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Review Article

Management of anticoagulation in patients with human immunodeficiency virus/acquired immunodeficiency virus☆

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ABSTRACT

Purpose: Limited guidance is available to assist practitioners in managing complex human immunodeficiency virus (HIV) related pharmacotherapy. Management recommendations of oral anticoagulation (warfarin and direct oral anticoagulants [DOACs]) and highly active antiretroviral therapy (HAART) based on drug-drug interactions (DDI) studies and pharmacokinetic (PK) data are provided.

Methods: Search of PubMed, EMBASE, and Google Scholar (01/1985 to 12/2018) using the terms "HIV," "DDI," and names of HAART. PK information and DDI screening were obtained from medication package inserts and drug information resources: Micromedex, Lexicomp, HIV-DDI Checker- University of Liverpool. All English literature on DDI or PK interactions was considered for inclusion. In the absence of data, PK principles were used to predict the likelihood of interactions.

Results: No clinically significant DDI are expected to occur between DOACs and nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), maraviroc, enfuvirtide, or integrase strand inhibitors (INSTIs) that do not include a pharmacologic booster. Potent cytochrome P (CYP) 450 enzyme inhibition by protease inhibitors (PIs) or pharmacologic boosters may lead to higher concentrations of the DOAC and potentially increase the risk of bleeding. CYP450 enzyme induction by non-nucleoside reverse transcriptase inhibitors (NNRTIs) may lower concentrations of DOACs, which may lead to treatment failure. Warfarin DDIs are variable, therefore close monitoring of the INR is recommended.

Conclusions: The potential for DDIs between HAART and oral anticoagulation exists based on PK profiles. Management of these interactions should involve careful selection based on patient characteristics and HAART and anticoagulants with a low potential for DDI should be selected.

1. Introduction

According to the Centers for Disease Control and Prevention, in 2017, there were 36.9 million people living with human immunodeficiency virus (HIV) around the world and 1.1 million people living with HIV in the United States (US) [1]. Historically, HIV/AIDS was a fatal diagnosis, but with the advent of highly active antiretroviral therapy (HAART) in industrialized areas, patients with HIV are living longer and thus, an aging population is emerging. In 2015, health officials reported 52% of people with HIV were over 50 years of age [2].

There is evidence of endothelial dysfunction and a dysregulation of coagulation and fibrinolysis in individuals with HIV [3]. In a study of 109 HIV-infected patients with advanced disease, 10% developed venous thrombosis and 6% developed arterial thrombosis [4]. A variety of laboratory abnormalities were reported, including protein C deficiency, increased factor VIII concentrations, high fibrinogen concentrations, and free protein S deficiency [4]. HIV infection is also associated with an increased D-dimer level, which suggests that HIV

Abbreviations: DDI, drug drug interaction; INR, international normalized ratio; HAART, highly active antiretroviral therapy; INSTI, integrase strand inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; OATP, organic anion transporter protein; OCT2, organic anion transporter 2; P-gp, permeability glycoprotein; PI, protease inhibitor; PK, pharmacokinetic.

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infection might be associated with a pro-thrombotic state [5,6]. HIV disease is theorized to produce a pro-thrombotic state through mechanisms related to activation of the innate and adaptive immune system by low level HIV replication, co-pathogens, and microbial products translocated from the gastrointestinal tract [7,8]. Given the aging HIV population, it is important to consider that the incidence of VTE increases dramatically with age and some studies have estimated that the risk of venous thromboembolic (VTE) disease is 2–10 fold higher than the general population after the age of 45 or more years [9].

The impact of HAART on coagulation is unclear. Protease inhibitors (PI) have been associated with higher fibrinogen levels [3] and lipodystrophy. PIs are also thought to interfere with cytochrome P (CYP) 450 metabolism and regulation of thrombotic proteins [10]. This may cause a pro-thrombotic state in HIV-infected individuals.

Direct oral anticoagulants (DOACs) are becoming more frequently prescribed for VTE. According to the CHEST Guideline and Expert Panel Report, DOACs are recommended over warfarin for treatment of VTE [11]. Evaluation of DDI between DOACs, warfarin, and HAART is important due to the potential of significant alteration of patient's exposure to each drug. Therefore, assessment of interactions is a necessary consideration in drug selection.

Treatment for HIV requires combination therapy and is recommended in all HIV-infected individuals. HAART is defined as any treatment regimen comprised of three or more drugs with different mechanisms of action. The choice of regimen must consider convenience to the patient, tolerability, potential toxic effects, viral resistance, and drug interactions. Current first line therapy recommendations according to the US Department of Health and Human Services consist of two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) administered in combination with an integrase strand inhibitor (INSTI) [12,13].

The objective of this review is to summarize the available data and PK information to provide a reference for actual and potential DDI with anticoagulation and HAART. Management strategies for specific DDI are provided when available.

2. Methods

Information was retrieved via a PubMed, EMBASE, and Google Scholar search (January 1985–December 2018) and limited to the English language using the following terms: (1) rivaroxaban, apixaban, dabigatran, edoxaban, (2) warfarin, and (3) antiretrovirals, highly active antiretroviral therapy, protease inhibitor, nonnucleoside reverse transcriptase inhibitor, nucleoside reverse transcriptase inhibitor, integrase strand transfer inhibitor, CCR5 antagonist, fusion inhibitor, pharmacokinetic booster, drug interaction, and drug metabolism. Literature searches intentionally included antiretrovirals found in national guidelines to reflect current practice. Articles and abstracts that described PK and DDI were identified and reviewed along with references, product monographs, and the following drug information resources: Micromedex, Lexicomp, HIV-Drug Interaction Checker-University of Liverpool. IRB exemption was obtained. Pertinent information, as assessed by the authors, was selected and summarized for discussion. In the absence of data, PK principles were used to predict the likelihood of interactions. Specific factors of clinical significance, likelihood of occurrence, and management options were considered. Drug monographs, conference abstracts, and case reports were used to draw inferences and conclusions.

3. Results

3.1. Drug interactions

The studies of warfarin and the DOACs that resulted in FDA approval did not include individuals with HIV/AIDS. To date, there is limited data evaluating oral anticoagulant and antiviral co-administration, therefore conclusions must be largely based on PK data. The package inserts of the DOACs provide general recommendations for dose adjustments when combined with inhibitors or inducers of CYP-450 metabolism or P-gp. Table 1 provides a summary of the PK profile of each oral anticoagulant currently available. Table 2 provides a summary of the metabolizing enzymes and transporter proteins associated with HAART. Recommendations for anticoagulation selection and management strategies for co-medication use with specific HAART drug classes are provided in Table 3. Additionally, individual HAART therapy recommendations were extrapolated to combination products currently available (Table 4).

3.1.1. Apixaban

Co-administration of HIV PIs and apixaban has not been studied. In a clinical study demonstrating the impact of CYP3A4 inhibitors, co-administration of ketoconazole (400 mg daily) increased the apixaban maximum concentration (Cmax) and AUC by 1.6- and 2-fold, respectively [14]. Combined use of PIs is not recommended in patients who require apixaban 2.5 mg twice daily and for patients requiring apixaban 5 mg or 10 mg twice daily, a 50% reduction of apixaban dose is recommended. This is due to the potential for PIs to strongly inhibit CYP3A4 and increase apixaban concentrations and potentially increase the risk of bleeding. Clinical efficacy of this 50% dosage reduction recommendation ought to be closely considered as this is not based on clinical data. Similarly, the combination of apixaban and PK boosters (cobicistat and ritonavir) is expected to increase apixaban concentrations due to inhibition of CYP3A4-mediated metabolism [15]. Data are not available for apixaban in combination with NNRTIs, however efavirenz and etravirine are predicted to decrease apixaban concentrations via CYP3A4 induction and are not recommended due to potential of failure to prevent or treat thrombosis.[16,] No significant interactions are expected with INSTIs, with the exception of elvitegravir, which is available in FDC with cobicistat. Apixaban dose adjustment should occur to mitigate PK booster drug interaction if co-administration of Apixaban and elvitegravir/cobicistat is unavoidable due to possible increase in apixaban exposure [17,18].

3.1.2. Rivaroxaban

HIV PIs have the potential to strongly inhibit CYP3A4 and increase rivaroxaban concentrations [19]. Data on the co-administration of rivaroxaban with ritonavir led to a 2.5-fold increase in rivaroxaban area under the curve (AUC) and a 1.6-fold increase in maximum concentration (Cmax). Therefore, combined use of HIV PIs and rivaroxaban is not recommended and alternative HAART or anticoagulants should be considered. The combination of rivaroxaban and cobicistat also has the potential to increase rivaroxaban plasma concentrations, thereby increasing bleeding risk, therefore combined use is not recommended. Rivaroxaban use combined with rifampicin (strong CYP3A4 inducer) led to ~50% decrease in mean rivaroxaban AUC [19]. Other strong CYP3A4 inducers may also lead to reduced rivaroxaban plasma concentrations. Efavirenz and etravirine are moderate CYP3A4 inducers, therefore use is also not recommended as they are predicted to decrease rivaroxaban concentration [16,20]. No significant interactions are expected with NRTIs, maraviroc, or enfuviritide [21,22]. Additionally, no significant interactions are expected with INSTIs, with the exception of elvitegravir, which is available in FDC with cobicistat; combined use should be avoided due to possible increase in rivaroxaban exposure via strong CYP3A4 inhibition [23]. P-gp inhibition should also be considered, as CYP3A4 inhibition alone may not result in clinically significant alterations in concentration.

3.1.3. Edoxaban

Edoxaban is a P-gp substrate and primarily renally excreted, therefore drug properties of P-gp inhibition and patient characteristics such as impaired renal function are major independent factors that may result in increased exposure to edoxaban. Co-administration of edoxaban with

Table 1
Profile of DOACs & warfarin.

	Apixaban [14]	Rivaroxaban [19]	Edoxaban [24]	Dabigatran [28]	Warfarin [34]
Mechanism	• Factor Xa inhibitor	• Factor Xa inhibitor	• Factor Xa inhibitor	• Direct thrombin inhibitor	• Vitamin K antagonist
Absorption - Effects of Food	• Bioavailability 50%; • None	• Bioavailability 66–100%; • 20 mg: 3% and 75% increases in AUC and Cmax	• Bioavailability 62%; • Increased, no significant effect on systemic exposure	• Bioavailability 3–7%; • None	• Bioavailability 79–100%; • None
Half-life	• 12 h	• 5–9 h (young) • 11–13 h (elderly)	• 10–14 h	• 12–17 h	• 20–60 h
Metabolism	• 25% hepatic, primarily CYP3A4; minor CYP1A2, 2C8/9, 2C19 • 27% renal clearance	• 51% hepatic, primarily CYP3A4/5, 2J2 • 35% renal clearance	• <4% CYP3A4 metabolism, primary hydrolysis • 50% renal clearance	• Prodrug; no CYP 450 metabolism • 80% renal clearance	• Hepatic, primarily CYP2C9; minor CYP2C19, 1A2, 3A4
P-gp substrate	• Yes	• Yes	• Yes	• Yes	• No
Elimination	• Urine (27%); feces (73%)	• Urine (66%); feces (28%)	• Urine (primarily unchanged)	• Urine (80%)	• Urine (92%)

Abbreviations: CYP, cytochrome P; P-gp, permeability glycoprotein.

PIs has not been studied [24]. The metabolism of edoxaban involves CYP3A4 (<4% hepatic metabolism), therefore combined use with HIV PIs may increase edoxaban concentrations and consideration of an alternative anticoagulant is recommended. Dose adjustment should be considered if combined use is deemed necessary. Data are not available to assess edoxaban in combination with NNRTIs, however etravirine may increase edoxaban concentrations via P-gp inhibition and is not recommended [16]. Co-administration of PK boosters has not been studied with edoxaban, but due to the concern for P-gp inhibition, alternative HAART or anticoagulation should be considered to avoid toxicities and renal function should be monitored if concomitant therapy is required. In-vitro data suggest maraviroc could inhibit P-gp in the gut and therefore affect bioavailability of certain drugs, however the clinical relevance of this data is unclear as no clinical studies have been conducted with P-gp substrates [21]. Interactions with P-gp substrates are unlikely but cannot be excluded, therefore use caution and monitor if used in combination with edoxaban. Although not studied, clinically significant interactions are not expected with NRTIs, efavirenz, INSTIs not included in FDC products, and enfuvirtide.

3.1.4. Dabigatran

Other case reports describing dabigatran use in atrial fibrillation utilized a target peak and/or trough levels to guide monitoring: lopinavir/r did not cause a significant interaction with dabigatran (110 mg twice daily) based on a lack of complications following 6 months of therapy [25] and ritonavir did not cause dabigatran accumulation [26]. Despite these case reports, dosing and monitoring of dabigatran based on levels is not supported by current guidelines and levels have not be correlated with therapeutic outcomes or safety in treatment. PK data exists exploring optimal administration time of ritonavir with dabigatran. In a cross over study of HIV-negative subjects, dabigatran (150 mg single dose) given 2 h prior to ritonavir (100 mg once daily administered at steady state) resulted in a reduction of the dabigatran AUC by 29% and Cmax by 27% compared to simultaneous administration. Authors hypothesize that no significant effect on dabigatran PK was seen with ritonavir when co-administered due to its mixed induction and inhibitory effect on P-gp and suggest if these medications are used in combination, dabigatran should be taken simultaneously with the ritonavir-boosted PI [27]. Co-administration with other PIs has not been studied. Dabigatran is a P-gp substrate and PIs are strong P-gp inhibitors, therefore use may increase dabigatran concentrations and consideration of an alternative anticoagulant is recommended. Potential interaction with dabigatran and cobicistat was evaluated in an open-label, single sequence drug interaction study of healthy HIV-negative volunteers. Co-administration of dabigatran (150 mg single dose) simultaneously with or 2 h before cobicistat (150 mg once daily) was studied in a phased approach. Simultaneous administration increased dabigatran AUC by 127% (n = 16) and separating the dosing by 2 h did not overcome the interaction; dabigatran AUC increased by 110% (n = 18). The authors concluded that the PK interaction was due to inhibition of P-gp by cobicistat and further studies are required to determine if extending the interval to 4 h or more may overcome the interaction since maximal dabigatran concentrations occur 3–4 h after administration [28]. Based on impact of dabigatran AUC due to potent inhibition of P-gp, antiretrovirals combined with cobicistat, such as atazanavir-cobicistat, darunavir-cobicistat, and elvitegravir-cobicistat, should not be used with dabigatran. Data are not available to assess dabigatran in combination with NNRTIs, however the prodrug of dabigatran is a substrate of P-gp and etravirine is a weak inhibitor of P-gp [16]. Therefore, combination use with etravirine could increase the exposure of dabigatran. In vitro data suggest maraviroc could inhibit P-gp in the gut and therefore affect bioavailability of certain drugs, however the clinical relevance of this data is uncertain [21]. Thus, use caution and monitor if used in combination with dabigatran. No significant interactions are expected with NRTIs, enfuvirtide, or INSTIs, with the exception of elvitegravir, which is available in FDC with cobicistat.

3.1.5. Warfarin

Warfarin is metabolized via CYP2C9 and PK interactions between warfarin and HAART are variable. Co-administration of warfarin with PIs is limited to data from case reports. One report of a patient receiving indinavir (800 mg every 8 h) and warfarin found prothrombin (PT) complex activity increased from 25–35% to 53% following initiation, and 43% at day 10 and day 25 after indinavir was discontinued. Authors attribute this increase in international normalized ratio (INR) and bleeding risk to inhibition of CYP3A4 [29]. Saquinavir was studied in a patient receiving warfarin and subsequent concentrations of warfarin increased along with INR (from 2.1 to 4.24). Authors suggest this INR increase may be due to inhibition of CYP3A4 by saquinavir [30]. Similarly, co-administration of tipranavir with low dose ritonavir and warfarin may alter warfarin metabolism. Per warfarin's package insert, co-administration of a single dose of tipranavir/ritonavir had no effect on S-warfarin Cmax and increased AUC by 18%. After multiple doses of tipranavir/ritonavir (500 mg/200 mg twice daily), S-warfarin Cmax and AUC decreased by 17% and 12%, respectively [31]. This may be due to inhibition of CYP 2C9 with first-dose tipranavir/ritonavir, then induction of CYP 2C9 with steady-state tipranavir/ritonavir. Tipranavir co-administered with low dose ritonavir may be associated with changes in INR, therefore frequent INR monitoring is recommended. Another case report reviewed warfarin use in a patient with an inferior vena cava thrombus receiving a ritonavir-based regimen (zidovudine, lamivudine, lopinavir/r). The warfarin dose needed to be doubled to maintain INR. Ritonavir has been shown to be a potent inhibitor of CYP3A4 and a potentiation of warfarin effect and subsequent decrease in the warfarin

Table 2
HAART: metabolizing enzymes & transporter proteins.

HAART drug class	Specific medication	CYP 450 enzymes: Substrate	CYP 450 enzymes: Inhibitor	CYP 450 enzymes: Inducer	Transporter proteins: Substrate	Transporter proteins: Inhibitor	Transporter proteins: Inducer	Other enzymes
NRTIs	Abacavir, ABC (*Ziagen*) [35]	–	–	–	–	MRP2	–	–
	Lamivudine, 3TC (*Epivir*) [36]	–	–	–	–	MRP2	–	–
	Emtricitabine, FTC (*Emtriva*) [37]	–	–	–	–	–	–	–
	Tenofovir disoproxil fumarate, TDF (*Viread*) [38]	–	–	–	BCRP/ABCG2; P-gp/ ABCB1	MRP2	–	–
	Tenofovir alafenamide, TAF	–	–	–	BCRP/ABCG2; P-gp/ ABCB1	MRP2	–	–
	Zidovudine, ZDV or AZT (*Retrovir*) [39]	CYP2A6, 2C19, 2C9, 3A4 (minor)	–	–	OAT3	–	–	–
	Stavudine, d4T (*Zerit*) [40]	–	–	–	–	–	–	–
	Didanosine, ddI (*Videx*) [41]	–	–	–	–	–	–	–
NNRTIs	Efavirenz, EFV (*Sustiva*) [20]	CYP3A4, 2B6 (major)	CYP2C9, 2C19	CYP3A4, 2B6 (moderate), 2C19 (weak)	–	–	–	Inhibits UGTIAI
	Etravirine, ETR (*Intelence*) [16]	CYP3A4 (major), 2C9, 2C19	CYP2C9, 2C19	CYP3A4 (moderate)	–	P-gp	–	–
PIs	Darunavir, DRV (*Prezista*) [42]	CYP3A4 (major)	CYP3A4 (major), 2D6 (moderate)	–	P-gp/ABCB1	–	–	–
	Atazanavir, ATV (*Reyataz*) [43]	CYP3A4 (major)	CYP3A4, 2C8 (weak)	–	–	–	–	Inhibits UGTIAI
	Fosamprenavir, FPV (*Lexiva*) [44]	CYP3A4 (major), 2C9, 2D6 (minor)	CYP3A4 (moderate)	CYP3A4	P-gp	–	–	–
	Indinavir, IDV (*Crixivan*) [45]	CYP3A4 (major)	CYP3A4 (strong), 2D6 (weak)	–	–	–	–	–
	Lopinavir + ritonavir, LPV/r (*Kaletra*) [46]	CYP3A4/5 (major), 2D6, 1A2, 2B6 (minor)	CYP3A4 (strong), 2D6 (weak)	CYP2B6 (moderate), 2C9, 2C19, 1A2 (weak)	P-gp/ABCB1 (minor)	P-gp/ABCB1, MRP2	–	–
	Nelfinavir, NFV (*Viracept*) [47]	CYP3A4 (major), 2C19, 2C9, 2D6 (minor)	CYP3A4 (strong)	–	–	–	–	–
	Saquinavir, SQV (*Invirase*) [48]	CYP3A4 (major)	CYP3A4 (strong)	–	P-gp		–	–
	Tipranavir, TPV (*Aptivus*) [31]	CYP3A4 (major)	CYP2D6 (strong)	–	–	–	–	–
PK Boosters	Ritonavir (*Norvir*) [49]	CYP3A4/5 (major), 2D6, 1A2, 2B6, (minor)	CYP3A4 (strong), 2D6 (weak)	CYP2B6 (moderate), 2C9, 2C19, 1A2 (weak)	P-gp/ABCB1	P-gp/ABCB1, MRP2	–	–
	Cobicistat (*Tybost*) [15]	CYP3A4 (major), 2D6 (minor)	CYP3A4 (strong), 2D6 (weak)	–	–	BCRP/ABCG2, OATP1B1/1B3	–	–
INSTIs	Bictegravir[a], BIC [18]	CYP3A4 (major)	–	–	–	–	–	Substrate UGTIAI
	Elvitegravir[b], EVG [17]	CYP3A4 (major), 2D6	CYP3A4 (strong), 2D6 (weak)	CYP2C9	–	BCRP/ABCG2, OATP1B1/1B3	–	Substrate UGTIAI
	Dolutegravir, DTG (*Tivicay*) [50]	–	–	–	BCRP/ABCG2 (major)	OCT2	–	Substrate UGTIAI
	Raltegravir, RAL (*Isentress, Isentress HD*) [51]	–	–	–	–	–	–	Substrate UGTIAI
CCR5 antagonist	Maraviroc, MVC (*Selzentry*) [21]	CYP3A4 (major)	–	–	–	P-gp in-vitro	–	–
Fusion inhibitor	Enfuvirtide, T20 (*Fuzeon*) [22]	–	–	–	–	–	–	–

Abbreviations ABCG2, ATP-binding cassette transporter G2: BRCP, breast cancer resistance protein; CCR5, C-C chemokine motif receptor 5; CYP, cytochrome P450; MRP2, multidrug resistance protein 2; INR, international normalized ratio; HAART, highly active antiretroviral therapy; INSTI: integrase strand inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; OATP, organic anion transporter protein; OCT2, organic anion transporter 2; P-gp, permeability glycoprotein; PI, protease inhibitor; PK, pharmacokinetic; UGTIAI, uridine diphosphate glucuronyltransferase IAI.

[a] Bictegravir: component of fixed-dose combination *Biktarvy*.

[b] Elvitegravir: component of fixed-dose combination with cobicistat.

Table 3
Management of potentially significant drug interactions with DOACs and HAART.

HAART drug class & specific medication	Apixaban	Rivaroxaban	Edoxaban	Dabigatran	Warfarin
NRTIs: abacavir, lamivudine, tenofovir disoproxil fumarate, tenofovir alafenamide, zidovudine, stavudine, didanosine	• Clinically significant interactions are not expected and no dose adjustment is necessary [35–36,38–41]				
NNRTIs: efavirenz, etravirine	• Efavirenz and etravirine may ↓ apixaban and rivaroxaban – not recommended [20, 37]		• Etravirine may ↑ edoxaban and dabigatran – not recommended [16] • Interaction with efavirenz not expected [20]		• Efavirenz, and etravirine may ↑/↓ warfarin – monitor INR and adjust warfarin as indicated [16,20]
PIs: darunavir, atazanavir, fosamprenavir, indinavir, lopinavir + ritonavir, nelfinavir, saquinavir, tipranavir	• Lopinavir/r may ↑ apixaban – not recommended [46] • Fosamprenavir may ↑/↓ apixaban – not recommended [44] • Atazanavir, indinavir, nelfinavir, and saquinavir may ↑ apixaban - consider alternative anticoagulant or dose adjustment of apixaban [43,45,47,48] • Interaction with darunavir, tipranavir unlikely but cannot be excluded; use caution and monitor [42, 31]	• Atazanavir, indinavir, lopinavir/r, nelfinavir, and saquinavir may ↑ rivaroxaban – not recommended [43,45,47,48] • Fosamprenavir may ↑/↓ rivaroxaban – not recommended [44] • Interaction with darunavir and tipranavir unlikely but cannot be excluded; use caution and monitor [42, 31]	• Fosamprenavir may ↑/↓ edoxaban – not recommended [44] • Atazanavir, indinavir, lopinavir/r, nelfinavir, and saquinavir may ↑ edoxaban - consider alternative anticoagulant [43,45,47,48] • Interaction with darunavir and tipranavir unlikely but cannot be excluded; use caution and monitor [42, 31]	• Lopinavir/r may ↑ dabigatran – not recommended [46] • Interaction with all other PIs unlikely but cannot be excluded; use caution and monitor	• Atazanavir, indinavir, nelfinavir, and saquinavir may ↑ warfarin – monitor INR and adjust warfarin as indicated [43,45,47,48] • Fosamprenavir and lopinavir/r may ↑/↓ warfarin- monitor and adjust warfarin as indicated [44] • Interaction with darunavir and tipranavir unlikely but cannot be excluded; use caution and monitor [42, 31]
PK Boosters: ritonavir, cobicistat	• Ritonavir and cobicistat ↑ apixaban and rivaroxaban – not recommended [15,49]		• Ritonavir and cobicistat may ↑ edoxaban – consider alternative anticoagulant [15,49]	• Ritonavir and cobicistat may ↑ dabigatran – not recommended [15,49]	• Ritonavir may ↑/↓ warfarin – monitor INR and adjust warfarin as indicated [49] • Cobicistat may ↑ warfarin – monitor INR and adjust warfarin as indicated [15]
INSTIs: bictegravir[a], elvitegravir[b], dolutegravir, raltegravir	• Elvitegravir ↑ apixaban and rivaroxaban – not recommended [17] • Interaction with bictegravir [18], dolutegravir [50], or raltegravir [51] not expected		• Elvitegravir may ↑ edoxaban – consider alternative anticoagulant [17] • Interaction with bictegravir [18], dolutegravir [50], and raltegravir [51] not expected	• Elvitegravir may ↑ dabigatran – not recommended [17] • Interaction with bictegravir [18], dolutegravir [50], and raltegravir [51] not expected	• Elvitegravir may ↑ warfarin – monitor INR and adjust warfarin as indicated [17]
CCR5 antagonist: maraviroc	• Clinically significant interactions are not expected and no dose adjustment is necessary [21]		• Interaction with maraviroc unlikely but cannot be excluded – use caution and monitor [21]		• Clinically significant interactions are not expected and no dose adjustment is necessary [21]
Fusion inhibitor: enfuvirtide	• Clinically significant interactions are not expected and no dose adjustment is necessary [22]				

Abbreviations: CCR5, C-C chemokine motif receptor 5; INR, international normalized ratio; HAART, highly active antiretroviral therapy; INSTI: integrase strand inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PK, pharmacokinetic.
[a]Bictegravir: component of FDC *Biktarvy*.

[b]Elvitrgravir: component of FDC with cobicistat.
↑/↓: reflect increase or decrease in serum concentration of drugs.
Red: not recommended or consider alternative anticoagulant. Green: no dose adjustment is necessary. Orange: increased monitoring as indicated.

Table 4
Dosing recommendations for potentially significant combination product & once-daily single tablet regimen interactions.

		Apixaban	Rivaroxaban	Edoxaban	Dabigatran	Warfarin
Combination product	Abacavir + lamivudine (Epzicom)	• Clinically significant interactions are not expected and no dose adjustment is necessary				
	Emtricitabine + tenofovir alafenamide (*Descovy*)	• Clinically significant interactions are not expected and no dose adjustment is necessary				
	Emtricitabine + tenofovir disoproxil fumarate (*Truvada*)	• Clinically significant interactions are not expected and no dose adjustment is necessary				
	Lamivudine + zidovudine (*Combivir*)	• Clinically significant interactions are not expected and no dose adjustment is necessary				
	Atazanavir + cobicistat (*Evotaz*)	• *Evotaz* ↑ apixaban and rivaroxaban – not recommended		• *Evotaz* may ↑ edoxaban – consider alternative anticoagulant	• *Evotaz* may ↑ dabigatran – not recommended	• *Evotaz* may ↑ warfarin – monitor INR and adjust warfarin as indicated
	Darunavir + cobicistat (*Prezcobix*)	• *Prezcobix* ↑ apixaban and rivaroxaban – not recommended		• *Prezcobix* may ↑ edoxaban – consider alternative anticoagulant	• *Prezcobix* may ↑ dabigatran – not recommended	• *Prezcobix* may ↑ warfarin – monitor INR and adjust warfarin as indicated
Once-daily single tablet regimens	Emtricitabine + tenofovir disoproxil fumarate + efavirenz (*Atripla*)	• *Atripla* may ↓ apixaban and rivaroxaban – not recommended		• Clinically significant interactions are not expected and no dose adjustment is necessary		• *Atripla* may ↑/↓ warfarin – monitor INR and adjust warfarin as indicated
	Emtricitabine + tenofovir disoproxil fumarate + rilpivirine (*Complera*)	• Clinically significant interactions are not expected and no dose adjustment is necessary		• Interaction with *Complera* unlikely but cannot be excluded – use caution and monitor		• Clinically significant interactions are not expected and no dose adjustment is necessary
	Emtricitabine + tenofovir alafenamide + rilpivirine (*Odefsey*)	• Clinically significant interactions are not expected and no dose adjustment is necessary		• Interaction with *Odefsey* unlikely but cannot be excluded – use caution and monitor		• Clinically significant interactions are not expected and no dose adjustment is necessary
	Bictegravir + emtricitabine + tenofovir alafenamide (*Biktarvy*)	• Clinically significant interactions are not expected and no dose adjustment is necessary				
	Elvitegravir + cobicistat + emtricitabine + tenofovir disoproxil fumarate (*Stribild*)	• *Stribild* ↑ apixaban and rivaroxaban – not recommended		• *Stribild* may ↑ edoxaban – consider alternative anticoagulant	• *Stribild* may ↑ dabigatran – not recommended	• *Stribild* may ↑ warfarin – monitor INR and adjust warfarin as indicated
	Elvitegravir + cobicistat + emtricitabine + tenofovir alafenamide (*Genvoya*)	• *Genvoya* ↑ apixaban and rivaroxaban – not recommended		• *Genvoya* may ↑ edoxaban – consider alternative anticoagulant	• *Genvoya* may ↑ dabigatran – not recommended	• *Genvoya* may ↑ warfarin – monitor INR and adjust warfarin as indicated
	Dolutegravir + abacavir + lamivudine (*Triumeq*)	• Clinically significant interactions are not expected and no dose adjustment is necessary				

Abbreviations: INR, international normalized ratio.
↑/↓: reflect increase or decrease in serum concentration of drug.
Red: not recommended or consider alternative anticoagulant. Green: no dose adjustment is necessary. Orange: increased monitoring as indicated.

dosage requirement was anticipated following ritonavir administration; however, the opposite occurred. Authors did not propose a mechanism for the decrease, however induction of CYP2C9 by ritonavir may have potentiated warfarin activity [32]. Therefore, close monitoring is recommended. Concurrent use of atazanavir and fosamprenavir have not been studied, however the potential to increase INR exists due to competition for CYP3A4-mediated metabolism. Interactions with darunavir are unlikely in the absence of ritonavir, but cannot be excluded, therefore it is recommended to use with caution. Co-administration of cobicistat and warfarin has not been studied, but there is the potential for increased warfarin concentrations via inhibition of CYP3A4 [15]. Recommendations include monitoring INR and adjusting warfarin as indicated. A case report of a patient on warfarin co-administered with HAART that included efavirenz (didanosine, lamivudine, efavirenz) demonstrated an increase in warfarin activity. Warfarin was prescribed for treatment of a DVT in the right lower extremity and the initial daily dose of 5 mg required reduction to 1.25 mg to reach target INR. The authors attributed the dose reduction to inhibition of CYP2C9, thereby potentiating the effect of warfarin [33]. Data are not available to assess warfarin in combination with etravirine, however etravirine may increase warfarin exposure due to inhibition of CYP2C9 [16]. Monitoring of INR and adjustment of warfarin is warranted if indicated due to possible NNRTI influence to increase or decrease coagulation time. Additionally, data are not available to assess warfarin in combination with NRTIs, maraviroc, enfuvirtide, or INSTIs not contained in FDC products. However, based on metabolism and clearance characteristics, a clinically significant interaction is unlikely. Concurrent use of elvitegravir with warfarin may result in reduced plasma concentrations of warfarin via induction of CYP2C9, therefore close monitoring of the INR is recommended along with adjusting warfarin as indicated.

4. Conclusion

This review summarizes available data on DDI between HAART and anticoagulation. There is an information deficit in the literature regarding drug-drug interactions with HIV therapy and anticoagulation. For example, no data were found for potential drug interactions with INSTIs. Similarly, the co-administration of common antiretrovirals such as dolutegravir and cobicistat-boosted regimens has not been firmly evaluated. Currently, the available literature relies heavily on PK studies

that enrolled small samples of relatively healthy individuals who may not predict drug disposition in the aging population. Greater variability can be expected in larger samples in a real-life setting therefore, further studies are required. Additionally, single-dose studies are not adequate to determine the true potential or drug-drug interactions, nor do they reflect the impact of complex concomitant therapies.

This review may assist providers with therapy selection and monitoring. Since the aging population may have been diagnosed earlier and maintained on other agents that were previously first line, such as PIs or NNRTIs, DDI are possible and must be considered. Although data is limited, the potential for DDIs between HAART and DOACs exists based on PK profiles. The commonly used DOACs are metabolized through CYP450 enzymes, and/or are substrates of P-gp transporters, or undergo renal excretion. Management of these interactions should involve careful clinical selection based on patient characteristics. When possible, HAART and DOACs with a low potential for DDI should be selected. In the setting of DDI, warfarin remains a viable anticoagulant choice as one can monitor the INR (more closely, if required) to ensure a therapeutic INR is achieved for the indicated treatment. As new information continues to emerge, readers are advised to consult drug interaction resources.

Declaration of competing interest

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