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REVIEW

Atrial fibrillation and human immunodeficiency virus type-1 infection: a systematic review. Implications for anticoagulant and antiarrhythmic therapy

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The prevalence and incidence of atrial fibrillation/flutter (AF/AFL) in patients with human immunodeficiency virus type-1 (HIV-1) infection have been poorly investigated. We performed a systematic review using PubMed and Cochrane Database of Systematic Reviews, and screening of references, searching for clinical studies reporting on the association between HIV-1 infection and AF/AFL. We also summarized the main interactions of antiretroviral agents with antithrombotic and antiarrhythmic drugs. We found a prevalence of AF/AFL ranging from 2.0% to 5.13% in patients with HIV-1, with an incidence rate of 3.6/1000 person-years. Low CD4+ count (<200–250 cells ml^{-1}) and high viral load were predictors of AF/AFL. Regarding drugs interactions, nucleoside reverse transcriptase inhibitors, integrase inhibitor and maraviroc have the lowest interactions with oral anticoagulants. Among anticoagulants, dabigatran presents the most favourable profile. Most of antiarrhythmic drugs interact with protease inhibitors, with beta blockers and diltiazem having fewer interactions. The few studies available suggest a non-negligible prevalence of AF/AFL in patients with HIV-1 infection. Awareness of potential interactions with anticoagulation and antiarrhythmic drugs is needed to offer optimal management in this population.

Introduction: cardiovascular disease risk in HIV-1 infection

The availability of highly effective antiretroviral therapy (ART) has resulted in markedly improved survival for people with human immunodeficiency virus type-1 (HIV-1) infection. While HIV-1 related mortality is declining, the incidence of new cases of HIV-1 infection remains stable, resulting in a growing number of older adults living with HIV-1 infection [1]. As a consequence of the increased life expectancy, the effects of ageing on HIV-1 infected persons have begun to be evident. In particular, long-term effects of HIV-1 infection, ART use and traditional risk factors may be significant contributors to the increased risk of premature cardiovascular disease (CVD) described in this population.

A pathogenic relevant role in CVD risk development is played by the chronic immune activation and inflammation caused by HIV-1 infection itself [2]. Indeed, monocytes are an important source of inflammatory mediators that promote CVD, even in treated HIV-1 patients [3]. Moreover, low CD4+ T cell count and/or failure to restore normal CD4+ T cell

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counts during ART have been associated with the occurrence of CVD and increased risk of morbidity and mortality due to CV events [4].

In addition, several antiretroviral drugs, such as nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs), could result in an altered fat redistribution that characterizes the so-called 'lipodystrophy syndrome' (subcutaneous fat tissue atrophy in the face, limbs and buttocks and/or lipo-accumulation in different body districts, i.e., neck, trunk, abdomen and viscera) [5]. These fat alterations were frequently associated with several metabolic and endocrine disorders similar to those of the metabolic syndrome (hypertriglyceridemia, low high-density lipoprotein cholesterol and insulin resistance), which are well-known risk factors for CVD [6]. A dyslipidaemia induced by integrase inhibitors has been also described, which could be considered a risk factor for increased CVD [7].

Beside drugs, several pathophysiological alterations potentially contributing to the increased CVD risk have been reported in association with HIV-1 infection. For instance, HIV-1 infected patients are characterized by increased oxidative stress [8], endothelial/vascular dysfunction [9] and platelet activation [10], again all factors potentially contributing to the atherosclerotic burden in HIV-1 patients [11].

Altogether these findings probably account for the increased risk of myocardial infarction (MI) with an incidence rate (IR) for type 1 MI of 2.57 per 1000 person-years [12], and a higher ischaemic stroke risk (IR of 2.79 per 1000 person-years) [13] described in HIV-1+ patients. Nonetheless, the association between HIV-1 and atrial arrhythmias, such as atrial fibrillation and atrial flutter (AF/AFL), has scarcely been investigated. HIV-1 patients have been excluded from the randomized trials of stroke prevention, and thus, limited data are available on stroke risk and appropriate thromboprophylaxis in such patients.

The aim of this systematic review was to summarize the available evidence on the risk of AF/AFL during HIV-1 infection. We also focused on the implications for the management of patients with concomitant AF/AFL and HIV-1, considering several drug–drug interactions of ART with oral anticoagulants and antiarrhythmic drugs.

Systematic review of risk of AF/AFL in HIV-1

Eligibility criteria for the systematic review

We included all original clinical research articles in English language with full text available. In particular, all observational studies (both prospective and retrospective) reporting data on the prevalence and/or incidence of AF/AFL in patients with HIV-1 were selected. We did not include the following: (1) case reports, (2) editorials/comments/letters and (3) review articles.

Information sources and search strategy

We performed a systematic review of the literature searching MEDLINE via PubMed, and Cochrane Database of Systematic Reviews, for a combination of the following keywords 'atrial fibrillation', 'HIV' and 'atrial flutter'. The research strategy had no time restriction and was performed according to PRISMA guidelines [14]. The screening of reference lists of studies was also performed.

Study selection process

The study selection was performed in multiple phases. In the first phase, potentially relevant studies were obtained by combined searches of electronic databases using the selected above-mentioned keywords. In the second phase, studies were reviewed and excluded by study typology; thus, letters, editorial, case reports and comments were excluded. Then we performed a detailed analysis of full-text articles to assess whether they addressed the specific study question (Supporting Information Figure S1).

Data collection process

Two physicians (D.P. and I.M.) independently screened the titles and abstracts of manuscripts identified through the database searches to identify studies potentially eligible for further assessment. For each study we collected the following information: authors, year of publication, study design, number of patients included, duration of follow-up, prevalence and/or incidence of AF/AFL.

Ethical review

Given the study type (review article), ethical approval was not necessary.

Study selection

We identified 127 results from the combined search (Supplementary Figure S1). Of these, 63 reports were excluded by study typology (i.e. non-clinical studies). Detailed analysis of the remaining results showed that 60 studies did not address the study question. Of the remaining four studies, one was excluded, as it included only patients who already had concomitant HIV-1 infection and AF [15]. Thus, three studies were eligible and are reported in Table 1.

The quality of the studies was assessed by the Newcastle–Ottawa quality assessment scale (NOS) for non-randomized studies, including case–control and cohort studies [16]. This scale evaluates observational study regarding (1) selection of patients (representativeness of the exposed and non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study); (2) comparability (comparability of cohorts on the basis of the design or analysis); (3) outcome (assessment of outcome; length of follow-up $\geq$ 12 months; adequacy of follow-up of cohorts) (Supplementary Table S1). The total score ranges from 0 to 9 points.

Study characteristics and results of individual studies

Only three clinical studies [17–19] investigated the risk of AF/AFL in patients with HIV-1 (Table 1). The studies were of good quality, with a NOS score of 7 out of 9 (Table S1). The prevalence of AF/AFL ranged from 2.0% to 5.13%.

The first report on the association between HIV-1 and AF was a retrospective study including 780 HIV-1 patients, of

Table 1

Clinical studies reporting prevalence/incidence of atrial fibrillation in HIV-1 patients

Study (Year)	Study design	Population	Male (%)	Age	FU (years)	Prevalence/incidence of AF	Other findings	NOS
Elnahar (2012) [17]	Retrospective	780 HIV-1 patients	67.5[a]	56.8 ± 9.4[a]	3	40/780 (5.13%) developed AF.	47% of HIV-1 patients who developed AF had CD4+ T cell count <250 cells ml^{-1} *vs.* 20% of controls ($P = 0.017$)	7
Hsu (2013) [18]	Registry	30 533 HIV-1 infected veterans	97.2	53.6 ± 11.4	6.8	780 incident cases (2.55%): 641 AF and 139 AFL. Incidence rate: 3.6 per 1000 person-years (95% CI 3.4–3.9).	CD4+ T cell count (<200 *vs.* >350 cells ml^{-1}; HR: 1.4; 95% CI: 1.1–1.8; $P = 0.018$) and viral load >100 000 *vs.* <500 copies ml^{-1}; HR: 1.7; 95% CI: 1.2–2.4; $P = 0.002$) were associated to incident AF.	7
Sanders (2018) [19]	Retrospective	5052 HIV-1 patients	82.5	48.2 ± 11.6	16	101 confirmed AF/AFL cases (2.00%)	OR 1.98, 95% CI 1.21–3.25 for nadir CD4+ T cell count <200 cells ml^{-1} for AF/AFL. No association between HIV viral load and AF/AFL (OR 1.03, 95% CI 0.86–1.24)	7

[a]Values refer to 40 patients developing AF

AF, atrial fibrillation; AFL, atrial flutter; CI, confidence interval; FU, follow-up; HR, hazard ratio; NOS, Newcastle–Ottawa quality assessment scale; OR, odds ratio

whom 40 developed AF [17]. In these patients, a low CD4+ cell count (<250 cells mm^{-3}) was observed more frequently than matched control patients and independently associated with new-onset AF (OR: 3.62, 95% CI 1.34–9.77) [17].

Similar findings were reported by Hsu *et al.* [18] who found in a national sample of HIV-1 infected veterans that low CD4+ cell count (<200 cells mm^{-3}, HR: 1.4; 95% CI 1.1–1.8, $P = 0.018$) and high viral load (>100 000 copies ml^{-1}, HR: 1.7, 95% CI 1.2–2.4, $P = 0.002$) were risk factors for the development of AF [18], along with age ≥ 65 years (HR: 7.9, 95% CI 5.1–12.3, $P < 0.001$), coronary artery disease (HR: 2.4, 95% CI 2.0–2.9, $P < 0.001$), congestive heart failure (HR: 4.8, 95% CI 3.9–5.9, $P < 0.001$), alcoholism (HR: 1.4, 95% CI 1.1–1.7, $P = 0.001$), hypothyroidism (HR: 1.5, 95% CI 1.1–2.0, $P = 0.010$), severe renal impairment (HR: 1.7, 95% CI 1.2–2.4, $P = 0.006$) and proteinuria ≥2000 mg dl^{-1} (HR: 2.5, 95% CI 1.5–4.3, $P = 0.001$). Black ethnicity was instead associated with a lower incidence of AF (HR: 0.6, 95% CI 0.5–0.7, $P < 0.001$).

Finally, a study by Sanders *et al.* included 5052 HIV-1 patients and found a prevalence of 2% of AF, which was marginally significant compared to 1.57% of 10 121 non-HIV patients ($P = 0.056$) [19]. In addition to low nadir CD4+ count (<200 cells mm^{-3}), older age, diabetes, hypertension and COPD were risk factors for AF/AFL [19]. Conversely, in this study, peak viral load was not associated with an increased risk of AF/AFL [19].

Of note, the majority of patients included in these studies were men, and thus risk factors for developing AF may be different in female HIV-1 patients. This difference is arguable as a sex-specific immune response to HIV-1 has been described, including HIV-1 viral load in women, partially due to a direct inhibition of viral transcription by oestrogen [20, 21]. Furthermore, women have an average higher T-cell activation for a given level of blood viraemia [21]. As a consequence, the threshold of CD4+ T cells representing a risk factor for the development of AF/AFL may be different in women than men.

HIV-1 and atrial abnormalities

HIV-1 has been shown to possess a specific cardiac tropism. Specifically, some surface components, such as Nef, seem to be relevant for cardiac toxicity [22]. In particular, Nef inhibits autophagy flux leading to cardio-cytotoxicity and death of cardiomyocytes [22]. Thus, a specific viral myocardial inflammation pattern has been described in HIV-1 patients, directly related to HIV-1 infection or to some mostly opportunistic microorganisms [23].

Atrial cardiomyopathies have been strongly associated with the development of atrial arrhythmias, such as AF/AFL [24]. Some abnormalities in cardiac and specifically atrial structure and function have been described in patients with HIV-1 infection. For example, cross-sectional study of 95 HIV-1 infected and 30 healthy subjects matched for characteristics and free from cardiovascular disease, showed that intramyocardial lipid levels, myocardial fibrosis and cardiac function (measured by strain) were both increased in patients with HIV-1 as compared to controls [25]. A large echocardiography study showed that 40% of 656 patients with HIV-1 showed a left atrial enlargement (LAE) [26]. Indeed, the latter has been associated to an increased risk of developing new AF [27] and AF recurrence [28], and to a high risk of ischaemic stroke [29–31] in patients with or without AF.

A study involving 42 HIV-1 patients and 40 healthy subjects showed that the atrial electromechanical delay, assessed

by tissue Doppler imaging, of both left and right atria was increased in patients compared to controls. This is a relevant finding as the atrial electromechanical delay reflects the electrical and structural morphology of the atria, and has been correlated with the development of new onset AF [32].

Managing drug–drug interactions in patients with HIV-1 and AF/AFL

Anticoagulant treatment

The development of AF/AFL, which is *per se* associated with a five-fold increased risk of ischaemic stroke [33, 34], may be an additional factor contributing to the increased thromboembolic risk in HIV-1 infection. Apart from established stroke risk factors in AF/AFL, associated valvular heart disease would require consideration of oral anticoagulants [35].

A recent study from the Veterans Affairs HIV Clinical Case Registry including 914 patients with HIV-1 and AF confirmed a high thromboembolic risk in this setting [15]. Thus, the rate of events according to a CHA_2DS_2-VASc score of 0, 1 and ≥2 was 5.4, 9.3 and 8.1 per 1000 person-years, respectively [15]. Furthermore, warfarin did not show a significant association with reduced rate of thromboembolic events raising concerns about the optimal thromboprophylaxis for HIV-1 infected persons with AF.

Given the association with CVD risk factors and structural abnormalities on cardiac imaging, many patients with HIV-1 and AF/AFL should be treated with oral anticoagulants, either vitamin K antagonists (VKAs) or non-vitamin K direct oral anticoagulants (NOACs), according to the CHA_2DS_2-VASc score. The choice of the most appropriate oral anticoagulant in patients with HIV-1 infection is challenging given the several drug–drug interactions between ART and anticoagulants. Also, HIV-1 infected subjects have been excluded from the randomized trials of stroke prevention in AF, thus robust trial data are lacking.

Most drugs used in combination ART for the treatment of HIV-1 infection have significant effects on liver cytochromes, such as CYP2C9 and CYP3A4 (Table 2), which are responsible for the metabolism of many drugs, including oral anticoagulants (CYP3A4: R-Warfarin, R-Acenocumarol, Apixaban, Rivaroxaban, Edoxaban; CYP2C9: S-Warfarin, S/R-Acenocumarol) [36]. For this reason, interactions between VKAs and ART are likely, especially with PIs or non-nucleoside reverse transcriptase inhibitors (NNRTIs) [37]. Conversely, NRTIs are renally excreted, thus presenting no interactions with drugs metabolized at liver site. Dolutegravir and maraviroc are CYP3A4 substrate and are influenced by drugs modulating this enzyme.

By the same mechanism, NOACs also have interaction with ART drugs [38, 39]. A case of decreased rivaroxaban concentration by concomitant nevirapine administration has been described, as the result of putative CYP3A induction and accelerated drug clearance [40].

Dabigatran is the only NOAC with non-enzymatic liver metabolism and predominant renal excretion, thus presenting fewer interactions with ART drugs. Table 3 reports expected interactions between NOACs and antiretroviral drugs [41, 42].

Table 2

Effect of antiretroviral drugs on liver cytochromes CYP2C9 and CYP3A4

	CYP2C9	CYP3A4
Protease inhibitors		
Saquinavir	Inhibition	Inhibition
Tipranavir	Induction	Inhibition
Ritonavir[a]	Modest Induction[a]	Strong Inhibition[a]
Atazanavir	Inhibition	Modest Inhibition
Darunavir	Induction	Modest Inhibition
Lopinavir	Induction	Strong Inhibition
Nelfinavir	Induction	Induction/inhibition
Indinavir	No significant effect	Inhibition
Non-nucleoside reverse-transcriptase inhibitors		
Delavirdine	Inhibition	Inhibition
Efavirenz	Modest Inhibition	Modest Induction
Nevirapine	Induction	Strong Induction
Etravirine	Inhibition	Modest Induction
Rilpivirine	No significant effect	Induction
Doravirine	–	Substrate
CCR5 inhibitor		
Maraviroc	–	Substrate
Integrase inhibitors		
Raltegravir	–	–
Dolutegravir	–	Substrate
Elvitegravir	Modest Induction	Inhibition
Cobicistat[b]	–	Strong Inhibition
Bictegravir	–	Substrate

[a]Ritonavir is used only as low 'boosting' dose (100–200 mg) in association with other PIs to enhance their pharmacokinetic properties by inhibiting CYP3A4

[b]Not an integrase inhibitor and available in combination with elvitegravir, atazanavir and darunavir

Despite results indicating a differential effect of NOACs with men being more protected from ischaemic stroke/systemic embolism and women more protected from major bleeding events, the application of these findings to the HIV-1 population remains uncertain [43].

Antiarrhythmic drugs

Similarly to antithrombotic drugs, significant drug–drug interaction may be detected also with antiarrhythmic treatments commonly used for the management of AF/AFL. A list of the most important interactions is reported in Table 4.

Drug serum concentration of antiarrhythmic medications can be significantly increased by an antiretroviral therapy containing a PI with or without booster (ritonavir/cobicistat). For instance, two case reports showed a significant increase of

Table 3

Expected interactions between non-vitamin K oral anticoagulants and antiretroviral drugs

Antiretroviral drugs	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Protease inhibitors	Increase of Apixaban expected with protease inhibitor/cobicistat, protease inhibitor/ritonavir. Use of strong inhibitors of both CYP3A4 and P-gp *contraindicated* in SPC. Coadministration not recommended; if necessary, reduce apixaban dose by 50% and monitor for apixaban toxicity [52].	Limited data but no significant interaction expected.	Increase of edoxaban expected. Coadministration is not recommended [52].	Increase of rivaroxaban concentration expected. Coadministration is not recommended [52]. Use of strong inhibitors of both CYP3A4 and P-gp *contraindicated* in SPC.
Non-nucleoside reverse-transcriptase inhibitors	Decrease of apixaban possible.	No drug interaction expected. Increase with etravirine possible.	No drug interaction expected. Increase with etravirine possible.	Decrease of rivaroxaban possible.
Nucleoside reverse transcriptase inhibitors	No drug interaction expected			
Integrase inhibitors Raltegravir Dolutegravir Bictegravir	No drug interaction expected			
Elvitegravir (always administered with cobicistat)	Drugs concentration increase expected. Coadministration is not recommended [52]			
Cobicistat	Increase of apixaban expected.	Increase in dabigatran concentration by 110% to 127%. Coadministration is not recommended [52].	Increase of edoxaban expected.	Increase of rivaroxaban expected.
CCR5 inhibitor	No drug interaction expected			

SPC, Summary of product characteristics

Table 4

Interactions between antiarrhythmic and antiretroviral drugs

Antiarrhythmic drug	Expected interaction
Beta blockers	Possible increase of drug levels with PIs. Adjust dose based on clinical response (see text).
Digoxin	Use with caution in patients with PIs, titrating the initial dose. Expected increase in digoxin concentration with DRV/r, RTV (200 mg), and COBI.
Amiodarone	Use with caution with PIs. Contraindicated with TPV/r.
Dronedarone	Increased drug levels with PIs and ATV. Do not co-administer with ATV. *Contraindicated with PIs.*
Flecainide	Increased drug levels with PIs. Do not co-administer with PIs (*contraindicated with TPV/r*).
Propafenone	Possible increased drug levels with PIs. Do not co-administer with PIs. *Contraindicated with TPV/r.* Possible interaction with ATV (unboosted).
Dofetilide	Possible increased drug levels with PIs. Do not co-administer with PIs and with dolutegravir. Possible interaction with ATV (unboosted).
Diltiazem	In patients treated with ATV(c/r), decrease the dose of diltiazem by 50%. Use with caution with DRV c/r, LPV/r, TPVr.
Verapamil	Possible increased drug levels with PIs. Titrate the initial dose and adjust based on clinical response.

ATV, atazanavir; COBI or c, cobicistat; DRV, darunavir; LPV, lopinavir; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; RTV or r, ritonavir; TPV, tipranavir

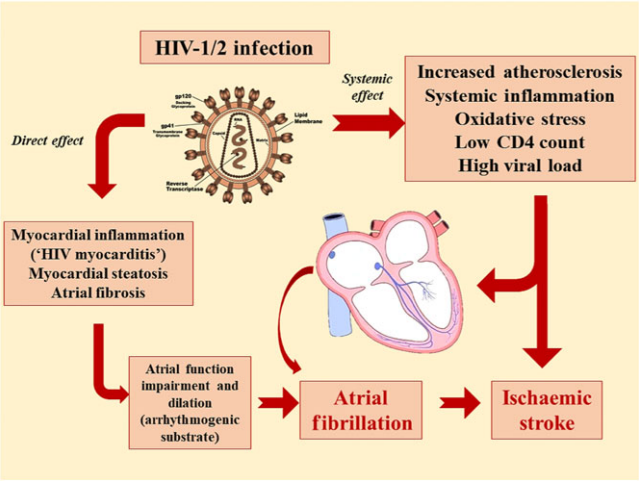

Figure 1

Mechanisms of HIV-1 related ischaemic stroke. HIV-1 infection may increase the risk of atrial fibrillation and ischaemic stroke through a direct mechanism of cardiac toxicity, or by increasing systemic inflammation and oxidative stress

serum digoxin concentration (SDC) in patients receiving ritonavir as part of ART regimen, possibly mediated by the inhibition of P-glycoprotein (P-gp) [44, 45]. These results were confirmed in healthy subjects where the co-administration of ritonavir 300 mg b.i.d. increased SDC up to 86% [46]. Currently, it is suggested to use ritonavir only as boosting dose of 100–200 mg.

The indication is to not co-administer flecainide, propafenone or dronedarone (contraindicated) in patients taking PIs. A significant increase of serum amiodarone concentrations has been described in a patient taking indinavir, which is, however, no longer widely used [47]. Another case report described a progressive accumulation of amiodarone 200 mg daily after the initiation of atazanavir [48], reinforcing the evidence that co-administration of amiodarone with PIs should be closely monitored.

In these patients, beta blockers, especially those not metabolized by CYP450 such as atenolol, labetalol, nadolol and sotalol, may be used, as well as diltiazem. Also, verapamil, digoxin and amiodarone could be used, but with caution as an increase of drug levels is possible.

The class of NNRTIs does not appear to have a clinically relevant interaction with antiarrhythmic therapy requiring clinical or laboratory monitoring. No significant interactions have been reported so far between integrase inhibitors and cardiac medications, with the exception of dolutegravir, which increases the serum concentration of dofetilide.

Conclusions

Effective management of HIV-1 infection may help lower the risk of AF/AFL, as the HIV-1 infection itself and its systemic effects such as high viral load and low CD4+ T cells count have been shown to be additive risk factors for ischaemic stroke [49, 50].

Until more data are available, thromboembolic risk stratification for patients with HIV-1 and AF/AFL should be performed according to the current guidelines developed for AF/AFL non-HIV patients [51]. Whether HIV-1 infection should probably be regarded to as an additional stroke risk factor beyond the CHA_2DS_2-VASc score is uncertain, although such patients are clearly at high risk. In one study involving 914 HIV-1 patients with AF (free from events at baseline) the event rate of thromboembolic events (including pulmonary embolism, peripheral embolism and ischaemic stroke) ranged from 5.4% per 1000 person-years for CHA_2DS_2-VASc score of 0, to 9.3% and 8.1% for score of 1 and ≥2, respectively [15]. Of note, none of the single components of the CHA_2DS_2VASC score was associated to thromboembolic risk in this cohort and most patients scored 0 for 'age' due to the low mean age of the study cohort. Furthermore, the therapy with warfarin showed no significant effect in preventing thromboembolic events, even if no data on the quality of anticoagulation were reported. All these findings raise concerns about the most appropriate thromboprophylaxis strategy for patients with HIV-1 and AF/AFL. Some additional HIV-specific factors, including the type of ART, CD4+ T cells count and viral load, may play a substantial role in this setting.

In summary, HIV-1 infection may increase the risk of stroke through systemic effects (i.e. systemic low-grade inflammation and increased oxidative stress), or with a direct mechanism of cardiac toxicity, which may favour AF onset, and in turn the risk of ischaemic stroke (Figure 1).

The choice of an ART with the lowest drug–drug interaction and with lower impact on the cardiovascular system, and the use of NOACs (particularly dabigatran) may help reduce the risk of stroke in this high-risk subgroup of patients.

However, the current evidence on the association between HIV-1 infection and AF/AFL stems from very few studies with retrospective designs. Prospective 'real-world' studies are needed to establish the real contribution of HIV-1 infection to the risk of developing cardiac arrhythmias and thromboembolic complications.

Competing Interests

There are no competing interests to declare.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13837/suppinfo

Table S1 Newcastle–Ottawa quality assessment scale for cohort studies (point assigned only to criteria marked with star)
Figure S1 Study selection process