Canadian Journal of Cardiology 35 (2019) 280–287

Review

Stroke in HIV

Milana Bogorodskaya, MD,[a] Felicia C. Chow, MD,[b] and Virginia A. Triant, MD, MPH[c]

[a] Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

[b] Weill Institute for Neurosciences, Department of Neurology and Division of Infectious Diseases, University of California, San Francisco, California, USA

[c] Divisions of Infectious Diseases and General Internal Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

ABSTRACT

Stroke is a heterogeneous disease in persons living with human immunodeficiency virus (HIV). HIV is thought to increase the risk of stroke through both HIV-related and traditional stroke risk factors, which vary with respect to the patient's age and clinical characteristics. Numerous studies show that detectable viremia and immunosuppression increase the risk of stroke across all ages, whereas traditional risk factors are more common in the aging population with HIV. As persons living with HIV age and acquire traditional stroke risk factors, the prevalence of stroke will likely continue to increase. Large- and small-vessel disease are the most common causes of stroke, although it is important to evaluate for infectious etiology as well. Research regarding the management of stroke in patients with HIV is scant, and recommendations often parallel those for the general population. Treatment of HIV and effective reduction of traditional stroke risk factors is important to reduce the risk of stroke in persons living with HIV. Future research will help elucidate the pathophysiology of HIV and stroke risk, investigate sex differences in stroke risk, and evaluate the safety and benefits of standard stroke preventative measures and HIV-specific interventions in this population.

RÉSUMÉ

L'accident vasculaire cérébral (AVC) est une maladie hétérogène chez les personnes vivant avec le virus de l'immunodéficience humaine (VIH). On pense que le VIH accroît le risque d'AVC par l'intermédiaire de facteurs de risques tant liés au VIH que traditionnels qui varient en fonction de l'âge et des caractéristiques cliniques du patient. De nombreuses études montrent que la virémie décelable et l'immunosuppression augmentent le risque d'AVC sans égard à l'âge, alors que les facteurs de risque traditionnels sont plus fréquents dans la population plus âgée infectée par le VIH. À mesure que les personnes vivant avec le VIH vieillissent et acquièrent des facteurs de risque d'AVC traditionnels, la prévalence de l'AVC est appelée à augmenter. Si les affections touchant les gros et les petits vaisseaux sont les causes les plus courantes d'AVC, il n'en demeure pas moins important d'évaluer aussi la possibilité d'une étiologie infectieuse. Les recherches sur la prise en charge de l'AVC chez les patients infectés par le VIH sont rares, et les recommandations sont souvent les mêmes que celles visant la population générale. Le traitement du VIH et la réduction réelle des facteurs de risque d'AVC traditionnels jouent un rôle important dans la réduction du risque d'AVC chez les personnes vivant avec le VIH. Les recherches futures contribueront à préciser la physiopathologie du VIH et du risque d'AVC, à analyser les différences entre les sexes quant au risque d'AVC et à évaluer l'innocuité et les effets bénéfiques des mesures standard de prévention de l'AVC et des interventions ciblant le VIH dans cette population.

Stroke has been recognized as a significant cause of morbidity and mortality since the beginning of the human immunodeficiency virus (HIV) epidemic. However, the epidemiology and pathophysiology of stroke have transformed over the years. The introduction of antiretroviral therapy (ART) revolutionized HIV to become a chronic, manageable disease. Consequently, as persons living with HIV survive and age, the impact of aging-related diseases such as stroke is likely to increase.[1-4]

This review will focus on the epidemiology, pathophysiology, clinical presentation, and management considerations of stroke in persons living with HIV, with a focus on women and individuals living in lower- and middle-income countries. Because the majority of strokes are of ischemic etiology, the review will focus on ischemic stroke.[1,4-8]

Epidemiology

The epidemiology of stroke in persons living with HIV has evolved over time and has been affected by the increasing average age of persons living with HIV, the decreasing prevalence of opportunistic infections, the evolution of ART regimens, and the widespread increasing prevalence of traditional risk factors in lower- and middle-income countries because of globalization.[9-12] Over the last 18 years, the percentage of persons living with

Received for publication September 18, 2018. Accepted November 30, 2018.

Corresponding author: Dr Milana Bogorodskaya, 110 Francis St. Ste. GB, Boston, Massachusetts 02215, USA. Tel: +1-617-754-7706; fax: +1-617-754-7626.

E-mail: mbogorod@bidmc.harvard.edu

See page 285 for disclosure information.

https://doi.org/10.1016/j.cjca.2018.11.032

HIV who are aged more than 50 years in the United States has increased from 17% to 45%. Worldwide, the number is approximately 13%, or 4.2 million people. As ART becomes more globally available and persons living with HIV live longer, this number is likely to increase.[13]

In the pre-ART era, stroke typically affected young persons living with HIV with acquired immunodeficiency syndrome (AIDS).[14,15] A retrospective study that looked at patients from 1990 to 1994 showed that persons living with HIV had more than a 3-fold higher odds of ischemic stroke than HIV-uninfected patients. A large proportion of the strokes were due to AIDS-related malignancies and coagulopathies.[15]

Recent studies have continued to demonstrate increased stroke risk in persons living with HIV (Fig. 1). A large, population-wide, retrospective Danish study showed that persons living with HIV had an incidence rate ratio of 1.6 (95% confidence interval, 1.32-1.94) of developing a cerebrovascular event compared with HIV-uninfected patients, even after controlling for intravenous drug use and other traditional vascular risk factors.[16] Another study found a hazard ratio of 1.82 of stroke comparing persons living with HIV and HIV-uninfected patients, adjusting for demographics and vascular risk factors.[17] Although showing consistent results, the majority of the studies linking HIV to stroke are observational, and risk factors such as socioeconomic status and substance use disorder can be difficult to accurately classify. Knowledge gaps remain regarding the extent to which sociodemographic and socioeconomic factors play a role in increasing the stroke risk in persons living with HIV.

It also remains unclear whether an increased risk of stroke persists in the setting of virologic control and immune reconstitution. Numerous studies have shown that patients with uncontrolled viremia or CD4 counts less than 200 have an increased risk of stroke,[16,18-21] but whether this risk persists in patients with viral suppression and CD4 recovery has not been well established. Although one study suggests that patients with CD4 recovery and viral suppression are at no increased risk of stroke compared with HIV-uninfected patients, no study has been conducted to specifically answer this question.[16]

Women

Stroke is the third leading cause of death in women in the United States and a significant cause of disability.[22] Because studies evaluating stroke in HIV are largely limited to men, less is known of the risk of stroke in women with HIV. A study among women in 2014 showed that women living with HIV had an increased risk of cardiovascular disease (CVD), which included ischemic stroke, compared with women without HIV.[23] The findings were consistent with prior studies that had shown a similar increase in men.[4,16,24] Several studies have also suggested that women with HIV may have an increased relative risk for ischemic stroke compared with men with HIV,[25-29] with diminishing of this effect with older age.[27,28] The mechanisms behind these findings remain unknown. Women may have a higher prevalence of traditional risk factors compared with men, yet these are often accounted for in many studies. Women also tend to live longer, thereby being at risk for ischemic stroke for a longer period. Another possibility is that HIV interacts with the host differently in

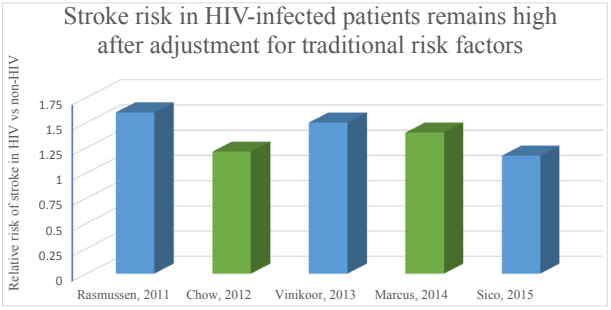

Figure 1. Studies demonstrating the increased relative risk of stroke in patients with human immunodeficiency virus (HIV) compared with patients without HIV. All *P* values were < 0.05.

women than in men. It is possible that endogenous sex hormone production modifies cardiovascular risk factors and pathways of immune activation and inflammation. HIV is known to cause earlier menopause, which is associated with increased visceral fat, reduced muscle mass, and changes in bone density, all precursors to risk factors for CVD.[30] Further research is necessary to understand what drives these disparities to provide appropriate management and prevention to women living with HIV.

Lower- and middle-income countries

Although the incidence of stroke in high-income countries is decreasing, the incidence in lower- and middle-income countries has more than doubled in the last 40 years. Stroke also affects a much younger patient population in lower- and middle-income countries, on average occurring 15 years earlier than in high-income countries.[31] Because more than two-thirds of the HIV population lives in Sub-Saharan Africa, it is expected that the burden of stroke in persons living with HIV there will increase as well.[1]

Research conducted in high-income countries may not be generalizable to lower- and middle-income countries because of differences in both HIV-associated and traditional risk factor distribution. Although ART access has increased significantly worldwide, a substantial portion of persons living with HIV in Sub-Saharan Africa still have a CD4 count of less than 200 and the burden of HIV is high.[32,33] One study in Malawi found that the second most common cause of stroke was HIV.[33] In a national hospital in the capital city of Tanzania, 20% of patients who presented with stroke were diagnosed with or already known to have HIV.[32] With a high burden of AIDS and increasing prevalence of traditional risk factors in those with controlled infection, persons living with HIV in lower- and middle-income countries are vulnerable to cardiovascular events, including stroke.[33,34] One of the important public health challenges in these regions will be developing the capacity to manage an aging HIV-infected population with multiple comorbidities.

Risk Factors

During the early epidemic, the increased risk of stroke in HIV was thought to be mostly a result of the high prevalence of opportunistic infections, older ART regimens that predisposed patients to dyslipidemia and lipodystrophy, and low

CD4 counts and uncontrolled viremia leading to inflammation. However, with the evolution of ART and increased rates of viral suppression and immune reconstitution, it has become less clear which risk factors are predominant in persons living with HIV presenting with stroke.[3,21,35]

HIV-associated risk factors

Immunosuppression and viremia. Numerous studies have demonstrated that low CD4 count[4,16,17,19,21,24,27,35] and higher viral load[4,16-19,21,24,27,35] are associated with higher incidence of stroke. In one study, the association between CD4 count and stroke was stronger when "stroke-like events" were included in the model, although the association retained statistical significance both with and without inclusion of opportunistic infection-associated strokes. Notably, it was also observed that patients who had never experienced immune depression had a lower frequency of all cardiovascular events, including ischemic stroke.[35]

Antiretroviral therapy. The effect of ART on CVD risk has been extensively debated. The majority of studies have focused on the risk of myocardial infarction, but some studies have shown an association between specific ART drugs and incidence of stroke.

Protease inhibitors. Protease inhibitors (PIs) have been implicated in CVD because of their association with dyslipidemia, lipodystrophy, and metabolic syndrome. However, the older PIs implicated in these studies, most notably indinavir and lopinavir, are rarely used in the current era.[36,37] With regard to current commonly used PIs, one recent study found an association between long-term darunavir use and increased stroke risk. In patients with exposure to darunavir for more than 6 years, the adjusted incidence rate ratio for overall CVD was 1.59 (95% confidence interval, 1.33-1.91) and remained significant for both myocardial infarction and stroke separately, even after adjustment for CVD risk factors including dyslipidemia and viral load.[37] Notably, only 4% of the 35,000-person cohort was exposed to darunavir. A smaller pharmaceutical-sponsored study showed no increased report of CVD events with darunavir exposure but did not specifically evaluate stroke.[38]

Atazanavir has not been shown to be associated with increased risk of stroke in multiple studies.[37,39,40] In fact, a large study of HIV-infected veterans demonstrated a 36% reduction in adjusted risk of stroke among users of atazanavir-containing vs non—atazanavir-containing regimens.[41] Atazanavir has also been associated with slowed progression of intima media thickness compared with other ART drugs, although the mechanism and implication of the findings remain unknown.[42] A recent study found that increased total bilirubin levels were associated with lower risk of CVD, heart failure, and ischemic stroke. In persons living with HIV, this association was independent of CD4 count, viral load, or ART regimen. Because atazanavir is known to increase indirect bilirubin levels, it was hypothesized that the mild elevation in bilirubin was the mechanism by which atazanavir may have a protective effect against CVD. However, in the study, no difference in outcome was found between those who had exposure to atazanavir and those who did not.[39]

Nucleoside reverse transcriptase inhibitors. Another drug that has been shown to be associated with increased CVD risk is the nucleoside reverse transcriptase inhibitor abacavir. Several observational studies[16,17,19,43] and a meta-analysis of these studies[36] have demonstrated an association between abacavir and increased risk of CVD, including ischemic stroke. However, these observational studies may be subject to confounding by indication, with patients prescribed abacavir potentially at higher CVD risk due to chronic kidney disease.[44]

Traditional risk factors

Persons living with HIV have been shown to have a higher prevalence of stroke risk factors, including hypertension, dyslipidemia, diabetes, coronary artery disease,[45] smoking,[17,21] and atrial fibrillation.[46] Age also plays a significant role in stroke risk in persons living with HIV. Multiple studies have shown that as age increases, the relative role of HIV-associated risk factors (ie, viral load, CD4 count) decreases and traditional risk factors play a more significant role in relation to CVD events.[24,47] This finding is likely due to 2 different factors: (1) Traditional risk factors are more prevalent with increasing age and thus will play a larger role as the prevalence of risk factors increases; and (2) as persons living with HIV age, they are more likely to be virally suppressed and immune reconstituted (because most individuals acquire the infection at less than 50 years of age),[48] and the contribution of HIV-related factors is therefore relatively less.

Mechanism and Pathophysiology

The etiology of ischemic stroke in persons living with HIV is multifaceted and can be grouped into several categories, including large-artery atherosclerosis (LAA), small-vessel disease (SVD), cardioembolism, and stroke due to other etiologies, including infection-related strokes, coagulopathy, and nonatherosclerotic HIV-associated vasculopathy. For some stroke presentations in persons living with HIV, no clear etiology is identified.[8,15,49] In addition to the standard approach to classifying ischemic stroke mechanisms, one important factor unique to persons living with HIV is consideration of immune status, which can influence the likelihood of certain stroke etiologies.

Large-artery atherosclerosis and small vessel disease

Atherosclerosis is the most common cause of ischemic stroke in persons living with HIV (Table 1).[4,8,18,33,49-53] LAA includes thrombosis or occlusion of and emboli to the large extracranial and intracranial arteries that supply the brain, whereas small vessel disease affects the cerebral arterioles and other small vessels in the brain. Although several studies have demonstrated that persons living with HIV who present with either form of atherosclerotic disease tend to be older (> 45 years of age),[4,8,24,33] risk factors specifically associated with LAA vs SVD in persons living with HIV have not been consistently demonstrated. Chow et al.[49] showed that those with LAA are more likely to be virally suppressed and have more traditional risk factors of cerebrovascular disease, whereas those with SVD were less likely to have controlled virus and CD4 recovery. In contrast, Gutierrez et al.[51]

Table 1. Summary of 7 studies that reported etiology of ischemic stroke in persons living with HIV

Study	Sample population	LAA	Cardioembolism	SVD	Infectious	Coagulopathy	Other	Cryptogenic/unknown
Gutierrez[51] (2018) New York, NY	N = 115 CD4: 312 ART use: 64%	22%	8%	17%	16%	6%	10%	21%
Chow[18,49] (2014, 2017) San Francisco, CA	N = 60 CD4: 276 ART use: 65%	23%	17%	20%	12%	3%	2%	23%
Benjamin[33] (2017) Blantyre, Malawi	N = 64 CD4: unknown ART use: 40%	11%	6%	2%	25%	9%	27%	20%
Silva-Pinto[52] (2016) Porto, Portugal	N = 23 CD4: 274 ART use: 71%	17%	17%	30%	5%	0%	5%	26%
Vinikoor[4] (2013) Chapel Hill, NC	N = 31 CD4: 267 ART use: 94%	42%	3%	35%	3%	0%	6%	10%
Corral[50] (2009) Madrid, Spain	N = 25 CD4 (mean): 355 VL< 50 copies/mL: 48%	24%	8%	24%	4%	0%	8%	32%
Ortiz[8] (2007) Miami, FL	N = 77 CD4 (mean): 113 ART use: 37%	13%	19%	19%	0%	9%	14%	25%

The percentage of ART use was used as a surrogate marker of viral load suppression in most of the studies. CD4 is the median CD4 count of the cohort, unless stated otherwise. N is the number of HIV-infected patients with ischemic stroke in the cohort. "Infectious" etiologies included (in order of higher prevalence to low) varicella-zoster virus,[33,51] bacterial endocarditis,[18,51,52] tuberculosis,[33,50] syphilis,[33,51] undifferentiated meningitis,[18] cryptococcosis,[51] toxoplasmosis,[51] bacterial meningitis,[51] mucormycosis,[51] unidentified opportunistic infection.[4] "Other" etiologies included (in order of higher prevalence to low) vasculitis,[8,33,50] cocaine use,[4,50-52] nonatherosclerotic vasculopathy,[33] multiple etiologies,[8,33] arterial dissection,[8,51] medication use,[51] sickle cell crisis,[51] carcinomatous meningitis,[18] stump syndrome.[4] "Cryptogenic/unknown": no etiology for stroke was found.

ART, antiretroviral therapy; HIV, human immunodeficiency virus; LAA, large-artery atherosclerosis; SVD, small-vessel disease; VL, viral load.

demonstrated that a nadir CD4 count of < 200, a longer duration of HIV infection, and prior stroke were all associated with LAA, whereas SVD was associated with nadir CD4 counts of > 200, no history of cardiac disease, and male sex.

Cardioembolism

The etiology of cardioembolic strokes can be divided into 3 categories: arrhythmias, cardiac wall/chamber abnormalities, and valve disorders. Persons living with HIV have been shown to have a higher risk of atrial fibrillation than HIV-uninfected patients[46] and are known to develop HIV cardiomyopathy in the setting of uncontrolled infection.[54] Valve disorders such as rheumatic heart disease and infective endocarditis also predispose to cardioembolic stroke, although studies show no increased risk of either in persons living with HIV.[55,56]

Infection-associated strokes

Certain opportunistic infections predispose an individual to developing arterial ischemic stroke, including tuberculosis meningitis, neurosyphilis, and varicella-zoster virus vasculitis. These infections are thought to induce extensive central nervous system (CNS) and cerebrovascular inflammation leading to endarteritis and a prothrombotic state. The combination of inflamed arterial walls with a predisposition to thrombus formation places the individual at significant risk for arterial thrombosis, which leads to an ischemic stroke. The recent increase of syphilis infections in Canada and the United States may lead to more infection-associated strokes in persons living with HIV.[57-59] Notably, strokes associated with these infections are distinct from stroke mimics, defined as nonvascular conditions that present with an acute neurological deficit simulating acute ischemic stroke.[60] Stroke mimics in persons living with HIV typically present as space-occupying lesions and include CNS toxoplasmosis, CNS tuberculomas, and brain abscesses.

Coagulopathy

HIV is known to be associated with coagulopathies, including HIV-associated thrombotic thrombocytopenic purpura, Protein S and C deficiency, and anti-phospholipid syndrome.[8,61,62] The extent to which these coagulopathies play a role in causing stroke in persons living with HIV is unclear. In a case-control study of 82 patients with HIV (77 of whom had ischemic stroke), Protein S deficiency was found in 45% (10/22) and anticardiolipin antibodies were found in 29% (9/31) of the tested patients.[8] However, a South African study found no statistically significant difference in the prevalence of Protein S deficiency in persons living with HIV with and without stroke.[63] Another study showed that persons living with HIV with stroke had significantly higher levels of von Willebrand factor compared with both uninfected patients with stroke and persons living with HIV without stroke.[64] The proposed mechanism suggests that HIV directly causes endothelial dysfunction that activates inflammatory cytokines, leading to a prothrombotic state. Whether these coagulopathies are incidental findings rather than etiologic remains unknown.

Nonatherosclerotic HIV-associated vasculopathy

It has been proposed that there is a separate entity of inflammatory arterial disease caused by HIV itself, termed "HIV vasculopathy," that predisposes patients to stroke through development of stenotic or aneurysmal lesions in the absence of atherosclerosis.[6,53,65-67] Individuals thought to have this stroke etiology tend to be young,[8] with one study

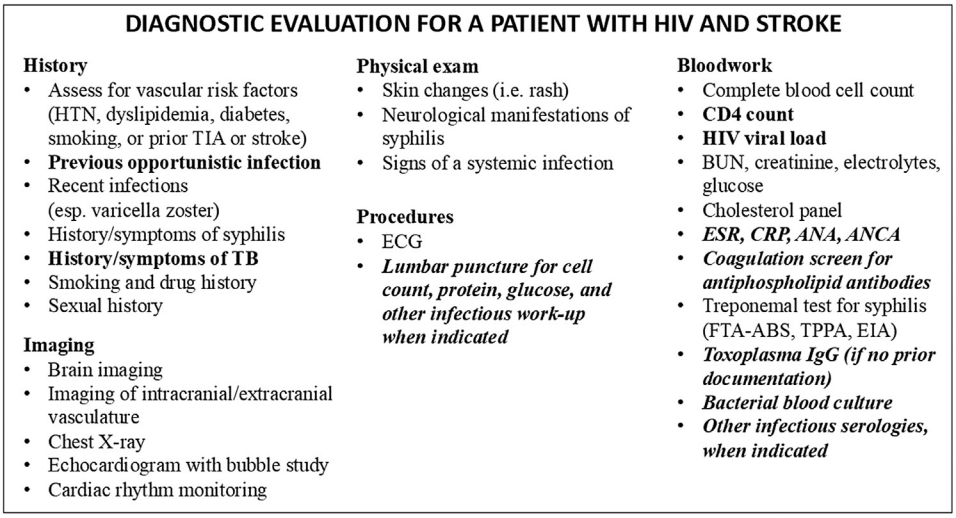

Figure 2. Diagnostic evaluation for a patient with HIV and stroke. Evaluation specific for HIV-positive patients is bolded. Evaluation that should be performed when clinically indicated (based on immune status, virologic control, or suspicion for infection or vasculitis) is italicized. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; BUN, blood urea nitrogen; CRP, C-reactive protein; ECG, electrocardiogram; EIA, enzyme immunoassay; ESR, erythrocyte sedimentation rate; FTA-ABS, fluorescent treponemal antibody absorption; HTN, hypertension; TB, tuberculosis; TIA, transient ischemic attack; TPPA, treponemal pallidum particle agglutination.

demonstrating a median age of 33 years for patients with nonatherosclerotic vasculopathy,[33] and typically have CD4 levels less than 200.[33] One study demonstrated that persons living with HIV were significantly more likely to develop adventitial inflammation than controls after adjusting for demographics and vascular risk factors, whereas inflammation in the intima and media remained the same between groups. This association was not explained by atherosclerosis.[2] The finding suggests that HIV, particularly with uncontrolled viremia, may preferentially affect the adventitia, leading to a different phenotype of vascular disease than atherosclerosis seen in the typical aging population.

Clinical Presentation and Diagnostic Evaluation

Persons living with HIV who develop stroke tend to present similarly to HIV-uninfected patients, with sudden onset of focal neurological deficits being the most common presentation. However, persons living with HIV who are immunocompromised may present atypically with symptoms of altered mental status, acute loss of consciousness, fevers, or stepwise focal neurological deficits occurring over hours to days.[65] Often, strokes in persons living with HIV can be subclinical. An evaluation of autopsy results noted that although only 1% to 5% of the HIV population are found to have strokes in clinical studies, approximately 4% to 34% of the HIV population have cerebral ischemic lesions at autopsy.[65] Cerebral infarcts are more common than cerebral hemorrhage, which follows the distribution seen in HIV-uninfected patients, but persons living with HIV presenting with stroke tend to be younger, with a mean age of 40 years, compared with HIV-uninfected patients.[5,8,18,33,65,68-71]

A stroke can represent the initial presentation of HIV infection, and HIV screening is an important element of stroke evaluation. If a patient is already known to be infected, assessment for risk for syphilis, tuberculosis exposure, and accompanying symptoms and signs that may suggest an infectious etiology of stroke is indicated. Diagnostic evaluation to be considered in persons living with HIV presenting with stroke is outlined in Figure 2.

Management

Research on the management of stroke in persons living with HIV is relatively limited, in part because of the heterogeneity of stroke etiology in this group. The current standard of care is to follow the guidelines for stroke management in the general population.

With regard to acute management, it has been reasoned that tissue plasminogen activator should be effective in persons living with HIV. One study evaluated administration of tissue plasminogen activator in persons living with HIV in comparison with HIV-uninfected patients and found that there was no difference in mortality or rates of intraparenchymal hemorrhage between the groups.[72] Secondary prevention of stroke includes modification of both novel and traditional stroke risk factors.

HIV-associated risk factors

Per HIV guidelines, ART should be initiated in all persons living with HIV regardless of CD4 count.[73] Given the association of CD4 count and viral load with stroke, ART itself may be the single most important intervention to reduce vascular risk among persons with uncontrolled infection. The selection of ART with regard to vascular risk should also be taken into consideration. Given data on abacavir and their association with vascular risk, many experts recommend avoiding abacavir in patients at elevated risk of stroke.

Traditional risk factors

The decision regarding whether aspirin should be administered for primary or secondary stroke prevention in persons

living with HIV parallels the decision-making process in the general population. However, studies have shown that persons living with HIV are less likely to be prescribed aspirin as a primary or secondary preventive therapy than HIV-uninfected patients, even in those in whom aspirin is indicated.[74] One pilot study suggested that aspirin may attenuate the systemic immune activation in patients with HIV,[75] although this finding was not confirmed in a larger study.[76]

Few studies have investigated the impact of statin use in the prevention of stroke. Theoretically, because statins have anti-inflammatory properties, they may be beneficial in reducing both low-density lipoprotein levels and inflammation. Studies have shown that statins can reduce the levels of certain inflammatory markers in persons living with HIV, but no study has investigated the effects of statins on CVD or stroke risk.[77] The ongoing REPRIEVE trial seeks to address this pivotal question.[78] Currently, statin administration is recommended for all persons living with HIV with stroke, with consideration of ART drug interactions when selecting a statin.

Few studies have evaluated the management of hypertension in persons living with HIV for secondary prevention of stroke. At this time, the blood pressure goals remain the same as for the general population. Because there are few drug interactions with ART drugs, the choice of antihypertensives is largely directed by the patient's other comorbidities.

Diabetes is shown to be more prevalent in persons living with HIV.[45] Furthermore, hemoglobin A1C, a common screening tool for diagnosis of diabetes, has been shown to underestimate glycemia in persons living with HIV.[79] Consequently, it is recommended that fasting plasma glucose be used for screening and diagnosis of diabetes in this patient population.[79] With regard to treatment of diabetes, persons living with HIV should be treated similarly to the general population, with special consideration given to drug interactions with ART. Specifically, dolutegravir increases the levels of metformin in the bloodstream and thiazolidinedione levels increase in the presence of many PIs. For patients on ritonavir or cobicistat, saxagliptin dose should be reduced while canagliflozin dose should be increased.[80]

Smoking cessation and lifestyle modification are essential in stroke prevention. Prevalence of cigarette smoking in persons living with HIV ranges from 47% to 71% and is the strongest risk factor for predicting CVD events.[81] However, one study showed that persons living with HIV are less likely to receive smoking-cessation counseling from their HIV providers compared with uninfected patients.[82] Diet and exercise are also vital to the prevention of stroke. In one study, an intensive lifestyle modification program effectively reduced blood pressure in persons living with HIV.[83]

Future Directions

As persons living with HIV age and develop traditional risk factors for stroke, the prevalence of stroke will continue to increase. Aggressive public health measures and improved primary care strategies are necessary to ensure all persons living with HIV are diagnosed and treated with ART and receive the appropriate primary and preventive care to reduce stroke risk. Future research will be important to further understand the pathophysiology of HIV and stroke risk, investigate sex differences in stroke risk, and evaluate the safety and benefits of standard stroke preventative care and HIV-specific interventions in this population.

Acknowledgements

The authors thank Dr Shibani Mukerji for critical review of sections of the article.

Funding Sources

This work was supported by the National Institutes of Health (R01HL132786 to VAT).

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Abdallah A, Chang J, O'Carroll C, et al. Stroke in human immunodeficiency virus-infected individuals in Sub-Saharan Africa (SSA): a systematic review. J Stroke Cerebrovasc Dis 2018;27:1828-36.
2. Gutierrez J, Menshawy K, Gonzalez M, et al. Brain large artery inflammation associated with HIV and large artery remodeling. AIDS 2016;30:415-23.
3. Koethe J, Jenkins C, Lau B, et al; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Rising obesity prevalence and weight gain among adults starting antiretroviral therapy in the United States and Canada. AIDS Res Hum Retroviruses 2016;32:50-8.
4. Vinikoor M, Napravnik S, Floris-Moore M, et al. Incidence and clinical features of cerebrovascular disease among HIV-infected adults in the Southeastern United States. AIDS Res Hum Retroviruses 2013;29:1068-74.
5. Ances B, Bhatt A, Vaida F, et al. Role of metabolic syndrome components in human immunodeficiency virus—associated stroke. J Neurovirol 2009;15:249-56.
6. Benjamin L, Khoo S. HIV infection and stroke. Handb Clin Neurol 2018;152:187-200.
7. Bogiatzi C, Hackam D, McLeod A, Spence J. Secular trends in ischemic stroke subtypes and stroke risk factors. Stroke 2014;45:3208-13.
8. Ortiz G, Koch S, Romano JG, Forteza AM, Rabinstein AA. Mechanisms of ischemic stroke in HIV-infected patients. Neurology 2007;68:1257-61.
9. Chapman A. Globalization, human rights, and the social determinants of health. Bioethics 2009;23:97-111.
10. BeLue R, Okoror T, Iwelunmor J, et al. An overview of cardiovascular risk factor burden in sub-Saharan African Countries: a socio-cultural perspective. Global Health 2009;5:10.
11. Sobngwi E, Mbanya J, Unwin N, et al. Exposure over the life course to an urban environment and its relation with obesity, diabetes, and hypertension in rural and urban Cameroon. Int J Epidemiol 2004;33:769-76.
12. Yeates K, Lohfeld L, Sleeth J, et al. A global perspective on cardiovascular disease in vulnerable populations. Can J Cardiol 2015;31:1081-93.
13. The Gap Report: People Aged 50 Years and Older. Geneva, Switzerland: UNAIDS, 2014.

14. Kieburtz K, Eskin T, Ketonen L, Tuite M. Opportunistic cerebral vasculopathy and stroke in patients with the acquired immunodeficiency syndrome. Arch Neurol 1993;50:430-2.

15. Qureshi A, Janssen R, Karon J, et al. Human immunodeficiency virus infection and stroke in young patients. Arch Neurol 1997;54:1150-3.

16. Rasmussen L, Engsig F, Christensen H, et al. Risk of cerebrovascular events in persons with and without HIV: a Danish nationwide population-based cohort study. AIDS 2011;25:1637-46.

17. Gutierrez J, Albuquerque A, Falzon L. HIV infection as vascular risk: a systematic review of the literature and meta-analysis. PLoS One 2017;12:e0176686.

18. Chow F, Bacchetti P, Kim A, Price R, Hsue P. Effect of CD4+ cell count and viral suppression on risk of ischemic stroke in HIV infection. AIDS 2014;28:2573-7.

19. Marcus J, Leyden W, Chao C, et al. HIV infection and incidence of ischemic stroke. AIDS 2014;28:1911-9.

20. Okeke NL, Hicks CB, McKellar MS, Fowler VG Jr, Federspiel JJ. History of AIDS in HIV-infected patients is associated with higher in-hospital mortality following admission for acute myocardial infarction and stroke. J Infect Dis 2016;213:1955-61.

21. Sico J, Chang C, So-Armah K, et al. HIV status and the risk of ischemic stroke among men. Neurology 2015;84:1933-40.

22. Bushnell C, McCullough L, Awad I, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:1545-88.

23. Womack J, Chang C, So-Armah K, et al. HIV infection and cardiovascular disease in women. J Am Heart Assoc 2014;3:e001035.

24. Moulignier A, Savatovsky J, Assoumou L, et al. Silent cerebral small-vessel disease is twice as prevalent in middle-aged individuals with well-controlled, combination antiretroviral therapy-treated human immunodeficiency virus (HIV) than in HIV-uninfected individuals. Clin Infect Dis 2018;66:1762-9.

25. Chow F, Regan S, Feske S, et al. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. J Acquir Immune Defic Syndr 2012;60:351-8.

26. Savès M, Chêne G, Ducimetière P, et al. Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. Clin Infect Dis 2003;37:292-8.

27. Chow F, Wilson M, Wu K, et al. Stroke incidence is highest in women and non-Hispanic blacks living with HIV in the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials cohort. AIDS 2018;32:1125-35.

28. Chow F, Regan S, Zanni M, et al. Elevated ischemic stroke risk among women living with HIV infection. AIDS 2018;32:59-67.

29. Tirschwell D, Chow F, Becker K, et al. Incidence of stroke in the US Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) Cohort. Abstract presented at: 69th Annual American Academy of Neurology Meeting, April 22-28, 2017, Boston, Massachusetts.

30. Stone L, Looby S, Zanni M. Cardiovascular disease risk among women living with HIV in North America and Europe. Curr Opin HIV AIDS 2017;12:585-93.

31. Johnson W, Onuma O, Owolabi M, Sachdev S. Stroke: a global response is needed. Bull World Health Organ 2016;94:634-634A.

32. Mlay M, Bakari M. The prevalence of HIV among patients admitted with stroke at the Muhimbili National Hospital, Dar es Salaam, Tanzania. Tanzan J Health Res 2010;12:1-12.

33. Benjamin L, Allain T, Mzinganjira H, et al. The role of human immunodeficiency virus-associated vasculopathy in the etiology of stroke. J Infect Dis 2017;216:545-53.

34. Feinstein M, Bogorodskaya M, Bloomfield G, et al. Cardiovascular complications of HIV in endemic countries. Curr Cardiol Rep 2016;18:113.

35. Sabin C, Ryom L, De Wit S, et al; D:A:D Study Group. Associations between immune depression and cardiovascular events in HIV infection. AIDS 2013;27:2735-48.

36. Bavinger C, Bendavid E, Niehaus K, et al. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. PLoS One 2013;8:e59551.

37. Ryom L, Lundgren J, El-Sadr W, et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. Lancet HIV 2018;5:e291-300.

38. Opsomer M, Dimitrova D, Verspeelt J, et al. Evaluation of cardiovascular disease risk in HIV-1-Infected patients treated with darunavir. Drugs R D 2018:199-210.

39. Marconi V, Duncan M, So-Armah K, et al. Bilirubin Is inversely associated with cardiovascular disease among HIV-positive and HIV-negative individuals in VACS (Veterans Aging Cohort Study). J Am Heart Assoc 2018;7.

40. Monforte A, Reiss P, Ryom L, et al. Atazanavir is not associated with an increased risk of cardio- or cerebrovascular disease events. AIDS 2013;27:407-15.

41. LaFleur J, Bress A, Rosenblatt L, et al. Cardiovascular outcomes among HIV-infected veterans receiving atazanavir. AIDS 2017;31:2095-106.

42. Stein J, Ribaudo H, Hodis H, et al. A prospective, randomized clinical trial of antiretroviral therapies on carotid wall thickness. AIDS 2015;29:1775-83.

43. Desai M, Joyce V, Bendavid E, et al. Risk of cardiovascular events associated with current exposure to HIV antiretroviral therapies in a US veteran population. Clin Infect Dis 2015;61:445-52.

44. Bedimo R, Westfall A, Drechsler H, Vidiella G, Tebas P. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. Clin Infect Dis 2011;53:84-91.

45. Triant V, Lee H, Hadigan C, Grinspoon S. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab 2007;92:2506-12.

46. Sanders J, Steverson A, Pawlowski A, et al. Atrial arrhythmia prevalence and characteristics for human immunodeficiency virus-infected persons and matched uninfected controls. PLoS One 2018;13:e0194754.

47. Benjamin LA, Corbett EL, Connor MD, et al. HIV, antiretroviral treatment, hypertension, and stroke in Malawian adults: a case-control study. Neurology 2016;86:324-33.

48. HIV Surveillance Report 2015: Diagnoses of HIV Infection in the United States and Dependent Areas. Atlanta, GA: Centers for Disease Control and Prevention, 2015.

49. Chow F, Price R, Hsue P, Kim A. Greater risk of stroke of undetermined etiology in a contemporary HIV-Infected cohort compared with uninfected individuals. J Stroke Cerebrovasc Dis 2017;26:1154-60.

50. Corral I, Quereda C, Moreno A, et al. Cerebrovascular ischemic events in HIV-1-infected patients receiving highly active antiretroviral therapy: incidence and risk factors. Cerebrovasc Dis 2009;27:559-63.

51. Gutierrez J, Hatleberg C, Evans H, Yin M. Role of pre-stroke immunity in ischemic stroke mechanism among patients with HIV. AIDS Care 2019;31:270-4.

52. Silva-Pinto A, Costa A, Serrão R, Sarmento A, Abreu P. Ischaemic stroke in HIV-infected patients: a case-control study. HIV Med 2016;18:214-9.

53. Tipping B, de Villiers L, Candy S, Wainwright H. Stroke caused by human immunodeficiency virus—associated intracranial large-vessel aneurysmal vasculopathy. Arch Neurol 2006;63:1640-2.

54. Pugliese A, Isnardi D, Saini A, et al. Impact of highly active antiretroviral therapy in HIV-positive patients with cardiac involvement. J Infect 2000;40:282-4.

55. Gleason B, Mirembe G, Namuyonga J, et al. Prevalence of latent rheumatic heart disease among HIV-infected children in Kampala, Uganda. J Acquir Immune Defic Syndr 2016;71:196-9.

56. Miró J, del Río A, Mestres C. Infective endocarditis in intravenous drug abusers and HIV-1 infected patients. Infect Dis Clin North Am 2002;16:273-95.

57. Ling D, Janjua N, Wong S, et al. Sexually transmitted infection trends among gay or bisexual men from a clinic-based sentinel surveillance system in British Columbia, Canada. Sex Transm Dis 2015;42:153-9.

58. Nguyen T, Kohn R, Ng R, Philip S, Cohen S. Historical and current trends in the epidemiology of early syphilis in San Francisco, 1955 to 2016. Sex Transm Dis 2018;45:S55-62.

59. Novak R, Ghanem A, Hart R, et al; HIV Outpatient Study Investigators. Risk factors and incidence of syphilis in HIV-infected persons, the HIV Outpatient Study, 1999-2015. Clin Infect Dis 2018;67:1750-9.

60. Vilela P. Acute stroke differential diagnosis: stroke mimics. Eur J Radiol 2017;96:133-44.

61. Stahl C, Wideman C, Spira T, et al. Protein S deficiency in men with long-term human immunodeficiency virus infection. Blood 1993;81:1801-7.

62. Vishnu P, Aboulafia D. Haematological manifestations of human immune deficiency virus infection. Br J Haematol 2015;171:695-709.

63. Mochan A, Modi M, Modi G. Protein S deficiency in HIV associated ischaemic stroke: an epiphenomenon of HIV infection. J Neurol Neurosurg Psychiatr 2005;76:1455-6.

64. Allie S, Stanley A, Bryer A, Meiring M, Combrinck M. High levels of von Willebrand factor and low levels of its cleaving protease, ADAMTS13, are associated with stroke in young HIV-infected patients. Int J Stroke 2015;10:1294-6.

65. Benjamin LA, Bryer A, Emsley HC, et al. HIV infection and stroke: current perspectives and future directions. Lancet Neurol 2012;11:878-90.

66. Goldstein D, Timpone J, Cupps T. HIV-associated intracranial aneurysmal vasculopathy in adults. J Rheumatol 2010;37:226-33.

67. Kossorotoff M, Touzé E, Godon-Hardy S, et al. Cerebral vasculopathy with aneurysm formation in HIV-infected young adults. Neurology 2006;66:1121-2.

68. AbdelRazek M, Gutierrez J, Mampre D, et al. Intravenous thrombolysis for stroke and presumed stroke in human immunodeficiency virus-infected adults: a retrospective, multicenter US study. Stroke 2018;49:228-31.

69. Carballo D, Delhumeau C, Carballo S, et al. Increased mortality after a first myocardial infarction in human immunodeficiency virus-infected patients; a nested cohort study. AIDS Res Ther 2015;12:4.

70. Chow F. HIV infection, vascular disease, and stroke. Semin Neurol 2014;34:35-46.

71. Edwards NJ, Grill MF, Choi HA, Ko NU. Frequency and risk factors for cerebral arterial disease in a HIV/AIDS neuroimaging cohort. Cerebrovasc Dis 2016;41:170-6.

72. Sweeney E, Thakur K, Lyons J, et al. Outcomes of intravenous tissue plasminogen activator for acute ischaemic stroke in HIV-infected adults. Eur J Neurol 2014;21:1394-9.

73. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed September 5, 2018.

74. Suchindran S, Regan S, Meigs J, Grinspoon S, Triant V. aspirin use for primary and secondary prevention in human immunodeficiency virus (HIV)-infected and HIV-uninfected patients. Open Forum Infect Dis 2014;1:ofu076.

75. O'Brien M, Montenont E, Hu L, et al. Aspirin attenuates platelet activation and immune activation in HIV-1-infected subjects on antiretroviral therapy: a pilot study. J Acquir Immune Defic Syndr 2013;63:280-8.

76. O'Brien M, Hunt P, Kitch D, et al. A randomized placebo controlled trial of aspirin effects on immune activation in chronically human immunodeficiency virus-infected adults on virologically suppressive antiretroviral therapy. Open Forum Infect Dis 2017;4:ofw278.

77. Funderburg N, Jiang Y, Debanne S, et al. Rosuvastatin reduces vascular inflammation and T-cell and monocyte activation in HIV-infected subjects on antiretroviral therapy. J Acquir Immune Defic Syndr 2015;68:396-404.

78. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29. Identifier NCT02344290, Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults (REPRIEVE); 2015 Jan 22. Available at: https://clinicaltrials.gov/ct2/show/NCT02344290. Accessed September 5, 2018.

79. Kim P, Woods C, Georgoff P, et al. A1C underestimates glycemia in HIV infection. Diabetes Care 2009;32:1591-3.

80. Monroe A, Glesby M, Brown T. Diagnosing and managing diabetes in HIV-infected patients: current concepts. Clin Infect Dis 2015;60:453-62.

81. Stein L, Urban M, Weber M, et al. Effects of tobacco smoking on cancer and cardiovascular disease in urban black South Africans. Br J Cancer 2008;98:1586-92.

82. Crothers K, Goulet J, Rodriguez-Barradas M, et al. Decreased awareness of current smoking among health care providers of HIV-positive compared to HIV-negative veterans. J Gen Intern Med 2007;22:749-54.

83. Fitch K, Anderson E, Hubbard J, et al. Effects of a lifestyle modification program in HIV-infected patients with the metabolic syndrome. AIDS 2006;20:1843-50.