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## Risk factors for atrial fibrillation in a multi-center US clinical cohort of people with HIV infection

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### SUMMARY

To assess atrial fibrillation (AF) risk factors in people with HIV, we identified incident AF in a large clinical cohort of people receiving care. Compared with 970 controls without AF, the 97 with adjudicated incident AF were older, less likely Hispanic, and had more coronary disease, heart failure, and chronic obstructive pulmonary disease. In multivariable analysis, non-use of antiretroviral therapy and prescription of antiretroviral regimens with multiple core agents were associated with increased AF risk.

### Keywords

AIDS; antiretroviral therapy; atrial fibrillation; cardiovascular disease; HIV

### Introduction

Cardiovascular diseases are common among aging PWH at rates higher than in the general population,[1, 2] likely due to a complex interplay of HIV infection, inflammation, antiretroviral therapy (ART), co-morbid conditions, and substance abuse. Atrial fibrillation (AF) is a common cardiac arrhythmia strongly associated with aging that increases risks of stroke, cognitive decline, and heart failure in the general population.[3–5] In PWH, therapeutic advances that reduce chronic inflammation, such as effective ART, may reduce

AF risk. Prior studies of AF risk factors in PWH have been limited by lack of validation of AF diagnoses,[6, 7] study of prevalent rather than incident AF,[8] lack of information on ART, and study in an earlier ART era.

## Methods

The Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) is a multi-site US clinical cohort of >37,000 PWH.[9] Institutional review boards approved CNICS at each site and participants provided written informed consent. We identified participants with an inpatient or outpatient International Classification of Diseases AF diagnosis code between 2008–2017. Adapting previously described methods for medical record review,[10] physician adjudicators verified incident AF, recorded medical conditions at AF onset, and classified echocardiographic findings.[11]

The CNICS Data Repository provided data on AF risk factors identified in the general population [12] including hypertension and diabetes diagnoses, laboratory test results, medications, and demographic data.[9] Coronary disease and heart failure were identified by ICD codes,[13] and chronic obstructive pulmonary disease (COPD) from a combination of ICD codes and medications.[14] Medication use was determined from pharmacy records; ART was defined as a multi-drug regimen including 1 drug from the 3 core classes: protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or integrase strand transfer inhibitor. Multi-core regimens contained drugs from >1 core class. Participants reported data on use of cigarettes, alcohol, [15] marijuana, methamphetamines/crystal, cocaine/crack, and opioids [16] via self-administered questionnaires [17].

We conducted a case-control analysis of risk factors for AF nested in the CNICS cohort. Using incidence density sampling, for every validated AF case, we identified 10 controls under observation at the date of the AF case diagnosis and matched on clinic site. For AF cases, the index date was the date of AF diagnosis and for controls, the date of the AF case with whom they were matched. Missing data ( 2% for each clinical characteristic, smoking, and alcohol use, and 4–9% for each of marijuana, methamphetamine/crystal, cocaine/crack, and opioids/heroin) were imputed using multiple imputation by chained equations.[18] Multivariable analysis was conducted using conditional logistic regression (Stata, v.17).

## Results

During 2008–2017, we identified 148 potential cases of AF among CNICS participants, of which 97 had validated incident AF at the event date, yielding a positive predictive value of 66%. At AF diagnosis, the median age was 56 years and 90% were men. The presenting rhythm was atrial fibrillation in 73%, atrial flutter in 14%, and both in 7%; 5% had AF identified only on an implanted device or ambulatory monitor. Common acute medical conditions at AF presentation were infection, post-operative state, intoxication, and thoracic disease in 32%, 10%, 6%, and 4%, respectively. Acute exacerbation of underlying coronary disease, heart failure, or COPD was noted in 4%, 11%, and 8%, respectively. In 85 participants with echocardiography results, the ejection fraction was normal in 68%, mildly

reduced in 19%, and moderately-severely reduced in 13%. Left atrial diameter was normal in 55%, mildly enlarged in 16%, and moderately-severely enlarged in 29%.

From among the 11,178 participants under observation at the participating CNICS sites, we selected 970 controls. In unadjusted analyses, AF cases had lower nadir CD4 count than controls (median 159 cells/mm<sup>3</sup>, IQR 57–268 vs. 195, IQR 64–357), lower recent CD4 count (median 391 cells/mm<sup>3</sup>, IQR 269–632 vs. 526, IQR 336–752), and more AF cases had a recent viral load > 400 copies/mL (23% vs. 16%). More AF cases than controls were not using ART at the index date (16% vs. 12%), and more had prescriptions for multi-core regimens (33% vs. 14%). The distribution of specific core agents and the proportions with current smoking, heavy alcohol use, or use of other substances were similar in AF cases and controls. In multivariable analysis, older age, a history of coronary disease, heart failure, or COPD, not being on ART at all, and prescription of a multi-core ART regimen were associated with incident AF, and Hispanic ethnicity with lower AF risk (Table 1).

## Discussion

In CNICS, accurate identification of incident AF required medical record review. AF risk factors well-studied in the general population were also identified in PWH, including advanced age, White race/ethnicity, and underlying coronary disease, heart failure, and COPD.[12, 19] Particular to PWH, non-use of ART or prescription of multi-core ART regimens was associated with incident AF.

Previous studies reported associations of lower CD4 count and higher viral load with AF after conventional risk factor adjustment,[20] but information is limited regarding the association of ART with AF. In one study, longer ART duration was associated with lower risk of prevalent AF, even after adjustment for CD4 nadir.[8] We found that both lack of ART and the prescription of multiple-core regimens, often an indicator of longer treatment history and potentially past treatment failure, were associated with increased AF risk. In our multivariable model examining ART use and multiple-core regimens, we did not include CD4 count and viral load because the estimates for these strongly correlated measures are difficult to interpret when all are included in the same model.

Strengths of our study include the geographic, racial, and ethnic diversity of the participants, collection of data from the current ART era, careful adjudication of AF, and the availability of extensive clinical data. Limitations include the relatively small number of AF cases, precluding the study of specific ART regimens, and the possibility of residual confounding.

In sum, PWH and uninfected individuals share many risk factors for AF. In addition, lack of ART and multi-core ART regimens were risk factors for incident AF in PWH. Research is needed to clarify the roles of specific antiretroviral regimens and inflammation in AF development.

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Author contributions:

Robin Nance conducted the data analysis

Robin Nance and Susan Heckbert composed the manuscript.

Joseph Delaney supervised Robin Nance and provided statistical expertise.

James Floyd, Heidi Crane, and Susan Heckbert adjudicated atrial fibrillation cases.

Michael Saag participated in study design and helped obtain funding.

Richard Moore and Jeanne Keruly are site investigators at the Johns Hopkins site who participated in the research project.

Mari Kitahata and Heidi Crane are site investigators at the University of Washington site who participated in the research project.

Bridget Whitney cleaned data and derived variables used in the analysis.

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#### Conflicts of interest:

Dr. Crane has received grant funding from ViiV in unrelated areas. Dr. Cachay has received funding from Gilead and Merck for unrelated fields. JSF has consulted for Shionogi Inc. For the remaining authors none were declared.

#### Data sharing statement:

Data from CNICS may be shared with investigators with an approved concept proposal. Instructions for data access and concept proposal forms may be found at: <https://www.uab.edu/cnics/submit-proposal>

## REFERENCES

1. Feinstein MJ, Hsue PY, Benjamin LA, Bloomfield GS, Currier JS, Freiberg MS, et al. Characteristics, prevention, and management of cardiovascular disease in people living with HIV: a scientific statement from the American Heart Association. *Circulation* 2019; 140(2):e98–e124. [PubMed: 31154814]
2. Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, et al. HIV infection and the risk of acute myocardial infarction. *JAMA internal medicine* 2013; 173(8):614–622. [PubMed: 23459863]
3. Kwok CS, Loke YK, Hale R, Potter JF, Myint PK. Atrial fibrillation and incidence of dementia: a systematic review and meta-analysis. *Neurology* 2011; 76(10):914–922. [PubMed: 21383328]
4. Piccini JP, Hammill BG, Sinner MF, Hernandez AF, Walkey AJ, Benjamin EJ, et al. Clinical course of atrial fibrillation in older adults: the importance of cardiovascular events beyond stroke. *Eur Heart J* 2014; 35(4):250–256. [PubMed: 24282186]

5. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002; 113(5):359–364. [PubMed: 12401529]
6. Hsu JC, Li Y, Marcus GM, Hsue PY, Scherzer R, Grunfeld C, et al. Atrial fibrillation and atrial flutter in human immunodeficiency virus-infected persons: incidence, risk factors, and association with markers of HIV disease severity. *J Am Coll Cardiol* 2013; 61(22):2288–2295. [PubMed: 23563125]
7. Jung H, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Prevalence and Associated Stroke Risk of Human Immunodeficiency Virus-Infected Patients With Atrial Fibrillation- A Nationwide Cohort Study. *Circulation journal : official journal of the Japanese Circulation Society* 2019; 83(12):2547–2554. [PubMed: 31619594]
8. Sanders JM, Steverson AB, Pawlowski AE, Schneider D, Achenbach CJ, Lloyd-Jones DM, et al. Atrial arrhythmia prevalence and characteristics for human immunodeficiency virus-infected persons and matched uninfected controls. *PLoS One* 2018; 13(3):e0194754.
9. Kitahata MM, Rodriguez B, Haubrich R, Boswell S, Mathews WC, Lederman MM, et al. Cohort profile: the Centers for AIDS Research Network of Integrated Clinical Systems. *International journal of epidemiology* 2008; 37(5):948–955. [PubMed: 18263650]
10. Crane HM, Heckbert SR, Drozd DR, Budoff MJ, Delaney JA, Rodriguez C, et al. Lessons learned from the design and implementation of myocardial infarction adjudication tailored for HIV clinical cohorts. *Am J Epidemiol* 2014; 179(8):996–1005. [PubMed: 24618065]
11. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2005; 18(12):1440–1463. [PubMed: 16376782]
12. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *Journal of the American Heart Association* 2013; 2(2):e000102.
13. Floyd JS, Blondon M, Moore KP, Boyko EJ, Smith NL. Validation of methods for assessing cardiovascular disease using electronic health data in a cohort of Veterans with diabetes. *Pharmacoepidemiol Drug Saf* 2016; 25(4):467–471. [PubMed: 26555025]
14. Crothers K, Rodriguez CV, Nance RM, Akgun K, Shahrir S, Kim J, et al. Accuracy of electronic health record data for the diagnosis of chronic obstructive pulmonary disease in persons living with HIV and uninfected persons. *Pharmacoepidemiol Drug Saf* 2019; 28(2):140–147. [PubMed: 29923258]
15. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med* 1998; 158(16):1789–1795. [PubMed: 9738608]
16. WHO ASSIST Working Group. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. *Addiction* 2002; 97(9):1183–1194. [PubMed: 12199834]
17. Crane HM, Lober W, Webster E, Harrington RD, Crane PK, Davis TE, et al. Routine collection of patient-reported outcomes in an HIV clinic setting: the first 100 patients. *Curr HIV Res* 2007; 5(1):109–118. [PubMed: 17266562]
18. Carlin JB, Galati JC, Royston P. A new framework for managing and analyzing multiply imputed data in Stata. *Stata Journal* 2008; 8:49–67.
19. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation* 1997; 96(7):2455–2461. [PubMed: 9337224]

20. Pastori D, Mezzaroma I, Pignatelli P, Violi F, Lip GYH. Atrial fibrillation and human immunodeficiency virus type-1 infection: a systematic review. Implications for anticoagulant and antiarrhythmic therapy. *Br J Clin Pharmacol* 2019; 85(3):508–515. [PubMed: 30575989]

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**Table 1.**

Multivariable analysis of risk factors for incident atrial fibrillation or flutter (AF) in CNICS (97 AF cases, 970 controls)

	Odds ratio	95% Confidence interval
Age, per 10 yrs	1.89	1.43, 2.49
Male sex	2.13	0.82, 5.54
Race/ethnicity		
White	Ref.	
Black	0.54	0.29, 1.00
Hispanic	0.33	0.13, 0.82
Other	0.64	0.16, 2.55
Treated hypertension	1.61	0.93, 2.79
Diabetes	1.56	0.89, 2.75
Current smoking	1.14	0.69, 1.87
Coronary disease	2.03	1.01, 4.06
Heart failure	3.96	1.84, 8.49
Chronic obstructive pulmonary disease	1.97	1.01, 3.83
Antiretroviral therapy at index date		
Regimen with INSTI, NNRTI, or PI core	Ref.	
Not on antiretroviral therapy	2.86	1.39, 5.88
Regimen with 2 or more cores	1.90	1.05, 3.41

INSTI=Integrase strand transfer inhibitor, NNRTI=Non-nucleoside reverse transcriptase inhibitor, PI=Protease inhibitor