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EDITORIAL COMMENTARY

# Toward Understanding the When and Why of Human Immunodeficiency Virus–Associated Stroke

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**(See the major article by Benjamin et al, on pages 545–53.)**

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Stroke is a leading cause of morbidity and mortality throughout the world. Despite its high incidence, with approximately 17 million strokes occurring worldwide every year [1], stroke remains difficult to study in large cohort studies because of the high rate of misdiagnosis and the high costs associated with a comprehensive diagnostic workup.

Stroke not only is difficult to diagnosis accurately, but also has multiple potential etiologies. Strokes may occur from occlusion of small penetrating arteries, what neurologists describe as a lacunar stroke. The occlusion may occur more proximally in the larger arteries such as the middle cerebral artery and, thus, a larger territory is involved. The occlusions themselves may result from local thrombosis of an artery, from generalized or focal atherosclerosis, or from a thromboembolism originating more proximally. Those proximal sites are typically 1 of the 4 large arteries entering the brain (the 2 carotids and 2 vertebrals), or it may occur more centrally at the heart. The etiology is important clinically because the management of a stroke requires knowledge of its type and location.

The symptoms and signs of a stroke all depend on the exact location affected within the brain, and imaging of a stroke is often especially helpful to define the exact pattern of what area is involved and what artery was occluded to lead to the stroke. Magnetic resonance imaging (MRI) is most sensitive for ischemic stroke, and diffusion-weighted imaging has near-universal sensitivity for detecting any acute or subacute ischemic stroke. This is critical for clinical research because many events with focal neurologic symptoms are misdiagnosed as stroke. In fact, approximately one-third of human immunodeficiency virus (HIV)–associated progressive multifocal leukoencephalopathy cases are initially diagnosed as stroke [2].

In the pre–combination antiretroviral (cART) era, persons living with HIV had a disproportionately high risk of ischemic stroke compared to those without HIV [3]. Infections occurring with HIV in patients without ART leads to several opportunistic infections known to cause stroke, most notably varicella zoster infection, which directly invades the vessels, as well as tuberculosis and syphilis. In the cART era, studies of the risk of stroke in persons with HIV are more limited. In large retrospective series, the risk of stroke does seem to be persistently increased compared to that in controls [4]; however, this has been limited by the lack of adjudication of the stroke diagnosis and confirmation by MRI, as well an incomplete characterization of the stroke types, especially in those with HIV infection on ART.

In the current issue of *The Journal of Infectious Diseases*, Benjamin et al report on the first-of-its-kind prospective study of stroke in patients with and without HIV infection in Blantyre, Malawi, a city with an infection prevalence >20%. This high prevalence is important because it allows the researchers to capture a large enough number of confirmed events. Such a study would take many years to complete in areas with lower HIV infection prevalence.

Over a 15-month period, 171 MRI-confirmed ischemic strokes were analyzed (64 HIV positive and 107 HIV negative). Each patient had a comprehensive diagnostic workup including brain MRI within 7 days of admission; blood tests for traditional stroke risk factors (cholesterol, blood glucose), opportunistic infections, and antiphospholipid syndrome; a cardiac workup that included electrocardiography and echocardiography; and a carotid/vertebral duplex ultrasound. Each stroke was then categorized using a validated classification system and, among the HIV-associated strokes, with the rater blinded to ART status, degree of immunosuppression, and HIV burden.

The authors found that, like other studies of stroke and HIV, patients with HIV are younger and have fewer traditional risk factors for stroke, including hypertension, hypercholesterolemia, diabetes mellitus, and smoking. And because each

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stroke was categorized and an etiology was determined, the authors were able to describe 2 patterns with distinct clinical importance for the field.

First, of the 23 patients with a stroke categorized as HIV-associated vasculopathy (ie, evidence of vascular disease but without atherosclerosis), 9 had evidence of cerebral vasculitis. These patients had the lowest CD4 levels among the etiologic groups (median, 88 cells/μL) and, furthermore, those with opportunistic infections were grouped separately, so these were not driven by overt, treatable opportunistic infections. These patients were much younger (median age, 35 years) compared to those with atherosclerosis (median age, 60 years).

Second, of the 64 strokes captured in patients with HIV, 16 (25%) occurred in patients who had started ART within 6 months and had the lowest level of viremia among the patient groups, suggesting immune reconstitution inflammatory syndrome (IRIS). These patients were most likely to have either cerebral vasculitis or vascular disease without atherosclerosis (eg, a focal stenosis), 2 relatively uncommon etiologies of ischemic stroke. Additionally, only 3 of the 16 patients had evidence of an opportunistic infection. With the onset temporally associated with ART initiation and the lack of a direct infectious etiology in the majority of patients, these potential IRIS-associated strokes raise the possibility of different management considerations than what would typically be indicated for ischemic stroke. Further outcomes and details of individual patient management in these cases are needed to understand whether treating the IRIS with corticosteroids would be warranted.

This study describes too few cases of ischemic stroke occurring in patients with HIV on long-term ART with high CD4 cell counts and virus less than the limit of detection to know whether HIV infection, despite successful ART, poses an increased risk of ischemic stroke. However, the study provides a thorough description of accurately diagnosed strokes in those with HIV and, in doing so, highlights areas in need of further research. Additional research support should be given to understanding whether the IRIS-associated strokes seen among this cohort are related to CNS virus or inflammation that could be managed with more directed therapy. Additionally, vessel imaging and CSF studies are needed to learn whether cerebral vasculitis is confirmed and what the underlying infectious or inflammatory cause may be, especially given the young age of these patients faced with significant mortality or lifelong morbidity.

## Notes

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