Journal of
HYPERTENSION RESEARCH
www.hypertens.org/jhr

Review

J Hypertens Res (2018) 4(3):78–89

Cardiovascular disease and HIV infection: a review of drug interactions with the antiretroviral therapy

Cristian-Mihail Niculae [1], Adriana Hristea [1,2], Adrian Streinu-Cercel [1,2] *

[1] National Institute for Infectious Diseases "Prof. Dr. Matei Bals", Bucharest, Romania
[2] University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania

Received: August 19, 2018, Accepted: September 21, 2018

Abstract

In the era of highly active antiretroviral therapy (HAART) people living with HIV (PLWHIV) live longer, HIV infection become a chronic condition, with a great impact not only for the infectious diseases specialists, but also for cardiologists and all the physicians from the much-needed "HIV team". These patients are at bigger risk for a variety of non-HIV/AIDS comorbidities, and the cardiovascular diseases (CVD) are major causes of morbidity and mortality.

Keywords: cardiovascular, HIV, antiretroviral

1. Introduction

1.1. The burden of cardiovascular disease and HIV infection

In the era of highly active antiretroviral therapy (HAART) people living with HIV (PLWHIV) live longer, HIV infection become a chronic condition, with a great impact not only for the infectious diseases specialists, but also for cardiologists and all the physicians from the much-needed "HIV team". These patients are at bigger risk for a variety of non-HIV/AIDS comorbidities, and the cardiovascular diseases (CVD) are major causes of morbidity and mortality.

In the D:A:D study (Data Collection of Adverse events of Anti-HIV Drugs) which is one of the major databases on cardiovascular risk factors, with 33.308 HIV-positive patients included, during the 10-year observation period (1999-2008), CVD-related deaths were the third most common cause after AIDS and liver-related death [1]. Although the global mortality has decreased over the last 10 years among HIV-positive patients, the pattern of CVD-related deaths has changed towards an important increase over the same period of time (from 1.9% to 4.6%) [2]. The risk of coronary heart disease (CHD) and acute myocardial infarction (AMI) is nearly twice greater in PLWHIV compared to uninfected people and can increase by 7- to 10-fold in patients with traditional cardiovascular risk factors [3].

A systematic review and a meta-analysis found that HIV infection represent a vascular risk factor and that geographical factors might influence the rates of vascular disease, reflecting on one hand different prevalence

* Correspondence to: Professor Adrian STREINU-CERCEL, MD, PhD
National Institute for Infectious Diseases "Prof. Dr. Matei Bals",
1 Dr. Calistrat Grozovici Str., Bucharest 021105, Romania.
e-mail: strega@mb.roknet.ro

Table 1. Risk of death and vascular disease among PLWHIV.

	United States (14 studies) vs Europe (13 studies) IRR (95%CI)	HIV positive vs HIV negative HR (95% CI)
All death	1.78 (1.69+/-1.88)	4.77 (4.55+/-5.00)
Myocardial infarction	1.61 (1.29+/-2.01)	1.60 (1.49+/-1.72)
Any coronary heart disease	2.27 (1.92+/-2.68)	1.20 (1.15+/-1.25)
Any stroke	1.94 (1.59+/-2.38)	1.82 (1.53+/-2.16)
Ischemic stroke	1.56 (1.23+/-1.98)	1.27 (1.15+/-1.39)
Intracranial hemorrhage	4.03 (2.72+/-6.14)	2.20 (1.61+/-3.02)

of vascular risk factors and on the other hand socioeconomic factors. The systematic review included 44 cohorts enrolling 334.417 PLWHIV and among them 49% were from the United States. The incidence rate ratio of death, myocardial infarction, any coronary heart disease, any stroke, ischemic stroke or intracranial hemorrhage between PLWHIV in the United States vs Europe are shown in Table 1, and also the hazard ratio for the same variables in HIV-infected people vs non-infected people [4].

The mechanisms associated with the CVD-related risk among PLWHIV are multifactorial and an important effort is necessary to elucidate, but also to prevent and/or reduce them in order to improve CVD outcomes.

1.2. CVD risk factors among HIV-positive patients

What contributes to HIV-associated CVD is a combination of traditional (eg, smoking, dyslipidemia, high blood pressure, diabetes, obesity) and non-traditional risk factors (eg hepatitis C co-infection, cocaine use) for CHD, the virus itself, through HIV mediated inflammation despite antiretroviral therapy (ART) but also the side effects of ART (table 2) [1-15]. Some traditional risk factors (like smoking, dyslipidemia) are more commonly seen among PLWHIV vs people HIV non-infected. Low nadir CD4 cell count, high viral load, long term HIV infection, the lack of ART are associated with a greater risk of CVD.

2. Cardiovascular drug-drug interactions with antiretroviral drugs

HIV infection become a chronic condition and antiretroviral drugs (ARVs) are used by an aging patient population who is and will be at increased risk for a variety of non-HIV/AIDS comorbidities, CVD being of important concern. Therefore, with the additional medications, we face a growing risk of potential drug-drug interactions, which can be very important for our clinical practice. Not only the multiple comorbidities and associated medications, but also a lot of other factors contribute to clinical interactions between drugs in general. Genetic polymorphisms, with interindividual differences regarding drug metabolization rates, but also age and sex, they are all important.

Metabolization and elimination of a drug requires some molecular steps in order to complete a complex process of inhibition/induction of enzymes production. Mainly two metabolic pathways are implicated: first, and most important, hemoproteins superfamily of cytochrome P450 (protease inhibitors and nucleoside reverse transcriptase inhibitors being metabolized especially by CYP3A4 in gastrointestinal tract and hepatocytes), which is a potential substrate for many other drugs and this can lead to clinically significant interactions; the other pathway is the glucuronidation process, but with a low potential to cause relevant drug-drug interactions.

Table 2. Cardiovascular disease risk factors in HIV-positive patient

1. Traditional CVD risk factors	**Smoking** 38 vs. 18 % (non-HIV)5 37.5 % (HIV study) [6]	**Hypertension** 21 vs. 16 % (non-HIV) [5]	**Metabolic disorders** **DM**: 12 vs. 7 % (non-HIV)5 **Dyslipidemia**: 23 vs. 18 % (non-HIV) [5]; 38.5 % (HIV study) [6]
2. Non-traditional CVD risk factors	**Hepatitis C co-infection** ≥ 10 milion people globally [7]; Higher risk of CVD vs. HIV-monoinfection in a meta-analysis (adjusted hazard ratios: 1.24) [8]; Higher levels of endothelial markers (sICAM-1 and sVCAM-1), CIMT, homocysteine, and IL-6; secondary inflammation/vascular dysfunction [7]		**Cocaine use** Associated with an ≈3-fold higher odds of carotid plaque at baseline – independent risk factor [9]; Higher CV risk in HIV+ maybe due to combined effect, but also secondary to kidney damage [10];
3. HIV infection related [11,12]	Microbial translocation, coinfections and immune activation & viral replication → Chronic inflammation, coagulation disorders, vascular-endothelial dysfunction and atherosclerosis;	↑ IL-6, TNF-α, CRP, LPS, sCD14, sCD163, activated monocytes/macrophages/other cells; ↑ D-dimers, fibrinogen, factor VII, tissue factor, von Willebrand factor, platelet activation; Endothelial cells and vascular smooth muscle cells: ↑ ROS, RAS, VCAM-1, ↓ NO	
4. Adverse effects of ARVs Drug Classes	**NRTIs**	**NNRTIs**	**PIs**
• **Ischemic heart disease (IHD) [13–15]**	ABC, ddI: ↑ risk of IHD and myocardial infarction in some cohort studies (D:A:D study, SMART study)	-	LPV/r, FPV, IDV and DRV/r: ↑ risk of IHD
• **Insulin resistance and/or DM13,15**	ddI, d4T, ZDV	-	IDV, LPV/r
• **Dyslipidemia[13-16]**	d4T > ZDV > ABC:↑ LDL and TG	EFV: ↑ TG, ↑ LDL, ↑ HDL -	All Ritonavir-boosted PIs LPV/r > DRV/r and ATZ/r: ↑ TG
• **Body fat [13]**	TAF: ↑ TG, ↑ LDL, ↑ HDL (no change in TC:HDL ratio) d4T, ZDV: lipoatrophy		IDV: ↑ abdominal fat

Abbreviations: DM: diabetes mellitus; ICAM: intracellular adhesion molecule; VCAM: vascular cell adhesion molecule; CIMT: carotid intima-media thickness; Il-6: interleukin 6; CRP: C-reactive protein; TNF: tumor necrosis factor; LPS: lipopolysaccharide; sCD14/CD163: soluble CD14/CD163; ROS: reactive oxygen species; NO: nitrogen oxide; Bold drugs: drugs available in Romania; NRTI: nucleoside reverse transcriptase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors; PIs: protease inhibitors; ABC: abacavir; ddI: didanosine; d4T: stavudine; ZDV: zidovudine; EFV: efavirenz; r: ritonavir; LPV: lopinavir; FPV: fosamprevir; IDV: indinavir; SQV: saquinavir; DRV: darunavir; ATZ: atazanavir; TAF: tenofovir alafenamide; ARVs: antiretrovirals.

2.1. Calcium channel blockers

Potential drug-drug interactions are expected with calcium channel blockers (CCB), especially when combined with PIs (can increase the serum levels of CCB) and NNRTIs (in this combination, serum levels of CCB might be fluctuating) (table 3). CCB are mainly metabolized by CYP3A4 and this is the mechanism of potential interaction with some NNRTIs

Table 3. Selected drug-drug interactions with some Ca2+ channel blockers [13, 16–18].

Drug	NRTI					NNRTI				PIs (boosted)			INSTIs	
	ABC	3TC	FTC	TDF	ZDV	EFV	ETV	NVP	RPV	ATV	DRV	LPV	RAL	DTG
Amlodipine	+	+	+	+	+	+/-	+/-	+/-	+	+/-[3]	+/-[3]	+/-[3]	+	+/-
Nifedipine	+	+	+	+	+	+/-	+/-	+	+	+/-	+/-	+/-	+	+
Nicardipine	+	+	+	+	+	+/-	+/-	+/-	+/-[4]	+/-	+/-	+/-	+	+
Verapamil	+	+	+	+/-[1]	+	+/-	+/-	+/-	+/-[4]	+/-	+/-	+/-	+	+
Diltiazem	+	+	+	+	+	+/-[2]	+/-	+/-	+/-[4]	+/-[3]	+/-	+/-	+	+

[1] Potential elevated exposure of TDF [13]; TDF is a substrate of the efflux pump P-glycoprotein (P-gp) – inhibitors such as verapamil might increase its absorbtion and TDF systemic concentration [17]

[2] Potential decreased diltiazem Cmax (60%), AUC (69%) and Cmin (63%); Cmax, Cmin and AUC of EFV are increased, but no dose adjustment is required [13,17]

[3] Unboosted ATV ↑ diltiazem AUC 125% and greater ↑ likely with boosted ATV (can consider to decrease diltiazem dose by 50%) [16,17] also, consider dose reduction of amlodipine with 50% if coadministered with ATV/r, LPV/r and DRV/r [17]

[4] Potential elevated exposure of ARV [13]; verapamil, diltiazem and nicardipine are metabolized by CYP3A4 and they can inhibits this cytochrome, therefore might increase RPV concentrations [17]

and PIs. Also, some PIs (ATV, LPV) could increase the PR interval (potential to induce first degree atrioventricular block). These potential clinically significant interactions may require additional clinical monitoring, especially blood pressure and serial electrocardiography (ECGs) and also dose adjustment. Low doses of CCB can be considered for starting therapy.

2.2. Beta-blockers

Drug-drug interaction with this class of drugs are few and if they occur, the potential interaction is likely

Table 4. Selected drug-drug interactions with some beta-blockers [13, 16-18].

Drug	NRTI					NNRTI				PIs (boosted)			INSTIs	
	ABC	3TC	FTC	TDF	ZDV	EFV	ETV	NVP	RPV	ATV	DRV	LPV	RAL	DTG
Atenolol	+	+	+	+	+	+	+	+	+	+/-[1]	+	+/-[1]	+	+/-
Carvedilol	+	+	+	+	+	+/-[2]	+/-[2]	+	+	+/-[2]	+/-[2]	+/-[2]	+	+
Metoprolol	+	+	+	+	+	+	+	+	+	+/-[3]	+/-[3]	+/-[3]	+	+
Propranolol	+	+	+	+	+	+	+	+	+	+/-[3]	+/-[3]	+/-[3]	+	+

[1] Potential interaction of weak intensity with pharmacological boosters such as ritonavir/cobicistat [13]

[2] Potential interaction of weak intensity (elevated/decreased exposure of beta-blocker) [13]

[3] Potential interaction of weak intensity (elevated exposure of beta-blocker) [13]

Table 5. Selected drug-drug interactions with some diuretics [13, 16-18].

Drug	NRTI					NNRTI			PIs (boosted)				INSTIs	
	ABC	3TC	FTC	TDF	ZDV	EFV	ETV	NVP	RPV	ATV	DRV	LPV	RAL	DTG
Furosemide	+	+	+	+/-[1]	+	+	+	+	+	+	+	+	+	+
Indapamide	+	+	+	+	+	+/-	+/-	+/-	+	+/-	+/-	+/-	+	+
Spironolactone	+	+	+	+	+	+	+	+	+	+	+	+	+	+

[1] Potential interaction of weak intensity [13]

to be of no clinical impact. In selected cases it is recommended to start with the lowest dose of beta-blocker and to adjust the dose if necessary, in order to obtain the desired clinical effect. Particular metabolism pathway for every beta-blocker drug could explain this low interaction potential in clinical practice. Atenolol is a hydrophilic beta-blocker, excreted mainly by kidneys via glomerular secretion and active tubular secretion via organic cation transporters (OCT2) and multidrug and toxin extrusion 1 (MATE1); there could be some potential interaction especially with dolutegravir by inhibiton of OCT2 and a secondary increase in atenolol exposure by 80% or 110% [17]. Carvedilol is glucuronidated especially by uridine diphosphate glucuronosyltransferases – UGT1A1, UGT2B4 and UGT2B7, but also metabolized by cytochromes CYP2D6, CYP2C9 and CYP1A2 [17]. Metoprolol is metabolized mainly by CYP2D6 and propranolol by CYP2D6, but also CYP1A2, CYP2C19 and direct glucuronidation [17].

2.3. Diuretics, angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers

2.3.1. Diuretics

Coadministration of ARVs with diuretics has not been studied but recommendations can be done based on particular drug metabolism and clearance.

Furosemide is glucuronidated especially in the kidney by uridine diphosphate glucuronosyltransferase (UGT1A9), but also in the liver by UGT1A1 [17,19,20]. A large proportion is eliminated unchanged renally via organic anion transporters (OATs) located in the renal proximal tubules [17,20]. Almost all ARVs are not expected to inhibit/induce UGTs at clinically relevant concentrations or to inhibit the renal transporters OATs. Therefore, significant drug-drug interactions between ARVs and furosemide are not expected (table 5) [13]. Spironolactone is metabolized in the liver partly by the protein family of flavin-containing monooxygenase (FMOs) [13,17,21]. Because ARVs do not interfere with this metabolic pathway, significant drug-drug interactions are not expected (table 5) [13,17]. Indapamide is metabolized by CYPP450.17 Therefore, both PIs and some NNRTIs, by interfering with CYP P450 complex, could increase (PIs) or decrease (NNRTIs) indapamide concentrations. It is important to monitor the clinical effects and to adjust the dose of indapamide if necessary (table 5).

2.3.2. Angiotensin-converting-enzyme inhibitors

Potential clinically significant drug-drug interactions between ARVs and angiotensin-converting-enzyme (ACE) inhibitors are unlikely. Although coadministrations were not studied, as well as with diuretics, recommendations can be done based on drug's metabolism and clearance.

Captopril is excreted in the urine in large amounts, half of it as an unchanged drug and the rest as disulfide forms and some other metabolites [17]. Therefore, none of the ARVs could interfere with its excretion pathway. Enalapril is a drug metabolised by hydrolyzation to enalaprilat which is eliminated by the kidneys via OATs. ARVs are not expected to inhibit these renal transporters at clinically relevant concentrations.

Table 6. Selected drug-drug interactions with some ACE inhibitors [13, 16-18].

Drug	NRTI					NNRTI				PIs (boosted)			INSTIs	
	ABC	3TC	FTC	TDF	ZDV	EFV	ETV	NVP	RPV	ATV	DRV	LPV	RAL	DTG
Captopril	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Enalapril	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perindopril	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ramipril	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Ramipril is metabolised by liver and kidneys to both a glucuronate conjugate and a diketopiperazine derivative. Therefore, most of it is excreted in the urine as ramiprilat, as well as the glucuronate conjugate of ramiprilat [22]. Perindopril is another drug metabolised by hydrolyzation to perindoprilat and other inactive metabolites, which are eliminated via urine, therefore no interactions with ARVs are expected [17].

2.3.3. Angiotensin antagonists

Coadministration of ARVs with angiotensin antagonists has not been studied but recommendations can be done based on particular drug's metabolism and clearance.

Drug-drug interactions are unlikely to occur at a clinically relevant level with candesartan, losartan, telmisartan and olmesartan (table 7). Candesartan is mainly excreted unchanged via urine and bile. Losartan is metabolized to its active form especially at the level of CYP2C9 and no clinically significant interaction is expected with ARVs.17 Telmisartan is glucuronidated especially by UGT1A3 and drug-drug interactions are unlikely [17]. Valsartan is a drug metabolized in the liver, being a substrate for an organic-anion-transporting polypeptide (OATP1B1) and for a multidrug resistance-associated protein (MRP2). Its concentrations may be increased due to inhibition of these hepatic transporters by PIs and pharmacologic boosters such as ritonavir and cobicistat [17]. It is recommended to

Table 7. Selected drug-drug interactions with some angiotensin antagonists [13, 16-18].

Drug	NRTI					NNRTI				PIs (boosted)			INSTIs	
	ABC	3TC	FTC	TDF	ZDV	EFV	ETV	NVP	RPV	ATV	DRV	LPV	RAL	DTG
Candesartan	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Losartan	+	+	+	+	+	+/-[2]	+/-[2]	+	+	+/-[1]	+/-[1]	+/-[1]	+	+
Telmisartan	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Valsartan	+	+	+	+	+	+	+	+	+	+/-[3]	+/-[3]	+/-[3]	+	+

[1] Potential interaction of weak intensity for ritonavir boosted PIs (decreased angiotensin antagonist levels) [13];

[2] Potential interaction of weak intensity (increased angiotensin antagonist levels) [13];

[3] Potential elevated exposure of valsartan [13,17]

Table 8. Selected drug-drug interactions with Class I antiarrhytmic drugs [16-18].

Drug	NRTI					NNRTI				PIs (boosted)			INSTIs	
	ABC	3TC	FTC	TDF	ZDV	EFV	ETV	NVP	RPV	ATV	DRV	LPV	RAL	DTG
Chinidine	+	+	+	+/-	+	+/-	+/-	+/-	+/-	-	-	+/-	+	+
Flecainide	+	+	+	+	+	+	+/-	+	?	-	+/-	-	+	+
Lidocaine	+	+	+	+	+	?	+/-	+/-	+	+/-	+/-	+/-	+	+
Propafenone	+	+	+	+	+	+/-	?	?	?	-	+/-	+/-	+	+

monitor the blood pressure and to adjust valsartan doses if necessary.

2.4. Antiarrhythmic drug classes

2.4.1. Class I antiarrhythmic drugs – Na+ channel blockers (eg, chinidine, flecainide, lidocaine, propafenone)

Drug interactions with this class of antiarrhytmic drugs can occur via inhibition of cytochrome CYP4503A4, CYP2C9 and CYP1A2 or the mechanism of interaction could be unknown for some ARVs [17,18]. The potential clinical effects could be those related to possible increased effects of the antiarrhytmic drug (eg, cardiac arrhythmias) or suboptimal concentration of the drug for effective clinical response.

Comments:

- Drug interactions with: PIs and/or pharmacologic boosters such as ritonavir and cobicistat. The mechanism of action is due to inhibition of cytochrome CYP4503A4 and increased concentrations of the antiarrhytmic drug, with possible secondary toxicity. It is recommended not to coadminister most of these drugs (contraindicated) [16-18].
- Potential drug interactions with: NNRTIs and some PIs. Levels of chinidine, flecainide, lidocaine and propafenone may be decreased with coadministration with some NNRTIs. RPV should be coadministered with caution with some ARVs, because of its potential role to cause prolonged QTc interval even in healthy subjects (especially at higher doses of 75/300 mg daily). Some PIs might increase antiarrhytmic drug levels and adverse reactions can occur. It is recommended to use these coadministrations with caution and to monitor the therapeutic effects of the antiarrhytmic drug.

2.4.2. Class II antiarrhythmic drugs – beta-adrenoceptor antagonists (see specific section – 2.2)

2.4.3. Class III antiarrhythmic drugs – prolong action potential and prolong refractory period - Amiodarone

Drug interactions can occur via inhibition of cytochrome CYP4503A4, CYP3A4 or induction of CYP2C8 [18,23]. In some cases, levels of amiodarone could be fluctuating if interactions occur at the level of two different cytochromes (eg, EFV, inducer of

Table 9. Selected drug-drug interactions with amiodarone [13, 16-18].

NRTI					NNRTI				PIs (boosted)			INSTIs	
ABC	3TC	FTC	TDF	ZDV	EFV	ETV	NVP	RPV	ATV	DRV	LPV	RAL	DTG
+	+	+	+	+	+/-	+/-	+/-	+/-	-	-	-	+	+

Table 10. Selected drug-drug interactions with Digoxin [13, 16-18].

NRTI					NNRTI				PIs (boosted)			INSTIs	
ABC	3TC	FTC	TDF	ZDV	EFV	ETV	NVP	RPV	ATV	DRV	LPV	RAL	DTG
+	+	+	+	+	+	+/-	+	+	+/-	+/-	+/-	+	+

CYP3A4 but also inhibitor of CYP2C8) [17,18]. Although effects on ARV levels are not well known, there is some concern regarding amiodarone levels and its increased CV effects (eg, cardiac arrhythmias, hypotension, bradycardia) with some ARVs (table 9) [16,18].

Comments:

- Drug interactions with: PIs and/or pharmacologic boosters such as ritonavir and cobicistat. The mechanism of action is due to inhibition of CYP4503A4 or CYP3A4. It is recommended not to coadminister these drugs (contraindicated) or, if used, caution and concentration monitoring of amiodarone and serial ECGs is recommended [16-18].
- Potential drug interactions with: NNRTIs. Levels of amiodarone might be fluctuating if coadministered with EFV (inducer of CYP3A4 but also inhibitor of CYP2C8). RPV should be coadministered with caution because of its potential role to cause prolonged QTc interval even in healthy subjects (especially at higher doses of 75/300 mg daily). They should be used with caution and close clinical/concentration monitoring of the therapeutic effect and dose adjustment is recommended [17]. Can start with the lowest dose of amiodarone.

2.4.4. Class IV antiarrhythmic drugs – calcium channel antagonists – Verapamil, Diltiazem (see specific section – 2.1).

2.5. Digoxin

Drug interactions can occur via inhibition of the efflux pump P-glycoprotein (P-gp), which results in an increase in digoxin absorbtion and a reduction of its elimination, primarily via the kidney [24]. Therefore, some ARVs can increase digoxin concentrations and if these drugs are used, caution is warranted (table 10).

Comments:

- Potential drug interactions with: PIs or pharmacologic boosters such as ritonavir and cobicistat (cobicistat can increase digoxin Cmax by 41%) [13, 16-18]. If these drugs are used, caution is warranted. Can start with the lowest dose of digoxin. Clinical and therapeutic drug monitoring of digoxin concentrations is recommended, if available [17].
- No interactions expected with: NRTIs, NNRTIs, INSTIs (in vitro data indicate that these drugs have the potential to induce or inhibit P-gp in the range of clinical concentrations), except for ETV (coadministration of 0.5 mg digoxin with usual dose of 200 mg ETV BID increased digoxin AUC and Cmax by 18 and 19% respectively) [13, 16-18].

2.6. Anticoagulants and antiplatelet agents

2.6.1. Anticoagulants

Drug-drug interactions are expected with coadministration of some novel oral anticoagulants (NOACs) such as apixaban and ritonavir/cobicistat boosted PIs (Table 11). Concentration of apixaban is increased due to significant CYP3A4 and P-gp inhibition by ritonavir/cobicistat [13,17]. Therefore, these drugs should not be co-administered.

Potential drug-drug interaction can occur between oral anticoagulants (acenocumarol, warfarin), NOACs (apixaban, dabigartran) and some NNRTIs and PIs (table 11). Mechanism of interaction with acenocumarol is at CYP2C9, CYP1A2 and CYP2C19 level [17]. Drug interactions with warfarin can be possible by inhibition/induction of CYP4503A4, CYP2C9 and/or CYP1A2 [18]. Mechanism of interaction consists of inhibition of apixaban and dabigartran metabolism via CYP3A4, with potential for increased

Table 11. Selected drug-drug interactions with some anticoagulants13, [16-18]

Drug	NRTI					NNRTI				PIs (boosted)			INSTIs	
	ABC	3TC	FTC	TDF	ZDV	EFV	ETV	NVP	RPV	ATV	DRV	LPV	RAL	DTG
Acenocumarol	+	+	+	+	+	+/-	+/-	+/-	+	+/-1	+/-1	+/-	+	+
Warfarin	+	+	+	+	+	+/-	+/-	+/-	+	+/-	+/-	+/-	+	+
Apixaban	+	+	+	+	+	+/-5	+/-5	+/-5	+	- 2	- 2	- 2	+	+
Dabigartran	+	+	+	+	+	+	+	+	+	+/-3	+/-3	+/-4	+	+
Enoxaparin	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fondaparinux	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heparin	+	+	+	+	+	+	+	+	+	+	+	+	+	+

[1] Potential decreased exposure to acenocumarol; potential interaction with pharmacological boosters such as ritonavir, but not cobicistat [13,17];

[2] Data available for ritonavir/cobicistat boosted PIs; potential elevated exposure to apixaban [13,17];

[3] Potential elevated exposure to dabigartran; coadministration with ritonavir-boosted possible, but caution is warranted; it is not recommended to coadminister dabigartran with cobicistat boosted ATV – drug-drug interaction of important magnitude [13,17];

[4] Limited data – may consider dose of 110 mg BID of dabigartran, but close clinical monitoring is recommended if ritonavir-boosted regiments are used [17];

[5] Potential decreased exposure to apixaban [13].

risk of bleeding [18]. These potential clinically significant interactions may require additional monitoring (clinical, INR) and dosage/timing adjustment.

No clinically significant interactions are expected with injectable anticoagulants, low-molecular-weight-heparin (LMWH), unfractioned heparin (UH) and anti-Xa factors (fondaparinux). Fondaparinux is eliminated especially by kidneys and it is not metabolized by cytochromes. UH is eliminated via a saturable mechanism represented by the reticuloendothelial system to which heparin binds with a high affinity [25]. Enoxaparin is mainly removed by a non-saturable renal excretion and does nor undergo cytochrome metabolism [25].

2.6.2. Antiplatelet agents

Drug-drug interactions are expected with coadministration of ticagrelor and PIs because of their strong potential to inhibit CYP3A4, which is the mainly metabolization pathway for ticagrelor (table 12) [13,17,18].

Potential drug-drug interaction can occur between clopidogrel and some NNRTIs and PIs because it is metabolized by CYP3A4, CYP2B6, CYP1A2 and CYP2C19 (table 12).13,17 Also, potential drug interactions with ticagrelor and some NNRTIs can ocur via induction of CYP3A4 and decreased exposure of the antiplatelet drug is expected [17].

No clinically significant interactions are expected with aspirin and prasugrel. Aspirin is metabolized in substantial proportion by glucuronidation by several UGTs (especially UGT1A6) [26]. Coadministration of prasugrel with a pharmacological booster (ritonavir/cobicistat) has been evaluated in a study that showed some decreased AUC (52%) and Cmax (43%) of prasugrel's active metabolite, but this potential decreased exposure did not impair its antiplatelet effect [17].

2.7. Lipid lowering drugs - HMG-CoA reductase inhibitors (statins)

Drug-drug interactions are expected with coadministration of simvastatin and PIs because of their

Table 12. Selected drug-drug interactions with some antiplatelets agents [13, 16-18].

Drug	NRTI					NNRTI				PIs (boosted)			INSTIs	
	ABC	3TC	FTC	TDF	ZDV	EFV	ETV	NVP	RPV	ATV	DRV	LPV	RAL	DTG
Aspirin	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Clopidogrel	+	+	+	+	+	+/-[2]	+/-[1]	+/-[2]	+	+/-[1]	+/-[1]	+/-[1]	+	+
Prasugrel	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ticagrelor	+	+	+	+	+	+/-	+/-	+/-	+	-	-	-	+	+

[1] Decreased exposure of clopidogrel and insufficient inhibition of platelet aggregation in patients treated with clopidogrel and ritonavir/cobicistat boosted PIs; an alternative to clopidogrel should be considered [13,17];
[2] Potential increased exposure of clopidogrel by increase in amount of active metabolite via induction of CYP3A4 and CYP2B6 [13]

strong potential to inhibit CYP3A4 with a markedly increase in simvastatin concentrations. Coadministration is contraindicated due to the potential for important adverse reactions such as myopathy and rhabdomyolysis.

Potential drug-drug interaction can occur between atorvastatin, rosuvastatin, simvastatin and some NNRTIs and PIs. Rosuvastatin is largely excreted unchanged via faeces. Coadministered with PIs can result in potential elevated exposure of the statin. Simvastatin and atorvastatin are substrates for CYP3A4 [17,18]. Coadministered with NNRTIs can result in potential decreased exposure of both statins and increased concentrations can result in combination with PIs. Cholesterol levels should be periodically monitored and dosage adjustments of statins may be required. Starting with the lowest dose of statins might be clinically useful.

No clinically significant interactions are expected with fluvastatin as it is metabolized by CYP2C9 and most ARVs do not inhibit or induce these enzymes at relevant concentrations for clinical use [17].

Conclusions

Cardiovascular disease is one of the most important concerns regarding patients living with HIV as a chronic condition, but this patient population has a

Table 13. Selected drug-drug interactions with some statins [13, 16-18].

Drug	NRTI					NNRTI				PIs (boosted)			INSTIs	
	ABC	3TC	FTC	TDF	ZDV	EFV	ETV	NVP	RPV	ATV	DRV	LPV	RAL	DTG
Atorvastatin	+	+	+	+	+	+/-	+/-	+/-	+	+/-	+/-	+/-	+	+
Rosuvastatin	+	+	+	+	+	+	+	+	+	+/-	+/-	+/-	+	+
Simvastatin	+	+	+	+	+	+/-	+/-	+/-	+	-	-	-	+	+
Fluvastatin	+	+	+	+	+	+	+	+	+	+	+	+	+	+

lot of comorbidities and co-medications. Therefore, drug-drug interactions checker is an important tool in clinical practice for every physician of the "HIV team".

In general, NRTIs and INSTIs are safe to use as co-medications with cardiovascular drugs, but the combination with NNRTIs and, especially with boosted PIs, can cause clinically significant interactions that require a special management for every case. Sometimes, even with these known interactions, drug combination with some adverse reactions might be unavoidable due to a lack of alternative co-medication and an individual approach for those clinical cases is necessary.

List of abbreviations (for tables 3-10)

+ Combination of these drugs possible;

+/- Potential interactions or combination has not been studied/unknown;

- Combination of these drugs should be avoided or is contraindicated;

? There are no definite data, actual or theoretical, to clarify whether an interaction will occur or data is contradictory to make a specific recommendation;

3TC – lamivudine;

ABC – abacavir;

ATV – atazanavir;

c – cobicistat;

DRV – darunavir;

DTG – dolutegravir;

EFV – efavirenz;

ETV – etravirine;

FTC – emtricitabine;

INSTI – Integrase Strand Transfer Inhibitors;

LPV – lopinavir;

NNRTI - Non-nucleoside Reverse Transcriptase Inhibitors;

NRTI - Nucleoside Reverse Transcriptase Inhibitors;

NVP – nevirapine;

PI – Protease Inhibitors;

r – ritonavir;

RAL – raltegravir;

RPV – rilpivirine;

TDF – tenofovir disoproxil fumarate;

ZDV – zidovudine

References

1. Data Collection on Adverse Events of Anti H. I. V. drugs Study Group, Smith C, Sabin CA, Lundgren JD, et al. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D study. AIDS 2010;24:1537–48.
2. Feinstein MJ, Bahiru E, Achenbach C, et al. Patterns of cardiovascular mortality for HIV-infected adults in the United States: 1999 to 2013. Am J Cardiol. 2016;117:214–20.
3. Paisible AL, Chang CC, So-Armah KA, et al. HIV infection, cardiovascular disease risk factor profile, and risk for acute myocardial infarction. J Acquir Immune Defic Syndr. 2015;68:209–16.
4. Gutierrez J, Leticia A, Falzon L. HIV infection as vascular risk: A systematic review of the literature and meta-analysis. PLoS One. 2017; 12(5): e0176686.
5. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab 2007;92:2506–12.
6. Streinu-Cercel A, Sandulescu O, Ceapraga G et al. Prevalence of osteo-renal impairment in the Romanian HIV cohort. BMC Infect Dis. 2016; 16(Suppl 1): 93.
7. Osibogun O, Ogunmoroti O, Michos ED et al. A systematic review of the associations between HIV/HCV coinfection and biomarkers of cardiovascular disease. Rev Med Virol. 2018;28:e1953. Available at: https://doi.org/10.1002/rmv.1953.
8. Osibogun O, Ogunmoroti O, Michos ED, et al. HIV/HCV coinfection and the risk of cardiovascular disease: A meta-analysis. J Viral Hepat. 2017;24(11):998-1004.
9. Lucas GM, Atta MG, Fine DM, et al. HIV, Cocaine Use, and Hepatitis C Virus, A Triad of Nontraditional Risk Factors for Subclinical Cardiovascular Disease. Available at: http://atvb.ahajournals.org/lookup/suppl/doi:10.1161/ATVBAHA.116.307985/-/DC1.
10. Fine DM, Garg N, Haas M, et al. Cocaine Use and Hypertensive Renal Changes in HIV-Infected Individuals. Clin J Am Soc Nephrol 2007; 2(6): 1125–1130.
11. Vachiat A, McCutcheon K, Tsabedze N, et al. HIV and Ischemic Heart Disease. J Am Coll Cardiol. 2017;69(1):73-82.
12. Lars G. Hemkens and Heiner C. Bucher. HIV infection and cardiovascular disease. European Heart Journal. 2014;35:1373–81.
13. European Guidelines for treatment of HIV-positive adults in Europe (EACS), October 2017.
14. Ryom L, Lundgren J, EL-Sadr W et al. for D:A:D CROI 2017, oral late-breaker Association between Cardiovascular Disease & Contemporarily Used Protease Inhibitors, CROI 2017.
15. Hemkens LG, Bucher HC. HIV infection and cardiovascular disease. Eur Heart J. 2014;35(21):1373-81.
16. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Available at: https://aidsinfo.nih.gov/guidelines. [Accesed: Aug-2018].

17. The University of Liverpool HIV Drug Interaction. Available at: http://www.hiv-druginteractions.org/. [Accesed: Aug-2018].
18. Interactions between Cardiovascular medications and Antiretrovirals. HIVInSite - Comprehensive, up-to-date information on HIV/AIDS treatment and prevention from the University of California San Francisco. Available at: http://hivinsite.ucsf.edu/insite?page=ar-00-02&post=10&param=18. [Accesed: Sep-2018].
19. Kathleen M Knights, Andrew Rowland, and John O Miners. Renal drug metabolism in humans: the potential for drug–endobiotic interactions involving cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT). Br J Clin Pharmacol. 2013;76(4): 587–602.
20. Yin J and Wang J. Renal drug transporters and their significance in drug–drug interactions. Acta Pharm Sin B. 2016;6(5):363–73.
21. Los LE, Pitzenberger SM, Ramjit HG et al. Hepatic metabolism of spironolactone. Production of 3-hydroxy-thiomethyl metabolites. Drug Metab Dispos. 1994;22(6):903-8.
22. Meisel S, Shamiss A, Rosenthal T. Clinical pharmacokinetics of ramipril. Clin Pharmacokinet. 1994;26(1):7-15.
23. Soyama A, Hanioka N, Saito Y. Amiodarone N-deethylation by CYP2C8 and its variants, CYP2C8*3 and CYP2C8 P404A. Pharmacol Toxicol. 2002;91(4):174-8.
24. Finch A and Pillans P. P-glycoprotein and its role in drug-drug interactions. Aust Prescr 2014;37:137–9.
25. Boneu B, Caranobe C, Sie P. Pharmacokinetics of heparin and low molecular weight heparin. Baillieres Clin Haematol. 1990;3(3):531-44.
26. Navarro SL, Saracino MR, Makar KW et al. Determinants of Aspirin Metabolism in Healthy Men and Women: Effects of Dietary Inducers of UDP-Glucuronosyltransferases. J Nutrigenet Nutrigenomics. 2011;4(2):110–8.