical effects and adjust indapamide dose if necessary
		EFV, ETR, NVP	Possible ↓ indapamide	
MIRAs	Spironolactone	None	N/A	Use standard doses with all antiretrovirals
	Eplerenone	EFV, ETR, NVP	Possible ↓ eplerenone	Monitor clinical effects and ↑ eplerenone dose as necessary
	Eplerenone	**PI/r, PI/c, EVG/c**	**Possible significant ↑ eplerenone**	**Contraindicated**
Vasoactive agents				
α-Adrenoreceptor inhibitors	Doxazosin, prazosin, terazosin	PI/r, PI/c, EVG/c	Possible ↑ doxazosin, prazosin, and terazosin	Monitor clinical effects and ↓ dose as necessary
	Doxazosin, terazosin	EFV, ETR, NVP	Possible ↓ doxazosin and terazosin	Monitor clinical effects and ↑ dose as necessary
ACE inhibitors	All	None	N/A	Use standard doses with all antiretrovirals
Angiotensin II receptor blockers	Candesartan, eprosartan, telmisartan	None	N/A	Use standard doses with all antiretrovirals
	Irbesartan, losartan	r, EVG/c	Possible ↑ losartan active metabolite; Possible ↓ irbesartan	Monitor clinical effects and ↓ losartan or ↑ irbesartan dose as necessary
		EFV, ETR	Possible ↓ losartan active metabolite; Possible ↑ irbesartan	Monitor clinical effects and ↑ losartan or ↓ irbesartan dose if necessary
	Valsartan	PI/r, PI/c	Possible ↑ valsartan	Monitor clinical effects and ↓ valsartan dose if necessary
	Sacubitril/valsartan	PI/r, PI/c	Possible ↑ sacubitril/valsartan	Monitor clinical effects and ↓ sacubitril/valsartan dose if necessary
β-Blockers	Atenolol, labetalol, nadolol,	None	N/A	Use standard doses with all antiretrovirals
	Carvedilol, metoprolol, bisoprolol	PI/r, PI/c, EVG/c	Possible ↑ BBs	Monitor clinical effects and ↓ BB dose if necessary
	Bisoprolol	EFV, ETR, NVP	Possible ↓ bisoprolol	Monitor efficacy and ↑ bisoprolol dose if necessary
Nitrates and other vasodilators	Hydralazine	MVC	Possible ↑ postural hypotension	Use standard doses with all antiretrovirals; caution is warranted particularly **when high dose MVC is used**
	Isosorbide dinitrate	MVC	Possible ↑ postural hypotension	Use standard doses with all antiretrovirals; caution is warranted particularly **when high-dose MVC is used**
		PI/r, PI/c, EVG/c	Possible ↓ active nitric oxide, but unknown clinical effect	Use standard doses and monitor efficacy of isosorbide dinitrate
		EFV, ETR, NVP	Possible ↑ active nitric oxide, but unknown clinical effect	Use standard doses and monitor toxicity of isosorbide dinitrate
	Transdermal nitrates	None	N/A	Use standard doses with all antiretrovirals

Figure 2. Summary table of DDIs between cardiac drugs and antiretrovirals. **Green** shading indicates no known or suspected interaction; **yellow**, interaction requiring dose modification or extra monitoring; and **red**, not recommended or contraindicated. ACE, angiotensin converting enzyme; BB, β-blocker; c, cobicistat; CV, cardiovascular; DDI, drug-drug interaction; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; HCTZ, hydrochlorothiazide; MRAs, mineralocorticoid receptor antagonists; MVC, maraviroc; N/A, not applicable; NVP, nevirapine; PI, protease inhibitor; r, ritonavir.

	CV agent	Antiretroviral with potential DDIs	Effect	Management
Bile acid sequestrants	Cholestyramine, colestipol	All	Possible ↓ ARV absorption	When coadministered, antiretrovirals should be spaced at least 1 hour before or 4-6 hours after bile acid sequestrants
	Ezetimibe	PI/r	Possible ↓ ezetimibe	Use standard doses and monitor clinical effects of ezetimibe
Fibrates	Bezafibrate, fenofibrate	None	N/A	Use standard doses with all antiretrovirals
	Gemfibrozil	PI/r	Possible ↓ gemfibrozil; LPV/r ↓ gemfibrozil AUC 41%	Use standard doses and monitor clinical effects of gemfibrozil
PCSK9 inhibitors	Alirocumab, evolocumab	None	N/A	Use standard doses with all antiretrovirals
Statins	Pitavastatin	None	N/A	Use standard doses with all antiretrovirals
	Pravastatin	PI/r, PI/c, EVG/c	Interactions not likely significant	Use standard doses and monitor toxicities
	Fluvastatin	PI/r, PI/c, EVG/c	Possible ↑ fluvastatin	Start with the lowest dose of rosuvastatin and adjust the dose on the basis of clinical effects and toxicities
	Pravastatin	EFV, ETR, NVP	Possible ↓ pravastatin; EFV ↓ pravastatin AUC 44%	Monitor clinical effects and ↑ pravastatin dose as necessary, but do not exceed maximum recommended dose
	Rosuvastatin	ATV/r, ATV/c, LPV/r	Possible ↑ rosuvastatin; ATV/r ↑ rosuvastatin AUC 213%; ATV/c ↑ rosuvastatin AUC 242%	Start with the lowest dose of rosuvastatin (ie, 5 mg/d) and adjust the dose on the basis of clinical effects and toxicities. Do not exceed 10 mg/d rosuvastatin
		DRV/r, DRV/c, EVG/c	Possible ↑ rosuvastatin; DRV/r ↑ rosuvastatin AUC 48%; DRV/c ↑ rosuvastatin AUC 93%; EVG/c ↑ rosuvastatin AUC 38%	Start with the lowest dose of rosuvastatin and adjust the dose on the basis of clinical effects and toxicities. Do not exceed 20 mg/d rosuvastatin
	Atorvastatin	ATV/r, DRV/r, DRV/c, LPV/r	Possible ↑ atorvastatin; DRV/c ↑ atorvastatin AUC 290%; DRV/r + atorvastatin 10 mg similar to atorvastatin 40 mg alone; LPV/r ↑ atorvastatin AUC 5.9-fold	Start with the lowest dose of atorvastatin (ie, 10 mg/d) and adjust the dose on the basis of clinical effects and toxicities. Do not exceed 20 mg/d atorvastatin
		EFV, ETR, NVP	Possible ↓ atorvastatin; EFV ↓ atorvastatin AUC 43%	Monitor clinical effects and ↑ atorvastatin dose as necessary, but do not exceed maximum recommended dose
	Atorvastatin	**ATV/c**	**ATV/c ↑ atorvastatin AUC 822%**	**Do not coadminister**
	Lovastatin, simvastatin	EFV, ETR, NVP	Possible ↓ simvastatin and lovastatin; EFV ↓ simvastatin AUC 68%	Monitor clinical effects and ↑ simvastatin or lovastatin dose as necessary
	Lovastatin, simvastatin	**PI/r, PI/c, EVG/c**	**Significant ↑ simvastatin and lovastatin; SQV/r ↑ simvastatin AUC 32-fold; NFV ↑ simvastatin AUC 5-fold**	**Contraindicated**

Figure 3. Summary table of DDIs between lipid-lowering agents and antiretrovirals. **Green** shading indicates no known or suspected interaction; **yellow**, interaction requiring dose modification or extra monitoring; and **red**, not recommended or contraindicated. ARV, antiretroviral; ATV, atazanavir; AUC, area under the plasma concentration-time curve; c, cobicistat; CV, cardiovascular; DDI, drug-drug interaction; DRV, darunavir; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; LPV, lopinavir; N/A, not applicable; NFV, nelfinavir; NVP, nevirapine; PI, protease inhibitor; PCSK9, proprotein convertase subtilisin/kexin 9; r, ritonavir; SQV, saquinavir.

Angiotensin II receptor blockers

Losartan is converted primarily via CYP2C9 to an active metabolite, which is responsible for most of its pharmacologic activity.[34] Irbesartan is also primarily metabolized by CYP2C9, but does not require biotransformation for its effects.[35] Ritonavir and elvitegravir are modest CYP2C9 inducers and might potentially increase the formation of the active metabolite of losartan or decrease irbesartan exposures.[36,37] In contrast, CYP2C9 inhibitors, such as efavirenz and etravirine (weak) could reduce the efficacy of losartan by decreasing the pharmacologically active losartan metabolite or increase irbesartan plasma concentrations.[38,39] Valsartan is a substrate of OATP1B1 and the hepatic efflux transporter, multidrug resistance-associated protein 2 (MRP2).[40] Plasma

	CV agent	Antiretroviral with potential DDIs	Effect	Management
Anticoagulants	Apixaban	PI/r, PI/c, EVG/c	Possible ↑ apixaban	Avoid coadministration or reduce apixaban dose by 50% as per manufacturer label. Consider alternative such as warfarin, or a change in antiretrovirals
		EFV, ETR, NVP	Possible ↓ apixaban	Avoid coadministration. Consider alternative such as warfarin, or a change in antiretrovirals
	Dabigatran	DRV/c	N/A	Use standard dose
	Dabigatran	PI/r	Dabigatran with r taken simultaneously: no change in dabigatran AUC; Dabigatran given 2 hours before r: dabigatran AUC ↓ 29%	Significance of the interaction is unknown. Consider alternative such as warfarin; If coadministered, dabigatran and PI/r should be taken at the same time.
		ATV/c, EVG/c	c ↑ dabigatran AUC 110%–127%	Coadministration depends on the DOAC indication and renal function. Refer to dabigatran dosing instructions for coadministration with P-gp inhibitors in the prescribing information. Consider alternative such as warfarin or change in antiretrovirals
	Edoxaban	PI/r	Possible ↑ or ↓ edoxaban	Coadministration depends on the DOAC indication and renal function. Refer to edoxaban dosing instructions for coadministration with P-gp inhibitors in the prescribing information. Consider alternative such as warfarin or change in antiretrovirals
		ATV/c, EVG/c	Possible ↑ edoxaban	
	Warfarin	EFV, ETR, NVP, EVG/c, PI/c	Possible ↑ or ↓ warfarin	Adjust warfarin dose as needed to maintain therapeutic INR
		PI/r	Possible ↓ warfarin	
	Rivaroxaban	**PI/r, PI/c, EVG/c**	**Possible ↑ rivaroxaban**	**Avoid coadministration. Consider alternative such as warfarin, or change in antiretrovirals**
		EFV, ETR, NVP	**Possible ↓ rivaroxaban**	
Antiplatelets	ASA	None	N/A	Use standard doses with all antiretrovirals
	Prasugrel	None	N/A	Use standard doses with all antiretrovirals
	Clopidogrel	EFV, ETR	Possible ↓ active metabolite of clopidogrel	Use with caution. Consider alternatives such as prasugrel
	Ticagrelor	PI/r, PI/c, EVG/c	Possible ↑ ticagrelor	Avoid coadministration. Consider alternative such as prasugrel
		EFV, ETR, NVP	Possible ↓ ticagrelor	

Figure 4. Summary table of DDIs between anticoagulants, antiplatelets, and antiretrovirals. **Green** shading indicates no known or suspected interaction; **yellow**, interaction requiring dose modification or extra monitoring; and **red**, not recommended or contraindicated. ASA, aspirin; ATV, atazanavir; AUC, area under the plasma concentration-time curve; c, cobicistat; CV, cardiovascular; DDI, drug-drug interaction; DOAC, direct oral anticoagulant; DRV, darunavir; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; INR, international normalized ratio; N/A, not applicable; NVP, nevirapine; P-gp, p-glycoprotein; PI, protease inhibitor; r, ritonavir.

concentrations could potentially be increased by protease inhibitors or cobicistat, but these interactions have not been clinically assessed.

Candesartan, eprosartan, and telmisartan are not metabolized by CYP450.[41-43] Thus, significant drug interactions between antiretrovirals and these angiotensin II receptor blockers are not expected.

β-Blockers

Metoprolol is primarily metabolized by CYP2D6.[44] Carvedilol is extensively metabolized by glucuronidation (UGT1A1) and CYP450, primarily the 2D6 and 2C9 isoenzymes.[45] Bisoprolol is partly metabolized by CYP3A4 and CYP2D6.[46] Other β-blockers, such as atenolol, labetalol, nadolol, and sotalol, are not metabolized by CYP450 isoenzymes.[47-50]

At boosting doses, ritonavir and cobicistat are not anticipated to act as CYP2D6 inhibitors.[36,51,52] Nonetheless, caution is warranted because cardiac adverse events have been reported in patients receiving ritonavir-boosted protease inhibitors and β-blockers.[36] Extreme bradycardia with complete atrioventricular block and severe hypotension occurred in a patient receiving metoprolol and lacidipine after initiation of a protease inhibitor treatment.[53] Efavirenz and etravirine could potentially increase carvedilol concentrations via CYP2C9 inhibition, and efavirenz might decrease carvedilol exposures via induction of UGT1A1.[54] Although not studied, protease inhibitors and cobicistat could potentially increase the concentrations of bisoprolol, whereas efavirenz, nevirapine, and etravirine could decrease bisoprolol exposures.

Nitrates and other vasodilators

Significant interactions with hydralazine are not expected, because it is primarily excreted in the form of acetylated and hydroxylated metabolites.[55]

	CV agent	Antiretroviral with potential DDIs	Effect	Management
Antiarrhythmics	Sotalol	None	N/A	Use standard doses with all antiretrovirals
	Amiodarone	PI/r, PI/c, EVG/c	Possible ↑ amiodarone	Use with caution and monitor for amiodarone toxicity. Consider ECG and amiodarone serum level
		EFV, ETR, NVP	Possible ↓ amiodarone	Monitor clinical effects. Consider amiodarone serum level
	Dronedarone	EVG/c	Possible ↑ dronedarone	Use with caution and monitor for dronedarone toxicity. Consider ECG and dronedarone serum level
		EFV, ETR, NVP	Possible ↓ dronedarone	Monitor clinical effects. Consider dronaderone serum level
	Dronedarone	**PI/r, PI/c**	**Possible ↑ dronedarone**	**Contraindicated**
	Flecainide	PI/r, PI/c, EVG/c	Possible ↑ flecainide	Not recommended. Use with caution and monitor for flecainide toxicity. Consider ECG and flecainide serum level
	Mexiletine	PI/r, PI/c, EVG/c	Possible ↑ mexiletine	Not recommended. Use with caution and monitor for mexiletine toxicity. Consider ECG and mexiletine serum level
	Propafenone	PI/r, PI/c, EVG/c	Possible ↑ propafenone	Not recommended. Use with caution and monitor for propafenone toxicity. Consider ECG and propafenone serum level
		EFV, ETR, NVP	Possible ↓ propafenone	Monitor clinical effects. Consider propafenone serum level
Calcium channel blockers	All	PI/r, PI/c, EVG/c	ATV ↑ diltiazem AUC 125%; possible ↑ other CCBs	Monitor clinical effects and ↓ CCB dose (consider ↓ 50% diltiazem) if necessary. ECG monitoring is recommended when CCB is used with PI/r, particularly ATV
		EFV, ETR, NVP	EFV ↓ diltiazem AUC 69%; possible ↓ other CCBs	Monitor efficacy and ↑ CCB dose if necessary
Other	Digoxin	PI/r, PI/c, EVG/c, ETR	Possible ↑ digoxin; DRV/r ↑ digoxin AUC 36%; c ↑ digoxin AUC 20%; ETR ↑ digoxin AUC 18%	Monitor digoxin levels closely and ↓ digoxin dose if necessary
	Ivabradine	EFV, ETR, NVP	Possible ↓ ivabradine	Monitor clinical effects and ↑ ivabradine dose as necessary
	Ivabradine	**PI/r, PI/c, EVG/c**	**Possible significant ↑ ivabradine**	**Contraindicated**

Figure 5. Summary table of DDIs between antiarrhythmics, related agents, and antiretrovirals. **Green** shading indicates no known or suspected interaction; **yellow**, interaction requiring dose modification or extra monitoring; and **red**, not recommended or contraindicated. ATV, atazanavir; AUC, area under the plasma concentration-time curve; c, cobicistat; CCB, calcium channel blocker; CV, cardiovascular; DDI, drug-drug interaction; DRV, darunavir; ECG, electrocardiogram; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; N/A, not applicable; NVP, nevirapine; PI, protease inhibitor; r, ritonavir.

An *in vitro* study suggested that CYP3A4 plays a role in nitric oxide formation from isosorbide dinitrate.[56] Thus, protease inhibitors and cobicistat could potentially reduce the production of nitric oxide, thereby compromising the efficacy of isosorbide dinitrate, whereas efavirenz, nevirapine, and etravirine could increase the formation of the active substance. Clinical implications of these potential interactions are unknown. Monitoring for efficacy and toxicity of isosorbide dinitrate is recommended. Transdermal nitrates are bio-activated by mitochondrial aldehyde dehydrogenase and therefore unlikely to have significant interactions with antiretrovirals.[57]

Neprilysin inhibitor/angiotensin II receptor blockers

The active metabolite of sacubitril is a substrate of OATP1B1.[58] Coadministration of sacubitril and antiretrovirals has not been studied, but ritonavir and cobicistat could inhibit OATP1B1, potentially increasing the exposures of sacubitril active metabolite.[59-61] Thus, sacubitril should be started at a low dose and titrated as tolerated.

Lipid-Lowering Agents

Bile acid sequestrants

Bile acid sequestrants are anion exchange resins that block enterohepatic circulation by binding to bile acids. However, bile acid sequestrants might also have strong affinity for anions other than the bile acids, leading to delayed or decreased absorption of drugs. Because of the lack of pharmacokinetic data with antiretrovirals, bile acid sequestrants should be avoided as much as possible. When coadministered, antiretrovirals should be given at least 1 hour before or 4-6 hours after bile sequestering agents.[62,63]

Ezetimibe

Ezetimibe is metabolized primarily via glucuronide conjugation with subsequent biliary and renal excretion.[64] Coadministration of ezetimibe with ritonavir-boosted protease inhibitors could reduce ezetimibe exposures via UGT induction. However, the clinical significance of this potential interaction is unknown. Cobicistat does not induce UGT and is not expected to affect concentrations of gemfibrozil or ezetimibe.

Fibrates

Approximately 50% of bezafibrate is eliminated unchanged in urine, and fenofibrate is metabolized via hydrolysis to its active form, fenofibric acid. Therefore, these drugs are not anticipated to have significant interactions with antiretrovirals.[65,66] Coadministration of ritonavir did not significantly affect the pharmacokinetics of fenofibrate.[67]

Gemfibrozil is mainly metabolized by UGT.[68] Coadministration of gemfibrozil with ritonavir-boosted protease inhibitors could potentially decrease gemfibrozil exposures via UGT induction. When gemfibrozil 600 mg was given together with a ritonavir-boosted protease inhibitor, gemfibrozil exposure was reduced by 41%.[69]

HMG-CoA reductase inhibitors

Simvastatin and lovastatin are extensively metabolized by CYP3A4.[70,71] A 32-fold increase in simvastatin AUC was observed with high-dose (> 100 mg) ritonavir and simvastatin 40 mg.[72] Severe rhabdomyolysis and hepatotoxicity has been reported with combined use of simvastatin and ritonavir.[73] In another study, 2 patients receiving lovastatin experienced myalgia and 1 also had creatinine kinase elevations of 5.4-fold above the upper limit of normal during protease inhibitor treatment.[74] Therefore, the use of simvastatin and lovastatin is contraindicated with all protease inhibitors and cobicistat.[70,71] In contrast, efavirenz, etravirine, and nevirapine could potentially decrease the concentrations of simvastatin and lovastatin. When efavirenz was coadministered with simvastatin 40 mg, the AUC of simvastatin was reduced by 68%, and active 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitory activity decreased by 60%.[38]

Atorvastatin is a substrate of CYP3A4 and OATP1B1.[75] Studies have shown that the extent of the interaction with atorvastatin is affected by the specific antiretrovirals used including the boosting agent (ritonavir or cobicistat). As an example, atorvastatin AUC was increased 822% when coadministered with atazanavir/cobicistat[76] and by 290% with darunavir/cobicistat. When darunavir was boosted with ritonavir, atorvastatin exposure with a dose of 10 mg was approximately equivalent to 40 mg when atorvastatin was used alone.[77] With the exception of atazanavir/cobicistat, which is not recommended, the current strategy for the dosing of atorvastatin with ritonavir or cobicistat is to limit the dose to 20 mg/d and monitor for typical adverse effects associated with statins.[8] However, efavirenz decreased the AUC of atorvastatin 10 mg/d by 43%,[38] therefore monitoring of lipid parameters and dose adjustment as necessary is recommended in patients when starting efavirenz and nevirapine treatment.

Rosuvastatin is partially metabolized by CYP2C9, and transported by OATP1B1 and BCRP.[78] The magnitude of interactions between rosuvastatin and protease inhibitors or cobicistat varies, because not all protease inhibitors are inhibitors of OATP1B1 and BCRP. Atazanavir, ritonavir, and cobicistat are inhibitors of both of these drug transporters,[36,60,61,79] whereas darunavir is not.[77] The largest increases in rosuvastatin exposures were observed with boosted atazanavir, with AUC increases of 213%-242% with either atazanavir/ritonavir or atazanavir/cobicistat.[76,80] Smaller increases in rosuvastatin AUC of 48% and 93% were seen with darunavir/ritonavir and darunavir/cobicistat, respectively.[76,81] Rosuvastatin AUC increased 38% when used in combination with elvitegravir/cobicistat.[82] In summary, there is a consensus in the literature that increased exposure of rosuvastatin is expected with cobicistat or ritonavir. Limiting the total daily dose of rosuvastatin to 20 mg and frequent monitoring are suggested strategies to prevent toxicity. Interactions between rosuvastatin and NNRTIs are not expected, because NNRTIs are not inhibitors of OATP1B1 and/or BCRP.[38,39,83,84]

Clinically significant interactions were not observed between pravastatin and various ritonavir-boosted protease inhibitors.[85,86] However, pravastatin AUC was reduced by 40% when coadministered with efavirenz.[87] Similar decreases might be anticipated with etravirine and nevirapine.

Fluvastatin is primarily metabolized by CYP2C9 and transported by OATP1B1/3 and OATP2B1.[88] Although coadministration has not been studied, plasma concentration of fluvastatin could possibly increase when coadministered with ritonavir- or cobicistat-boosted protease inhibitors or elvitegravir/cobicistat via inhibition of OATP1B1. Because ritonavir and elvitegravir also induce CYP2C9, the opposite effects might limit the magnitude of the interaction. Although there are no clear recommendations, fluvastatin should be initiated at the lowest dose and titrated up as tolerated and clinically indicated.

Pitavastatin (not approved in Canada) is not expected to have drug interactions with antiretrovirals. Significant interactions were not observed between pitavastatin and either ritonavir-boosted darunavir or efavirenz.[89]

Proprotein convertase subtilisin/kexin 9 inhibitors

The proprotein convertase subtilisin/kexin 9 is a new target, which has led to the development of monoclonal antibodies alirocumab and evolocumab, resulting in an increased clearance of low-density lipoprotein cholesterol. Similar to other immunoglobulins, proprotein convertase subtilisin/kexin 9 inhibitors are not metabolized by CYP450 isoenzymes and not expected to interact with antiretrovirals.[90]

Anticoagulant and Antiplatelet Agents

Anticoagulants

Dabigatran is primarily eliminated renally. However, the prodrug dabigatran etexilate is a substrate for P-gp.[91] Administration of dabigatran and ritonavir simultaneously did not change dabigatran AUC. However, when dabigatran was given 2 hours before ritonavir, the AUC of dabigatran decreased by 29%.[92]

Cobicistat, whether administered simultaneously or separated by 2 hours, increased dabigatran AUC by 110%-127%.[92]

Two case reports of concomitant dabigatran use with ritonavir-boosted protease inhibitors in patients with atrial fibrillation have been published.[93,94] In the first case, the authors found no significant difference in dabigatran plasma concentrations at a dose of 110 mg twice daily in a patient receiving ritonavir-boosted lopinavir.[93] In the second case, dabigatran was titrated from 110 mg daily to 150 mg twice daily with dabigatran concentrations within the expected range in a patient receiving ritonavir-boosted atazanavir.[94] Dabigatran treatment was well tolerated and no bleeding or thrombotic events were observed over a 12-month follow-up period.[94]

Rivaroxaban and apixaban are substrates of CYP3A4 and P-gp.[95,96] Although drug interaction data are not available for apixaban, ritonavir 600 mg twice daily increased the AUC of rivaroxaban by 2.5-fold.[95] Two case reports of bleeding associated with rivaroxaban and concomitant protease inhibitors have been published.[97,98] Likewise, a case report described decreased clinical effect of rivaroxaban with concurrent use of nevirapine.[99] Thus, on the basis of available data, protease inhibitors and cobicistat are expected to increase concentrations of rivaroxaban and apixaban, whereas efavirenz, etravirine, and nevirapine might decrease concentrations of rivaroxaban and apixaban.

Edoxaban is a substrate of P-gp *in vitro*; although data are limited, P-gp inhibitors or inducers might increase or decrease edoxaban concentrations, respectively.[100]

There are no agreements with regard to the coadministration of direct oral anticoagulants (DOACs) and cobicistat or ritonavir. According to Canadian product monographs for cobicistat, rivaroxaban and apixaban are contraindicated whereas dabigatran and edoxaban coadministration with cobicistat should include enhanced monitoring for bleeding and/or dose adjustment of DOAC as necessary.[37] The US Food and Drug Administration recently announced label changes for several HIV regimens containing cobicistat to highlight interactions with DOACs. It is recommended to avoid rivaroxaban with all cobicistat-boosted regimens. When used with elvitegravir/cobicistat, the dose of apixaban should be reduced by 50% as per the manufacturer recommendations, whereas dosing of dabigatran and edoxaban depends on DOAC indication and renal function.[8,101] Cobicistat-boosted darunavir can be coadministered without dose adjustment with dabigatran and edoxaban.[102] Regardless of specific recommendations, there is agreement in product labelling in Canada and the United States that the DOAC anticoagulation effect might be increased when used with ritonavir or cobicistat. Switching antiretrovirals to those without CYP450 inhibition should be considered.

Warfarin is available as a racemic mixture; S-warfarin is more potent and is primarily metabolized by CYP2C9, whereas the R-isomer is metabolized by CYP1A2 and CYP3A4.[103] A number of case reports have described interactions between warfarin and protease inhibitors, NNRTIs, as well as cobicistat-boosted elvitegravir.[104,105] Depending on the specific drug used, induction or inhibition of warfarin metabolism might occur, and therefore close monitoring of international normalized ratio is recommended.

Antiplatelet agents

There are limited studies evaluating drug interactions between antiplatelet and antiretroviral drugs. Therefore, potential interactions are in many cases derived on the basis of *in vitro* data or pharmacokinetic characteristics of individual agents. Clinically significant interactions between antiretrovirals and low-dose aspirin or prasugrel are unlikely. Although prasugrel is a prodrug that is bioactivated to its active metabolite by CYP3A4,[106,107] administration of the potent CYP3A4 inhibitor ketoconazole did not significantly affect the AUC of the prasugrel active metabolite or inhibition of platelet aggregation.[108] This might be due to additional CYP450 isoenzymes involved in formation of the prasugrel active metabolite.[107] Clopidogrel is bioactivated by CYP2C19[109]; efavirenz and etravirine are inhibitors of CYP2C19[110,111] and might reduce formation of the clopidogrel active metabolite. On the basis of *in vitro* data, efavirenz is predicted to reduce the AUC of clopidogrel's active metabolite by up to 30%.[110] Ticagrelor, however, is primarily metabolized by CYP3A4.[112,113] Inhibitors of CYP3A4 (eg, protease inhibitors, cobicistat) as well as inducers (eg, efavirenz, etravirine, nevirapine) are likely to increase or decrease ticagrelor concentrations, respectively, and therefore should be avoided. In these cases, alternative antiplatelet agents such as prasugrel may be considered.

Antiarrhythmics

Amiodarone

Amiodarone is primarily metabolized to its major active metabolite, desethylamiodarone, via CYP3A4. It is also a substrate for CYP2C8 and P-gp and an inhibitor of CYP3A4, 2C9, 2D6, and P-gp. Although studies have not been done, coadministration of amiodarone with protease inhibitors and cobicistat would be expected to increase the exposures of amiodarone, potentially increasing the risk of serious or life-threatening cardiovascular toxicities including cardiac arrhythmias.[59,114] In one case report, a patient receiving stable amiodarone of 200 mg/d started the protease inhibitor indinavir for 4 weeks as part of HIV post-exposure prophylaxis.[115] Amiodarone concentrations increased by 44%, from 0.9 mg/L before the start of indinavir to 1.3 mg/L, and gradually decreased to baseline after stopping indinavir. Desethylamiodarone concentrations remained unchanged. No symptoms of amiodarone toxicity were observed, possibly because this patient did not achieve amiodarone concentrations that would be expected to be associated with toxicity.[114] Thus, precaution is still warranted in patients receiving concurrent amiodarone, particularly those with higher baseline amiodarone concentrations. Because protease inhibitors are also P-gp substrates, amiodarone could also theoretically increase the exposures of protease inhibitors through P-gp inhibition; however, the interaction is unlikely to be clinically significant. In contrast, efavirenz, nevirapine, and etravirine might decrease amiodarone exposures via CYP3A4 induction.

Dronedarone

Dronedarone is primarily metabolized by CYP3A4 and is a moderate inhibitor of CYP3A4 and a mild inhibitor of

CYP2D6.[116] Coadministration of dronedarone with protease inhibitors or cobicistat is contraindicated because of a potentially significant increase in dronedarone exposures and risk of cardiac arrhythmia.

Flecainide and mexiletine

Flecainide is a substrate and inhibitor of CYP2D6,[117,118] whereas mexiletine is metabolized by CYP2D6 and CYP1A2.[119] Although ritonavir and cobicistat are not anticipated to inhibit CYP2D6 at boosting doses, coadministration of flecainide and mexiletine with ritonavir or cobicistat-boosted regimens is not recommended because these agents have a narrow therapeutic index.[36,51,52,59,61,77] Cardiac and neurologic events have been reported when ritonavir was given concurrently with mexiletine.[36] An increase in flecainide exposures could lead to serious adverse events, including arrhythmias. If concurrent administration is necessary, electrocardiogram (ECG) monitoring and therapeutic drug monitoring should be considered.[117]

Propafenone

Propafenone is metabolized by CYP2D6, CYP3A4, and CYP1A2.[120] Although coadministration has not been studied, propafenone should not be given together with protease inhibitors or cobicistat because of a potential increase in propafenone exposures, causing serious adverse events, such as cardiac arrhythmia.[36,59,61,77] If coadministration is necessary, ECG monitoring and therapeutic drug monitoring of propafenone should be considered. Use of propafenone with efavirenz, nevirapine, and etravirine could theoretically result in decreased propafenone exposures.

Other Cardiac Agents

Calcium channel blockers

Calcium channel blockers (CCBs) are primarily metabolized by CYP3A4 and therefore pharmacokinetic and pharmacodynamic interactions can be expected when coadministered with agents that inhibit or induce this CYP isoenzyme.[121-125] CCB exposures might be increased by protease inhibitors or cobicistat. Amlodipine and diltiazem exposures were increased 90% and 27%, respectively, in the presence of twice daily ritonavir-boosted protease inhibitors, with 15% of participants having greater than fourfold increases in diltiazem AUC.[126] Furthermore, the protease inhibitor atazanavir used without ritonavir increased diltiazem AUC by 125% and had an added effect on the PR interval.[79] Reports describing cases of second- or third-degree atrioventricular block, PR prolongation and severe hypotension with coadministration of nifedipine and ritonavir-boosted protease inhibitors have been published.[126,127] Coadministration of a CCB with ritonavir-boosted protease inhibitors, especially atazanavir, should be undertaken with caution and ECG monitoring is recommended.[8] Dose reduction of CCBs by 50% should be considered when using regimens containing protease inhibitors or cobicistat. In contrast, the NNRTI efavirenz was shown to decrease diltiazem AUC by 69%.[38] Etravirine and nevirapine might also be expected to reduce CCB exposures.

Others

Digoxin is a P-gp substrate,[128] and exposures were increased by 36% when coadministered with ritonavir-boosted protease inhibitors[77] and by 20% with cobicistat.[51] Etravirine is also a weak P-gp inhibitor and increased digoxin AUC by 18%.[39] There are 2 case reports that described elevated digoxin concentrations and symptoms of toxicity in patients receiving stable digoxin therapy who initiated antiretrovirals, including ritonavir at doses of 100-400 mg/d.[129,130] Because digoxin has a narrow therapeutic index, caution is recommended when coadministered with cobicistat, ritonavir, and etravirine; monitoring of digoxin serum concentrations might be helpful in guiding possible dose adjustments.

Ivabradine and its major active metabolite are extensively metabolized by CYP3A4. Coadministration of potent CYP3A4 inhibitors with ivabradine led to an increase in ivabradine AUC by seven- to eightfold.[131] Substantial increases in ivabradine exposures are expected with protease inhibitors and cobicistat, potentially increasing the risk of bradycardia. Conversely, CYP3A4 inducers such as efavirenz, nevirapine, and etravirine could reduce the concentrations of ivabradine, compromising its efficacy. Severe adverse events, including sinus bradycardia and hypotension, were observed in a patient receiving ritonavir-boosted atazanavir after starting treatment with ivabradine 5 mg twice daily, which resolved upon ivabradine discontinuation.[132]

QTc Prolongation

People living with HIV have a higher prevalence of QTc interval prolongation when compared to the general population.[133-135] Although the specific mechanisms leading to QTc prolongation are not entirely clear, concomitant drug therapy, the presence of other comorbidities, as well as the viral infection itself might be contributing factors.[136-139] Studies have shown that prolongation of QTc interval is associated with the duration of HIV infection,[136] low CD4 count,[138,140] and high viral load,[140] as well as being naive to antiretroviral therapy,[141] suggesting that uncontrolled or advanced HIV disease might play a role. Studies have also shown that cardiac autonomic neuropathy can occur in patients with advanced HIV,[142] and that autonomic neuropathy is linked to QTc prolongation.[139] Traditional risk factors for QTc interval prolongation such as female sex, diabetes mellitus, and arterial hypertension are also important in people living with HIV.[137]

Certain antiretrovirals, particularly those belonging to the protease inhibitor class, have been associated with QTc prolongation in healthy volunteer studies.[143] *In vitro* data showed that protease inhibitors block human ether-a-go-go-related gene potassium channels in a dose-dependent manner.[144] However, data from large HIV cohorts as well as prospective studies have not shown an association between specific drugs and QTc prolongation.[135,137,145] Nonetheless, people living with HIV are frequently prescribed other agents known to prolong the QTc interval including methadone, clarithromycin, pentamidine, moxifloxacin, and several psychotropic medications.[146] Methadone especially has a strong

dose-dependent effect on the QTc interval[147] and has been independently associated with QTc prolongation in HIV patients.[141] ECG monitoring might therefore be needed in people living with HIV, who are receiving medications and/or have comorbidities that increase the risk of QTc prolongation and torsades de pointes.

HIV Drug Interaction and Other Useful Resources

There are a few trusted HIV drug interaction resources that can be valuable tools for health care professionals,[148] understanding that these are limited to drug-drug interactions with antiretrovirals. Drug-drug interactions between non-HIV drugs still need to be considered using general drug-drug interaction resources such as product monographs, Micromedex, or LexiComp.

HIV/HCV Drug Therapy Guide. University Health Network - Toronto General Hospital (http://app.hivclinic.ca)

- Mobile app available for free download on the Google and Apple stores.
- This Web site/app provides up-to-date and evidence-based data on HIV and hepatitis C virus drug interactions with recommendations and references. It also provides a link to interaction checks with medications from similar classes.

University of Liverpool. HIV Drug Interactions (https://www.hiv-druginteractions.org/checker)

- Mobile app available for free download on the Google and Apple stores.
- This Web site/app provides current and evidence-based information on HIV drug interactions with recommendations. Users can switch to "table view" to see a summary table of interactions between HIV and non-HIV medications. Results could be downloaded in PDF format and printed. There is a separate Web site for hepatitis C virus drug interactions with other comedications.

HIV InSite. University of California, San Francisco (http://hivinsite.ucsf.edu/insite?page=ar-00-02)

- This resource provides comprehensive and evidence-based data on HIV drug interactions. Users can search by antiretroviral agent, interacting drug, or interacting drug class.

US Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV (https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/367/overview)

- Mobile app available for free download on the Google and Apple stores.
- This Web site provides evidence-based guidelines regarding the management of people living with HIV with a section on useful HIV drug interactions.

CredibleMeds (https://www.crediblemeds.org)

- This Web site provides a list of drugs associated with QTc prolongation and torsade de pointes. An app is also available.

Conclusion

In summary, as people living with HIV infection age and experience general age-related comorbidities including heart disease, there is potential for clinically significant interactions between antiretrovirals and commonly used drugs in cardiology medicine. Cardiologists should pay close attention when etravirine, nevirapine, efavirenz, protease inhibitors such as darunavir and atazanavir, and pharmacokinetic enhancers cobicistat and ritonavir are prescribed. These antiretrovirals might increase or decrease exposures of certain cardiology drugs such as statins, anticoagulants, antiplatelets, CCBs, or antiarrhythmics, thereby increasing the risk of toxicity or suboptimal efficacy. Conversely, with the exception of bile acid sequestrants, cardiac drugs are not expected to lead to significant drug interactions affecting antiretroviral activity. Although not discussed in this review, people living with HIV might be also using drugs for the management of related conditions (eg, opportunistic infections, mental health and substance use issues, etc), which add to the complexity of treatment. Drug-drug interactions can be managed by using antiretroviral agents or cardiac drugs that are less likely to interact, adjusting the dose of cardiac drugs, and/or close monitoring depending on the specific drugs involved. A number of up-to-date on-line HIV drug interaction resources are available to help in the recognition and management of these interactions. Collaboration and good communication between cardiologists, HIV physicians, and pharmacists are key elements for the provision of safe and optimal patient care.

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