



Commentary

Every Minute Counts—The Time Is Now to Understand Predictors of Stroke in HIV

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Cerebrovascular disease is a major contributor to cardiovascular morbidity and mortality in the well-treated HIV population. However, we have little understanding of stroke with regard to etiology, risk, progression, and treatment in HIV. Rather, more abundant data are available among persons living with HIV (PLWHIV) on other critical types of cardiovascular disease (CVD), such as myocardial infarction and heart failure [1,2].

With the advent of contemporary antiretroviral (ART) regimens, many HIV-related stroke risk factors including uncontrolled viremia, immunosuppression, as well as ART-induced dyslipidemia, have been significantly reduced. Moreover, well-treated PLWHIV may be older and thus predisposed to other potentiators of stroke typically acquired with age. In addition, chronic inflammation and immune activation are underlying non-traditional mediators of metabolic disease in HIV, which may have an important role in the pathogenesis of stroke.

Prior studies have demonstrated an increased relative risk of stroke among PLWHIV [3], and to date most studies have been primarily observational [4]. Utilizing a large healthcare database, Alonso et al. recently demonstrated the rate of incident stroke was almost three times higher among PLWHIV compared to uninfected individuals who were age and sex matched [5]. The majority of prior analyses could not differentiate between relevant clinical subtypes of stroke—hemorrhagic vs. ischemic, as in the current study.

In this issue of *EClinicalMedicine*, Hatleberg et al. take advantage of the D:A:D cohort to uniquely discern relevant risk factors, including traditional and HIV-related, that are predictors of cerebrovascular subtypes among PLWHIV [6]. The D:A:D study has provided landmark evidence linking ART and CVD [7] and now informs us further about stroke subtypes among PLWHIV, adding new information to the field. The data show that traditional stroke risk factors, such as hypertension and age, were predictors of both stroke subtypes. Male sex, prior CVD, and

tobacco use conferred an increased risk of ischemic stroke, while HCV and kidney disease conferred an increased risk of hemorrhagic stroke.

Participants were assigned a diagnosis of either ischemic or hemorrhagic stroke based on a validated algorithm. A large number of strokes could not be classified which may have affected the analyses. In addition, the diagnosis of hypertensive disorder was based on a single blood pressure measurement, which could have led to overdiagnoses of hypertension. Other critical known stroke-related risk factors, such as atrial fibrillation and history of cardiomyopathy, and other non-traditional HIV-related risk factors, including generalized inflammation and inflammatory-induced endothelial dysfunction, could not be investigated. Even deeper stratification of ischemic stroke into large or small vessel disease or thromboembolic disease could have been performed, but was outside the scope of this study.

Animal models which mimic HIV infection show that the virus impacts ischemic stroke by directly affecting the blood brain barrier integrity, contributing to small vessel disease and heightening the inflammatory response [8]. The CNS is home to viral reservoirs, so this is still a relevant mechanism to those well-treated PLWHIV [9]. In addition, ART that penetrate the CNS may dampen injury and hasten post-stroke recovery [8]. Those on ART with limited penetration of the CNS may be a subpopulation at higher risk for stroke, which needs to be formally investigated.

The authors conclude many predictors were otherwise traditional risk factors associated with stroke and do not necessarily warrant generation of a specific risk prediction score in HIV. This remains to be seen as we could hypothesize other relevant factors such as inflammation were not adequately studied and that each of these more traditional risk factors could be weighted differently when compared to the uninfected population. Moreover, many of the risk factors highlighted by this study could be inflammatory-driven (hypertension, CVD, HCV, kidney disease). While stroke prediction in HIV has not been specifically assessed utilizing the ASCVD calculator, we know the ASCVD risk algorithm as a composite calculator may be suboptimal and underestimate CVD risk among PLWHIV [10]. Further characterization of risk factors may help strengthen risk algorithms originally designed for use in the general population to be harnessed as a primary prevention tool with the goal of reducing overall stroke incidence in HIV.

The REPRIEVE trial will test for the first time the effects of statins on composite MACE events, inclusive of nonfatal stroke or transient ischemic attack. If hypertension is a strong risk factor for stroke in HIV, future guidelines may evolve to optimize preferred antihypertensive agents.

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Data are available to suggest increased aldosterone may be present in the HIV population [11]. As excess aldosterone has important implications for hypertension, targeting aldosterone blockade with classes of medications, such as ACE inhibitors, ARBs, and mineralocorticoid antagonists may be clinically useful in HIV to reduce stroke risk.

Disclosure Summary

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