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Journal

AIDS, 36(6)

ISSN

0269-9370

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Publication Date

2022-05-01

DOI

10.1097/qad.0000000000003180

Peer reviewed

HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2023 May 01.

Published in final edited form as:

AIDS. 2022 May 01; 36(6): 903–905. doi:10.1097/QAD.0000000000003180.

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

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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^3, IQR 57–268 vs. 195, IQR 64–357), lower recent CD4 count (median 391 cells/mm^3, 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.

Acknowledgments

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.

Chris Mathews and Edward Cachay are site investigators at the UC San Diego site who participated in the research project.

Greer Burkholder and Amanda Willig are site investigators at the University of Alabama site who participated in the research project.

Joseph Eron and Sonia Napravnik are site investigators at the University of North Carolina site who participated in the research project.

Heidi Crane and Susan Heckbert are multiple principal investigators on the NIH R56 grant that funded this research.

All authors reviewed the manuscript.

Sources of funding:

This study was funded by grants from the National Institutes of Health: R56 AG057262, R01 HL126538, R24 AI067039, P30 AI027757, P30 AI027767, P30 AI050410, P30 AI036214, and P30 AI094189. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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

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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