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Review

Stroke and Systemic Thromboembolism Prevention in People Living With Human Immunodeficiency Virus With Atrial Fibrillation: A Review of Its Implications for Clinical Practice

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ABSTRACT

In the last few decades, types of diseases affecting people living with human immunodeficiency virus (PLHIV) have shifted as the population ages, with cardiovascular disease becoming a leading cause of death in this population. Atrial fibrillation (AF) is an increasingly common arrhythmia both in the general population and in PLHIV, with an estimated prevalence of 2% to 3% among PLHIV. Prevention of stroke and systemic thromboembolism (SSE) with antithrombotic therapy is a cornerstone of AF treatment and substantially decreases AF-related morbidity and mortality. Although updated guidelines extensively discuss this issue, they do not address the peculiarities of PLHIV. The role of human immunodeficiency virus (HIV) infection as an independent factor for SSE in individuals with AF and whether the presence of HIV should alter the threshold for SSE thromboprophylaxis are unknown. Nevertheless, a growing body of evidence describes the increasing burden of comorbidities such as hypertension and stroke in PLHIV, which predispose them to AF and SSE. In the absence of

RÉSUMÉ

Au cours des dernières décennies, les types de maladies qui touchent les personnes vivant avec le virus de l'immunodéficience humaine (PVVIH) ont évolué à mesure que la population vieillit. Les maladies cardiovasculaires deviennent ainsi les principales causes de décès dans cette population. La fibrillation auriculaire (FA) est une arythmie de plus en plus fréquente dans la population générale et chez les PVVIH. On estime que sa prévalence est de 2 % à 3 % chez les PVVIH. La prévention de l'accident vasculaire cérébral (AVC) et de la thromboembolie systémique (TES) par un traitement antithrombotique constitue la pierre angulaire du traitement de la FA et diminue considérablement la morbidité et la mortalité liées à la FA. Bien que les lignes directrices actualisées traitent en profondeur de cette question, elles ne portent pas sur les particularités des PVVIH. On ignore si l'infection par le virus de l'immunodéficience humaine (VIH) est un facteur indépendant de la TES chez les individus atteints de FA et si la présence du VIH devrait contribuer à modifier le seuil de

After the introduction of combination antiretroviral therapy (ART) for the treatment of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome, there has been a marked decrease in acquired immunodeficiency syndrome–related morbidity and mortality with a concomitant improvement in the life expectancy of people living with HIV (PLHIV).[1-3] However, this has been accompanied by a rising incidence of other comorbidities. In particular, cardiovascular disease (CVD) has become a leading cause of death in this population.[4,5] The shift in the morbidities affecting PLHIV implies that a large portion of their care will be focused on the management of chronic diseases such as CVD.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting 3% to 6% of the general population.[6,7] The severity and type of symptoms attributed to

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HIV-specific AF guidelines, PLHIV with AF should be comprehensively assessed for their risk of SSE and bleeding using commonly available scores despite them having been primarily validated in the non-HIV population. Both vitamin K antagonists and direct oral anticoagulants can be used in PLHIV. Addressing HIV-related comorbidities and potential drug–drug interactions with antiretrovirals is crucial to prevent SSE and reduce adverse reactions of oral anticoagulants. This review summarizes the current guidelines for SSE prevention in patients with AF and describes key considerations for their implementation among PLHIV receiving antiretroviral therapy.

thromboprophylaxie de la TES. Néanmoins, de plus en plus de données probantes décrivent le fardeau accru des comorbidités comme l'hypertension et l'AVC chez les PVVIH, qui les prédisposent à la FA et à la TES. En l'absence de lignes directrices en matière de FA lors de VIH, on devrait réaliser une évaluation exhaustive chez les PVVIH atteints de FA à l'aide des scores couramment disponibles même s'ils n'avaient pas d'abord été validés auprès de la population non atteinte du VIH. Les antagonistes de la vitamine K et les anticoagulants oraux directs peuvent être utilisés chez les PVVIH. Il est primordial de se pencher sur les comorbidités liées au VIH et sur les interactions médicamenteuses potentielles avec les antirétroviraux pour prévenir la TES et réduire les effets indésirables des anticoagulants oraux. La présente revue résume les lignes directrices actuelles en matière de prévention de la TES chez les patients atteints de FA et décrit les principales considérations quant à leur mise en œuvre auprès des PVVIH qui reçoivent un traitement antirétroviral.

AF vary significantly ranging from no symptoms to debilitating palpitations, presyncope, syncope, nausea, fatigue, or functional limitation. Furthermore, AF is an important risk factor for stroke, increasing the risk by approximately 5-fold.[8] There are 3 pillars of AF treatment: stroke and systemic thromboembolism (SSE) prophylaxis, prevention of tachycardia-related cardiomyopathy, and symptom improvement.[7]

Although a growing body of literature exists describing CVD in PLHIV,[9-11] little is known about the impact of HIV infection and ART on SSE prophylaxis in AF. Moreover, it is unclear whether contemporary AF treatment guidelines can be applied to PLHIV because they are predominantly based on clinical trials that exclude this population. The aim of this review is to summarize the current guidelines for the prevention of SSE in AF and describe key considerations for their implementation in PLHIV receiving ART.

Methods

Manuscripts included in this review were systematically identified from searching PubMed and MEDLINE (via PubMed) including the following key Medical Subject Heading terms: "atrial fibrillation," "thromboembolism," "stroke," "warfarin," "dabigatran," "rivaroxaban," "apixaban," and "edoxaban" alone or in combination with the terms "antiretroviral agents" or "HIV." Our search was focused on English and Spanish language articles published from January 2000 to April 2018.

Results

The literature search yielded 1235 abstracts. Additionally, we included 2 current guidelines on ART and 3 on AF treatment. The initial screening resulted in 112 articles. After reviewing full-text articles, we selected 53 relevant studies pertaining to AF epidemiology and SSE prevention; 22 were focused on the general population, and 31 were focused on PLHIV. The study selection process is described extensively in Figure 1. Next, we summarize the results of the review according to relevant subheadings. The characteristics of included full-text articles providing data on AF epidemiology and oral anticoagulation (OAC) in PLHIV are shown in Table 1. Supplemental Table S1 provides a full-length version of all articles included.

Epidemiology

The estimated incidence of AF in the general population ranges from 4 to 30 per 1000 person-years,[12] with a lifetime hazard after age 40 years of approximately 25%.[7] This risk increases in older persons and in the presence of heart failure, structural heart disease, hypertension, alcoholism, thyroid disease, diabetes, obesity, and obstructive sleep apnea.[7]

Among PLHIV, Hsu et al.[13] described an incidence rate of AF of 3.6 per 1000 person-years in a large cohort of PLHIV from the Veteran Affairs HIV Clinical Case Registry. Moreover, a meta-analysis investigating the predictors for stroke in PLHIV reported a prevalence of AF of 3%.[14] Sanders et al.[15] performed the first comparison of AF in PLHIV with uninfected controls, yielding a prevalence of AF of 2% in PLHIV. It is expected that the frequency of AF in this population will increase given its strong association with advanced age and traditional CVD risk factors.[1,12]

Many of the pathogenic mechanisms predisposing to AF result in abnormalities in the atrial structure or electrophysiology.[7] After adjustment for cardiovascular comorbidities, PLHIV with CD4 cell count $<$ 200 cells/mm^3 had between 1.4- and 2-fold higher rates of AF, and those with HIV-RNA viral load $>$ 100,000 copies/mL had 1.7-fold increased risk of incident AF compared with individuals with higher CD4 cell counts and HIV-RNA viral load $<$ 500 copies/mL, respectively.[13,15] Purported mechanisms for this relationship include residual excess inflammation, endothelial dysfunction, and macrophage activation present in PLHIV. These factors lead to accelerated atherosclerosis and early aging despite ART and viral suppression.[13,15,16] Moreover, risk factors for AF in the general population were also associated with AF in PLHIV, such as older age, diabetes, hypertension, chronic obstructive pulmonary disease, coronary artery disease, heart failure, alcoholism, hypothyroidism, and kidney disease.[13,15]

Hyperhomocysteinemia is an additional risk factor for stroke, particularly in patients with AF.[17] Several observational studies found that the mean homocysteine concentration was higher in PLHIV compared with uninfected controls, and among PLHIV, individuals exposed to ART had higher

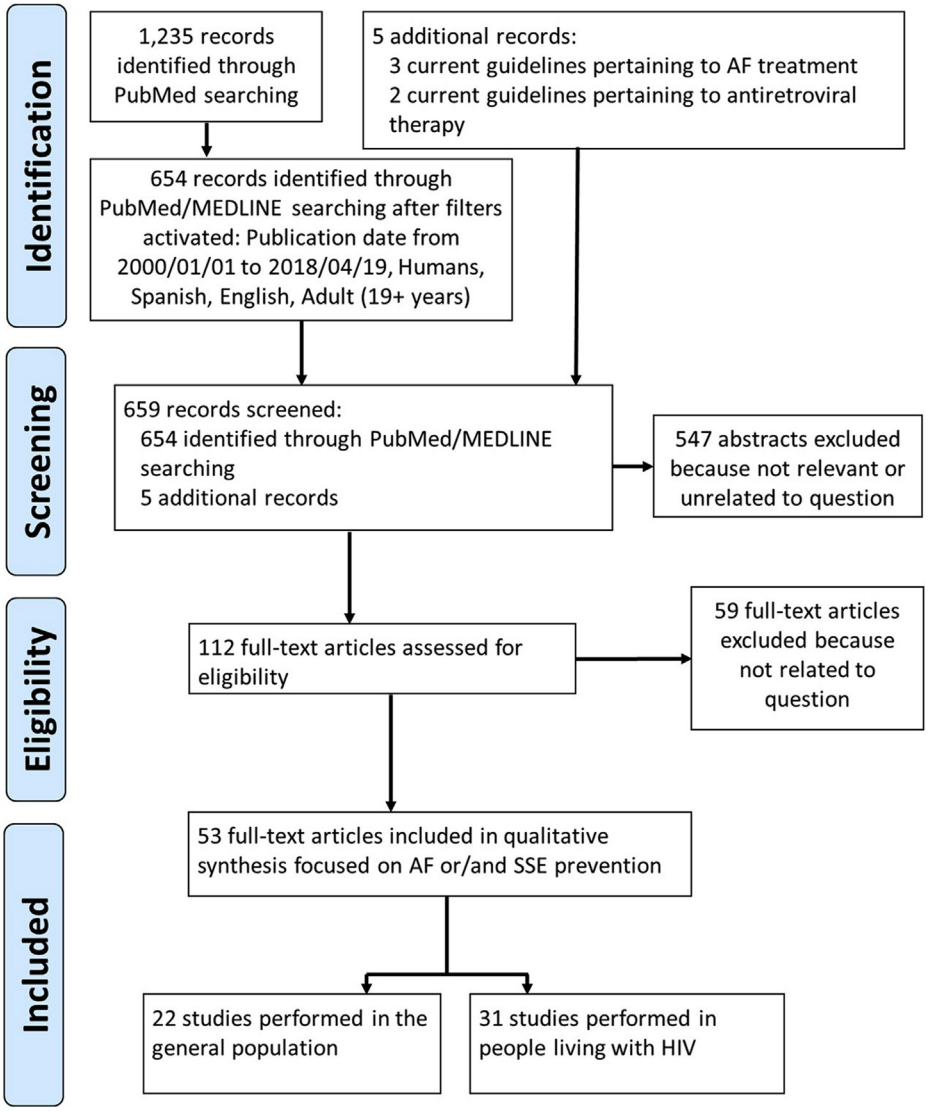

Figure 1. Flow diagram of the study selection process. AF, atrial fibrillation; ART, antiretroviral therapy; PLHIV, people living with human immunodeficiency virus; SSE, stroke and systemic thromboembolism.

concentrations than those without ART.[18] However, inclusion criteria were heterogeneous regarding ART use, stage of HIV infection, and comorbidities. Although multifactorial, vitamin B12 and folate deficiencies can cause hyperhomocysteinemia, and these deficiencies are frequent among PLHIV, with a prevalence of up to 40% and 32%, respectively.[19,20] Vitamin B supplementation significantly reduces homocysteine plasma levels and might reduce the risk of stroke.[21] For PLHIV with AF, measurement of homocysteine plasma levels should be performed, and if raised, assessment and supplementation with vitamin B12 or folate might be beneficial for stroke prevention.

SSE risk and prevention

The estimated risk of SSE in patients with AF is 4% to 6% per year,[8] which vary depending on the presence of certain comorbidities. The Cardiac failure, Hypertension, Age, Diabetes, Stroke ($CHADS_2$) and Congestive heart failure, Hypertension, Age $\geq$75, Diabetes, Stroke, Vascular disease, Age 65-74, and female Sex (CHA_2DS_2-VASc) scores are commonly used schemas that incorporate the most frequent factors to assess the risk of SSE and guide in a practical decision-making process.[7,22,23]

The current guidelines for the treatment of AF from the American College of Cardiology and American Heart Association recommend the use of OAC therapy in patients with a prior transient ischemic attack or stroke or CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in woman.[24] The Canadian Cardiovascular Society (CCS) recommends patients with AF be stratified using the "CCS algorithm" named "CHADS-65." Overall, OAC should be prescribed for the prevention of SSE in patients aged 65 years or older with at least 1 $CHADS_2$ factor or in the presence of valvular heart disease.[25]

Assessment for bleeding risk is also crucial when considering OAC in patients with AF given the rate of major bleeding with these drugs is 2 to 4 per 100 patient-years.[25,26]

Table 1. Characteristics of included full-text articles providing data on AF epidemiology and OAC in PLHIV

Subject	Study	Design	Population	Main outcomes	Summary of main findings
Epidemiology of AF and SSE in PLHIV	Sanders[15] (2018)	Cohort study	PLHIV and uninfected controls	AF	Prevalence of AF in PLHIV: 2%. OR of AF with a nadir CD4 cell count < 200 cells/mm^3: 1.98. Comorbidities associated with increased odds of AF: older age, diabetes, hypertension, and chronic obstructive pulmonary disease.
	Chau[29] (2017)	Cohort study	PLHIV with AF	SSE	HR of SSE by CHA_2DS_2-VASc score: 1.70 for score 1 ($P = 0.28$), 1.34 for score ≥ 2 ($P = 0.55$) vs score 0. CHA_2DS_2-VASc score did not perform well to predict SSE in PLHIV.
	Barnes[62] (2017)	Review	PLHIV	CVD	High rates of heart failure, AF, and ischemic stroke in PLHIV. Underlying mechanisms include chronic inflammation and vasculopathy. Pulmonary hypertension continues affecting PLHIV.
	Adhikari[20] (2016)	Cross-sectional	PLHIV	Vitamin B and folic acid levels	Prevalence of folic acid deficiency up to 32% in PLHIV, highest in individuals with neuropsychiatric symptoms. Prevalence of vitamin B12 deficiency up to 19%.
	Klein[27] (2016)	Cohort study	PLHIV	ESLD	Prevalence of HCV-HIV coinfection = 19%, HBV-HIV = 5% and HCV-HBV-HIV = 2%. ESLD incidence per 1000 person-years was 11.57 in HCV-HBV-HIV infected vs 1.27 in HIV-monoinfected patients. Little use of antivirals for HBV and HCV infection.
	D'Ascenzo[14] (2015)	Meta-analysis	PLHIV	Ischemic stroke	Incidence of ischemic stroke: 1.78%. CD4 cell count < 200 cells/mm^3, HIV-VL, older age, hypertension, smoking, hyperlipidemia, AF, and diabetes were associated with incident stroke.
	Deminice[18] (2015)	Meta-analysis	PLHIV	Levels of homocysteine, vitamin B12, and folate	PLHIV had higher plasma homocysteine and lower folate levels compared with uninfected individuals. PLHIV on ART had higher plasma homocysteine levels compared with PLHIV not on ART.
	Tsoukas[16] (2014)	Review	PLHIV	Immune senescence, atherosclerosis	Chronic inflammation and the immune risk phenotype are responsible for early aging in PLHIV. In addition to traditional CVD risk factors, this contributes to atherosclerosis development.
	Hsu[13] (2013)	Cohort study	PLHIV	AF	Incidence of AF: 3.6/1000 person-years. HR of AF: 1.4 for CD4 cell count < 200 cells/mm^3 and 1.7 for HIV-VL > 100,000 copies/mL. Comorbidities associated with incident AF: older age, white race, CAD, heart failure, alcoholism, kidney disease, and hypothyroidism.
	Elnahar[63] (2012)	Case-control	PLHIV	Risk factors for AF	OR of AF for CD4 cell count < 250 cells/mm^3: 3.62 ($P = 0.017$).
	Franco Moreno[64] (2012)	Case series	PLHIV	VTE	Incidence of VTE: 3.5%. Pulmonary embolism was the most frequent form (42.9%). Altered thrombophilia tests results in 71.4% of cases.
	Hepburn[19] (2004)	Cohort study	PLHIV	Vitamin B12 levels	Prevalence of low vitamin 12 levels: 13%. Significant increment in vitamin B12 levels after ART initiation.
Contemporary ART	DHHS[41] (2018)	Guidelines	PLHIV	Use of ART	ART is recommended for all PLHIV, based on 2 NRTI plus an INSTI for most PLHIV. Different regimens may be needed in certain clinical situations. ART goals include to maintain a suppressed HIV-VL and prevent HIV transmission.
	World Health Organization[42] (2016)		PLHIV	HIV infection treatment and prevention	HIV testing should be offered for all people. All PLHIV should be provided with ART. Fixed-dosed tenofovir disoproxil fumarate/lamivudine (or emtricitabine)/efavirenz is the preferred option for ART initiation. Consider pre-exposure prophylaxis for people at substantial risk of HIV infection.

Use of warfarin with ART	Kumar[54] (2017)	Clinical drug interaction study	Healthy volunteers	Drug interactions	Ritonavir administrated 2 h after dabigatran decreased dabigatran exposure without significant changes in thrombin time. Cobicistat increased dabigatran exposure and thrombin time measures when given simultaneously and separately from dabigatran. Close clinical monitoring is suggested when coadministered with cobicistat.
	Pelufo-Pellicer[52] (2017)	Case report	PLHIV	Bleeding, drug interactions	Bleeding event after switching ART from LPV/r to dolutegravir, probably due to the displacement of warfarin albumin-binding by dolutegravir or interruption of LPV/r CYP2C9 inhibition.
	Good[51] (2015)	Case report	PLHIV	INR, drug interactions	60% higher dose of warfarin required when coadministered with elvitegravir, probably due to elvitegravir CYP2C9 induction.
	Liedtke[46] (2012)	Case report	PLHIV	INR, drug interactions	45% ($P < 0.001$) increase in the mean weekly warfarin dose when switching ART to etravirine, raltegravir, and darunavir/ritonavir, probably due to ritonavir CYP2C9 induction.
	Honda[50] (2012)	Case series	PLHIV	INR, drug interactions	Initiation of raltegravir in patients receiving warfarin was safe. Modifications in warfarin were not necessary. Etravirine can induce CYP3A4 and inhibit CYP2C9 and CYP2C19, potentially interacting with warfarin therapy.
	Anderson[44] (2012)	Cohort study	PLHIV on warfarin therapy	INR, drug interactions	Low proportion (34.5%) of therapeutic INR among adherent patients. Injection drug use was an independent risk factor for subtherapeutic INR; 50% higher dose of warfarin required in patients on ritonavir vs efavirenz.
	Manji[43] (2011)	Cohort study	Patients on OAC	TTR	PLHIV represented 25% of study population. HIV infection was associated with lower TTR (47%, $P = 0.02$). ART was not related with TTR.
	Fulco[45] (2008)	Case report	PLHIV on warfarin	INR, drug interactions	Increased warfarin doses required due to induction of CYP3A4 by nevirapine, CYP2C9 by nelfinavir, or CYP2C9 by LPV/r therapy. Close monitoring of INR in patients receiving warfarin with concomitant ART may be necessary.
	Dionisio[47] (2001)	Case series	PLHIV	INR, drug interactions	Increased warfarin doses required, probably due to nevirapine induction of CYP P450.
Use of DOACs with ART	Yoong[57] (2017)	Case report	PLHIV	Bleeding, drug interactions	Extensive bruising and high rivaroxaban plasma level when coadministered with elvitegravir/cobicistat, probably due to inhibition of rivaroxaban metabolism by cobicistat. Warfarin therapy may be safer when cobicistat is included in the ART regimen.
	Perram[59] (2015)	Case report	PLHIV	Drug interactions	Dabigatran is a suitable anticoagulant for PLHIV receiving ritonavir-boosted atazanavir. Monitoring of dabigatran through levels can be useful in this setting.
	Corallo[56] (2015)	Case report	PLHIV	Bleeding, drug interactions	Surgical site bleeding, prolonged prothrombin time, and high rivaroxaban plasma level when coadministered with darunavir/ritonavir, probably due to CYP3A4 inhibition. Concomitant use of rivaroxaban with darunavir/ritonavir should be avoided.
	Lakatos[55] (2014)	Case report	PLHIV	Bleeding, drug interactions	Gastrointestinal bleeding and high rivaroxaban plasma level when coadministered with darunavir/ritonavir, probably due to inhibition of CYP3A4, CYP2J2, P-gp, and BCRP.
	Barco[58] (2014)	Case report	PLHIV	Drug interactions	Trough levels of dabigatran 110 mg twice daily coadministered with LPV/r were similar to results from the Randomized Evaluation of Long-Term Anticoagulation Therapy trial.
	Egan[49] (2014)	Review	PLHIV on DOACs	Drug interactions	Protease inhibitors or cobicistat may inhibit rivaroxaban and apixaban metabolism. NNRTI possible induce rivaroxaban and apixaban metabolism. No clinically relevant interaction expected with dabigatran. No expected effect on DOACs with INSTI, NRTI, or maraviroc.
	Mueck[53] (2013)	Clinical drug interaction study	Healthy volunteers	Drug interactions	A single high dose of ritonavir (600 mg twice daily) increased rivaroxaban exposure by 153%, probably due to CYP3A4, P-glycoprotein, and breast cancer resistance protein inhibition.
	Bates[60] (2013)	Case report	PLHIV	VTE, drug interactions	VTE event when rivaroxaban was coadministered with nevirapine probably due to CYP3A4 induction by nevirapine.

AF, atrial fibrillation; ART, antiretroviral therapy; CAD, coronary artery disease; $CHADS_2$, cardiac failure, hypertension, age, diabetes, stroke; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75,diabetes, stroke, vascular disease, age 65-74, and female sex; CVD, cardiovascular disease; CYP, cytochrome; DOACs, direct oral anticoagulants; ESLD, end-stage liver disease; HIV-VL, HIV-RNA viral load; HR, hazard ratio; INR, international normalized ratio; INSTI, integrase strand transfer inhibitors; LPV/r, lopinavir/ritonavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitors; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulation; OR, odds ratio; PLHIV, people living with human immunodeficiency virus; SSE, stroke and systemic thromboembolism; TTR, time in therapeutic range; VTE, venous thromboembolism.

Table 2. Prevalence of CHA_2DS_2-VASc and bleeding risk factors in PLHIV

Condition	Prevalence in PLHIV	Prevalence in general population
Congestive heart failure*	7%[62]	5%[62]
Hypertension*,†	33%[15]	19%-62%[15,65]
Age ≥ 65 y*,†	14%[15]	14%[15]
Diabetes mellitus*	9%[15]	6%-9%[15,65]
Stroke/transient ischemic attack/ thromboembolism*,†	1%-6%[15,64]	3%-4%[15,65]
Myocardial infarction*	11%[15]	4%-5%[15,65]
Coronary heart disease*	14%[15]	7%[15,65]
Abnormal renal function†	7%-14%[13]	4%[65]
Abnormal liver function/hepatitis C infection†	3%-23%[15,28]	1%[15]
TTR†,‡	31%-47%[43,44]	56%-70%[32,36]
Alcohol excess†	7%-35%[13,28,30]	3%-16%[65]

INR, international normalized ratio; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75, diabetes, stroke, vascular disease, age 65-74, and female sex; PLHIV, people living with HIV; TTR, time in therapeutic range.

* Risk factor for stroke.

† Risk factor for bleeding.

‡ TTR < 60% is considered as labile INR.

The Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio (INR) measurements for patients on warfarin, Elderly (> 65 years), Drugs/alcohol concomitantly (HAS-BLED) estimates bleeding risk before starting anticoagulation.[7,25] In patients taking OAC, particularly in those with HAS-BLED scores ≥ 3, potential bleeding risk factors should be revised, such as avoidance of nonsteroidal anti-inflammatory drugs/aspirin and alcohol misuse, more strict INR monitoring, careful selection of invasive procedures, and control of hypertension, anemia, or liver disease.[23,25,26] With regard to liver function, it is noteworthy that coinfection with hepatitis B or C viruses is considerably prevalent in PLHIV (3%-15% and 10%-30%, respectively).[27,28] Coinfected patients have accelerated progression to end-stage liver disease and hepatocarcinoma, potentially increasing bleeding risk while on OAC. Specific antiviral therapy for hepatitis C or B viruses should be considered in these patients to prevent deleterious outcomes.[27] Table 2 summarizes CHA_2DS_2-VASc and bleeding risk factors frequency in PLHIV and in the general population.

Stroke is more prevalent in PLHIV than in HIV-negative individuals.[29] Nevertheless, it is unclear whether the presence of HIV infection alters the risk of stroke in individuals with AF. Likewise, the ability of available scores to estimate the need of OAC in PLHIV with AF has been scarcely studied. Chau et al.[29] found a rate of 8.1 SSE events per 1000 person-years in PLHIV with CHA_2DS_2-VASc score ≥ 2, lower than expected for the same score in the general population. This may be explained by the lower mean age of PLHIV with AF vs the general population. Moreover, there was not a gradual increment on SSE rate with increasing CHA_2DS_2-VASc score, suggesting that it is not well calibrated for PLHIV.[29] HIV-specific factors not considered by the CHA_2DS_2-VASc score, such as CD4 cell count, HIV-RNA viral load,[29] and ART, may affect the rate of SSE in PLHIV. Until more evidence is available, it appears reasonable to apply the CCS or American College of Cardiology and American Heart Association guidelines to PLHIV with AF.[24,25]

OACs used for SSE prophylaxis in AF include vitamin K antagonists (VKAs) (eg, warfarin/Coumadin) or direct oral anticoagulants (DOACs), such as direct thrombin inhibitors (eg, dabigatran) and factor X—activated inhibitors (eg, rivaroxaban, apixaban, edoxaban). VKAs have reduced stroke rates vs aspirin or no treatment by 37% and 64%, respectively, and mortality rate by 26% vs control.[23,26] Furthermore, widely available reversal agents exist in case of severe bleeding. However, activity of VKAs can be affected by many medications and foods, and requires frequent monitoring of INR to ensure time in therapeutic range (TTR).[7,30,31]

The efficacy and safety of DOACs on SSE prophylaxis have been compared with VKAs. In randomized controlled trials, dabigatran 150 mg twice daily and apixaban 5 mg twice daily were superior to warfarin,[32,33] whereas dabigatran 110 mg twice daily, rivaroxaban 20 mg daily, and edoxaban 30 mg or 60 mg daily were noninferior to warfarin.[32,34,35] Furthermore, all DOACs reduced the risk of intracranial haemorrhage compared with VKAs.[32-35] Observational studies supported these results[31,36] and reported the comparative effectiveness and safety of DOACs. Overall, dabigatran, rivaroxaban, apixaban, and edoxaban demonstrated similar effectiveness in preventing SSE, whereas rivaroxaban treatment was associated with a higher risk of bleeding.[30,37-40] DOACs have a predictable effect and do not require blood testing for anticoagulation monitoring. Currently approved DOAC reversal agents are idarucizumab, a humanized monoclonal antibody for reversal of dabigatran, and andexanet alfa, a recombinant factor Xa without intrinsic catalytic activity for reversal of apixaban and rivaroxaban.[25,38] Reversal agents should be administrated for major or life-threatening bleeding unresponsive to supportive measures or before urgent procedures associated with high bleeding risk.[25] There is lack of evidence on the administration of DOAC reversal agents with ART or in PLHIV.

Contemporary ART

ART has dramatically altered the natural history of HIV infection averting associated morbidity, mortality, and transmission.[41] There are sufficient data to offer ART to all PLHIV irrespective of CD4 cell count to achieve utmost and sustained HIV-RNA viral load suppression.[41,42] Availability of new treatment options modifies therapeutic preferences periodically. Current World Health Organization antiretroviral guidelines recommend first-line regimens consisting of 2 nucleoside reverse transcriptase inhibitors (NRTI) (tenofovir disoproxil fumarate plus emtricitabine or lamivudine) in addition to a non-nucleoside reverse transcriptase inhibitor (NNRTI) (efavirenz) or an integrase strand transfer inhibitor (INSTI) (dolutegravir), prioritizing fixed-dose combinations.[42]

The US Department of Health and Human Services antiretroviral guidelines recommend an initial regimen based on a combination of 2 NRTIs (tenofovir disoproxil fumarate, tenofovir alafenamide, or abacavir plus lamivudine or emtricitabine) and a third active drug from the INSTI family (bictegravir, dolutegravir, or raltegravir) for most PLHIV. Pharmacologically enhanced protease inhibitors (PIs), elvitegravir/cobicistat, and NNRTIs are recommended as third drugs in certain clinical scenarios.[41] Specific factors such as

viral resistance, comorbidities, toxicity, drug interactions, and adherence can determine alternative first-line regimens.[41]

Antithrombotic therapy in PLHIV

Current AF guidelines pertaining to antithrombotic therapy do not assess PLHIV as a special population,[24,25] and PLHIV are typically excluded from clinical trials evaluating OAC. Therefore, knowledge of antithrombotic therapy in PLHIV stems from observational studies and clinical drug-interaction studies in healthy volunteers. Only 1 article assessed OAC effectiveness for SSE prevention in PLHIV with AF.[29] In this study, warfarin was not protective for SSE events.[29] Although the reason for this challenging finding requires further inquiry, it is suspected to be related to an increased thrombogenic state, diverse stroke etiologies, and difficulties in attaining appropriate warfarin therapy among PLHIV.

Use of warfarin with antiretrovirals

The risk of stroke or bleeding with warfarin therapy directly correlates to the proportion of time within the INR TTR. PLHIV have a substantially lower TTR compared with the general population.[43] Cohort studies have shown that the TTR for PLHIV on warfarin therapy was only 47%[43] vs 56% to 70%[31,36] in the general population. In those with INR outside the target, 50% had subtherapeutic INR and 17% had supratherapeutic INR.[44] A subtherapeutic INR exposes the patient to an increased risk of stroke, whereas a supratherapeutic INR increases the bleeding hazard.

Difficulty to attain TTR may be caused by drug−drug interactions and unreported nonadherence. Drug−drug interactions are primarily a result of alterations in warfarin metabolism through increases or decreases in cytochrome P450 (CYP) 2C9 enzyme activity.[45] Warfarin dose requirements substantially increase in patients receiving boosted PI and nevirapine, an NNRTI, due to CYP2C9 induction.[45-47] On the other hand, efavirenz was associated with warfarin overdosing and bleeding due to CYP2C9 inhibition.[44,48] This inhibition of warfarin metabolism can theoretically occur with etravirine, a weak CYP2C9 inhibitor,[48] contributing to the INR variability shown by Liedtke et al.[46] Warfarin is not expected to interact with NRTI[49] or maraviroc, a drug that antagonizes C-C chemokine receptor type 5 averting infection of the cell by HIV.[48,49]

Among INSTI, elvitegravir is the only drug that influences CYP450 isoenzymes by inducing the CYP2C9 activity.[49-51] Because it is coformulated with cobicistat (a pharmacokinetic enhancer without antiviral activity that is a strong CYP3A4 inhibitor with no effect on CYP2C9), mild opposite effects might be seen. Only 1 case reported by Good et al.[51] showed that increased warfarin dosages were necessary when coadministered with elvitegravir/cobicistat, suggesting that CYP2C9 induction by elvitegravir was predominant. Conversely, raltegravir can be safely used with warfarin, as described by Honda et al.[50] Recently, a case of a woman who presented with haemorrhages after switching from lopinavir/ritonavir (LPV/r) to dolutegravir was reported. The reason for this bleeding event may have been the displacement of warfarin albumin-binding by dolutegravir or the end in warfarin metabolism induction after stopping LPV/r.[52] So far, no data have been reported on the coadministration of bictegravir and warfarin. More frequent monitoring of INR is prudent in PLHIV who are on warfarin and have any ART regimen modification.

Use of DOACs with antiretrovirals

DOACs are metabolized by CYP3A4 and P-glycoprotein transporter (P-gp) with the exception of dabigatran and edoxaban, which are mainly substrates for P-gp.[35,49] Next, we discuss pertinent issues of using DOACs with specific antiretroviral agents or drug classes.

Protease inhibitors and cobicistat

The anticoagulant effect of factor X−activated inhibitors is potentiated when coadministered with strong inhibitors of CYP3A4 and P-gp such as ritonavir[53] or cobicistat,[54] potentially leading to bleeding events. With the exception of tipranavir, other PIs are inhibitors to a lesser extent.[49] Evidence of rivaroxaban interacting with PI has been demonstrated. Mueck et al.[53] showed a significant increase in rivaroxaban exposure after ritonavir administration in healthy volunteers. Lakatos et al.[55] and Corallo et al.[56] reported bleeding events related to ritonavir-boosted darunavir and rivaroxaban coadministration. Regarding cobicistat, Yoong et al.[57] described a case of extensive bruising after rivaroxaban introduction in a patient with AF. Although no published data are available on the interaction between other factor X−activated inhibitors and PI or cobicistat, it is recommended to avoid their use concomitantly.[41]

Because of the unique metabolism of dabigatran among DOACs, it can be coadministered with much current ART. Among PIs, Kumar et al.[54] found no significant interactions when dabigatran was simultaneously taken with ritonavir in healthy subjects despite being a potent P-gp inhibitor. Barco et al.[58] described favourable outcomes with LPV/r and full-dosed dabigatran in a person living with HIV requiring dabigatran peri-AF ablation. Likewise, Perram et al.[59] revealed the successful combination of ritonavir-boosted atazanavir with dabigatran. Conversely, it has been shown that simultaneous cobicistat administration significantly increased dabigatran anticoagulant effect by 51% in healthy volunteers.[54] To minimize the impact of cobicistat, the authors suggested closely monitoring of dabigatran anticoagulant effect, reduced dabigatran dosing (eg, 75 mg twice daily), separate dosing by at least 4 hours, or monitoring of DOAC levels.[54] Therefore, consider avoiding this association in view of its challenging management.[41]

Non-nucleoside reverse transcriptase inhibitors

The NNRTIs nevirapine, efavirenz, and etravirine share the capacity to induce CYP3A4 potentially leading to the loss of anticoagulant effect of DOACs metabolized that way.[41,49,55] Accordingly, Bates et al.[60] reported a case in which concurrent nevirapine may have increased the clearance of rivaroxaban, leading to deep venous thrombosis with pulmonary embolism. Weak P-gp inhibitors such as etravirine[41] and rilpivirine[61] might potentiate the anticoagulant effect of DOACs even though no bleeding events were reported. Because efavirenz or nevirapine do not appreciably affect P-gp, their coadministration with dabigatran and edoxaban is likely to be safe.[41] So far, no data regarding the administration of the

		Warfarin*	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Protease Inhibitors						
	Ritonavir	↓	↑**	↑	↑	↑
	Lopinavir	↓		↑	↑	↑
	Atazanavir	↓	↑	↑	↑	↑
	Darunavir	↓	↑	↑	↑	↑
Cobicistat		↑	↑	↑	↑	↑
Non-Nucleoside Reverse Transcriptase Inhibitors						
	Nevirapine	↓		↓	↓	
	Efavirenz	↑		↓	↓	
	Etravirine	↑	↑	↓	↓	↑
	Rilpivirine		↑			
	Doravirine					
Integrase Strand Transfer Inhibitors						
	Raltegravir					
	Dolutegravir					
	Bictegravir					
	Elvitegravir/cobicistat	↓	↑	↑	↑	↑
Nucleoside Reverse Transcriptase Inhibitors						
	TDF/FTC					
	TAF/FTC					
	Abacavir/lamivudine					
CCR5 Antagonist						
	Maraviroc					
No Interaction Expected		**Potential interaction**		**Do not administer**		
↓=ART decreases OAC concentration; ↑=ART increases OAC concentration. *Potentially solved by increasing INR monitoring. **Co-administrate simultaneously.						

Figure 2. Drug interactions between oral anticoagulants and antiretrovirals. ↓ = ART decreases OAC concentration; ↑ = ART increases OAC concentration. *Potentially solved by increasing INR monitoring. **Coadministrate simultaneously. ART, antiretroviral therapy; CCR5, C-C chemokine receptor type 5; FTC, emtricitabine; INR, international normalized ratio; OAC, oral anticoagulant; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Data sources: References[41,43-60].

novel NNRTI, doravirine, with DOACs have been reported. However, given the lack of induction/inhibition of CYP450 isoenzymes or P-gp by this drug, no significant interactions are expected.

Integrase strand transfer inhibitors

Although not extensively studied, there are no expected interactions between INSTIs and DOACs. However, elvitegravir must be coadministered with a pharmacokinetic booster (cobicistat or ritonavir) to achieve appropriate plasma levels. Therefore, this combination is generally not recommended when prescribing DOACs.[41,49]

Other antiretrovirals

NRTIs and maraviroc do not affect DOAC metabolism and can be used concomitantly without expected interactions.[49] It is recommended to avoid factor X—activated inhibitors (rivaroxaban, apixaban) in combination with cobicistat, PIs, or NNRTIs.[41,55] The direct thrombin inhibitor dabigatran can be prudently administrated with ritonavir-boosted PIs and NNRTIs. Figure 2 summarizes possible drug—drug interactions.

Conclusions

The focus of HIV-related care has changed substantially over the past decades, with CVD becoming an increasingly prominent cause of death in PLHIV. Although AF risk factors are prevalent in PLHIV, there are limited data regarding AF outcomes and management in this population. Moreover, stroke prediction scores commonly used in the general population, such as the CHA_2DS_2-VASc, have low accuracy in PLHIV. Until additional literature regarding AF in PLHIV becomes available, the guidelines developed for the general population should be followed with some considerations. PLHIV with AF should have a comprehensive evaluation that includes SSE risk estimation, bearing in mind the lack of validation of available scores in this population. OACs should be prescribed when appropriate, taking into account potential drug—drug interactions. Further research is needed to advance this understanding and define the best approach for AF management in PLHIV.

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Supplementary Material

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