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Stroke in HIV

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Abstract

Stroke is a heterogeneous disease in persons living with HIV (PLWH). 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 while traditional risk factors are more common in the aging HIV population. As PLWH age and acquire traditional stroke risk factors, the prevalence of stroke will likely continue to rise. 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 HIV patients 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 PLWH. 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.

Brief summary

Stroke is a heterogeneous disease in persons living with HIV. HIV is thought to increase the risk of stroke through both HIV-related and traditional stroke risk factors. As PLWH age and acquire traditional stroke risk factors, the prevalence of stroke will likely continue to rise. Little is known about optimal effective stroke prevention in PLWH and further research will help to determine whether tailored stroke treatment and prevention approaches are indicated for HIV populations.

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Introduction

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 has transformed over the years. The introduction of antiretroviral therapy (ART) revolutionized HIV to become a chronic, manageable disease. Consequently, as persons living with HIV (PLWH) 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 PLWH, with a focus on women and individuals living in lower- and middle-income countries (LMIC). Since the majority of strokes are of ischemic etiology, the review will focus on ischemic stroke[1, 4–8].

A. Epidemiology

The epidemiology of stroke in PLWH has evolved over time and has been impacted by the increasing average age of PLWH, the decreasing prevalence of opportunistic infections (OI), the evolution of ART regimens, and the widespread increasing prevalence of traditional risk factors in LMICs due to globalization[9–12]. Over the last 18 years, the percentage of PLWH who are above the age of 50 in the U.S. has risen from 17% to 45%. Worldwide, the number is close to 13%, or 4.2 million people. As ART becomes more globally available and PLWH live longer and HIV becomes, this number is likely to rises[13].

In the pre-ART era, stroke typically affected young PLWH with acquired immunodeficiency syndrome (AIDS)[14, 15]. A retrospective study that looked at patients from 1990 to 1994 showed that PLWH had more than three-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 PLWH (Figure 1). A large, population-wide, retrospective Danish study showed that PLWH had an incidence rate ratio (IRR) of 1.6 [95% CI 1.32–1.94] of developing a cerebrovascular event compared to HIV-uninfected patients, even after controlling for intravenous drug use (IVDU) and other traditional vascular risk factors[16]. Another study found a hazard ratio (HR) of 1.53–2.16] of stroke comparing PLWH and HIV-uninfected patients, adjusting for demographics and vascular risk factors[17]. While 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 socioeconomic factors play a role in increasing the stroke risk in PLWH.

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 to HIV-uninfected patients, no study has been conducted to specifically answer this question[16].

Women—Stroke is the 3rd leading cause of death in women in the U.S. and a significant cause of disability[22]. As 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 to 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 to 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 to 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 women than in men It is possible that endogenous sex hormone production modifies cardiovascular risk factors as well as 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 cardiovascular disease[30]. Further research is necessary to understand what drives these disparities to provide appropriate management and prevention to women living with HIV.

LMIC—While the incidence of stroke in high income countries (HICs) is decreasing, the incidence in LMICs has more than doubled in the last 40 years. Stroke also affects a much younger patient population in LMICs, on average occurring 15 years earlier than in HICs[31]. Since over two-thirds of the HIV population lives in sub-Saharan Africa (SSA), it is expected that the burden of stroke in PLWH there will increase as well[1].

Research conducted in HICs may not be generalizable to LMICs due to differences in both HIV-associated and traditional risk factor distribution. Although ART access has increased significantly worldwide, a substantial portion of PLWH in SSA 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 2nd 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 either diagnosed with or already known to have HIV[32]. With a high burden of AIDS as well as increasing prevalence of traditional risk factors in those with controlled infection, PLWH in LMICs 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.

B. 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 PLWH 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 (MI), but some studies have shown an association between specific ART drugs and incidence of stroke.

a) Protease inhibitors: Protease inhibitors (PIs) have been implicated in CVD due to 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 regards 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, adjusted IRR for overall CVD was 1.59 [95% CI 1.33–1.91] and remained significant for both MI 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 versus non-atazanavir-containing regimens[41]. Atazanavir has also been associated with slowed progression of intima media thickness (IMT), compared to 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 PLWH, this association was independent of CD4 count, viral load, or ART regimen. Since 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 cardiovascular disease. However, in the study, no difference in outcome was found between those who had exposure to atazanavir versus those who did not [39].

b) Nucleoside Reverse Transcriptase Inhibitors: Another drug that has been shown to be associated with increased CVD risk is the nucleoside reverse transcriptase inhibitor (NRTI)

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 cardiovascular disease, 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—PLWH have been shown to have a higher prevalence of stroke risk factors including hypertension, dyslipidemia, diabetes, CAD [45], smoking[17, 21] and atrial fibrillation[46]. Age also plays a significant role in stroke risk in PLWH. Multiple studies have shown that as age increases, the relative role of HIV-associated risk factors (i.e. 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 two 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 PLWH age, they are more likely to be virally suppressed and immune reconstituted (as most individuals acquire the infection at less than 50 years of age)[48], and the contribution of HIV-related factors is therefore relatively less.

C. Mechanism/Pathophysiology

The etiology of ischemic stroke in PLWH 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 non-atherosclerotic HIV-associated vasculopathy. For some stroke presentations in PLWH, no clear etiology is identified[8, 15, 49]. In addition to the standard approach to classifying ischemic stroke mechanisms, one important factor unique to PLWH 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 PLWH (Table 1)[4, 8, 18, 33, 49–53]. Large artery atherosclerosis includes thrombosis of 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. While several studies have demonstrated that PLWH 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 versus SVD in PLWH have not been consistently demonstrated. Chow et al. showed that those with LAA are more likely to be virally suppressed and have more traditional risk factors of cerebrovascular disease while those with SVD were less likely to have controlled virus and CD4 recovery[49]. In contrast, Gutierrez et al. demonstrated that a nadir CD4 count of <200, a longer duration of HIV infection, and prior stroke were all associated with LAA, while SVD was associated with nadir CD4 counts of >200, no history of prior cardiac disease, and male sex[51].

Cardioembolism—The etiology of cardioembolic strokes can be divided into 3 categories: arrhythmias, cardiac wall/chamber abnormalities, and valve disorders. PLWH 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, though studies show no increased risk of either in PLWH[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 rise of syphilis infections in Canada and the United States may lead to more infection-associated strokes in PLWH[57–59]. Notably, strokes associated with these infections are distinct from stroke mimics, defined as non-vascular conditions that present with an acute neurological deficit simulating acute ischemic stroke[60]. Stroke mimics in PLWH 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 PLWH is unclear. In a case-control study of 82 HIV patients (77 of whom had ischemic stroke), Protein S deficiency was found in 45% (10/22) and anticardiolipin antibodies 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 PLWH with and without stroke[63]. Another study showed that PLWH with stroke had significantly higher levels of von Willibrand factor (vWF) compared with both uninfected patients with stroke as well as PLWH 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.

Non-atherosclerotic 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 demonstrating a median age of 33 for patients with non-atherosclerotic vasculopathy[33], and typically have CD4 levels less than 200[33]. One study demonstrated that PLWH were significantly more likely to develop adventitial inflammation than controls after adjusting for demographics and vascular risk factors, while 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.

D. Clinical Presentation and Diagnostic Evaluation

PLWH who develop stroke tend to present similarly to HIV-uninfected patients, with sudden onset of focal neurological deficits being the most common presentation. However, PLWH 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 PLWH can be subclinical. An evaluation of autopsy results noted that while only 1–5% of the HIV population are found to have strokes in clinical studies, about 4–34% of the HIV population have cerebral ischemic lesions at autopsy[65]. Cerebral infarcts are much more common than cerebral hemorrhage, which follows the distribution seen in HIV-uninfected patients, but PLWH presenting with stroke tend to be younger, with a mean age of 40 years, compared to 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/signs that may suggest an infectious etiology of stroke are indicated. Diagnostic evaluation to be considered in PLWH presenting with stroke is outlined in Table 2.

E. Management

Research on the management of stroke in PLWH 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 (tPA) should be effective in PLWH. One study evaluated administration of tPA in PLWH in comparison to 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 PLWH 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 its 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 PLWH parallels the decision-making process in the general population. However, studies have shown that PLWH are less likely to be prescribed aspirin as a primary or secondary preventive therapy than HIV-uninfected patients, even in cases where aspirin is indicated[74]. One pilot study suggested that aspirin may attenuate the systemic immune activation in HIV patients[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, since statins have anti-inflammatory properties, they may be beneficial in reducing both low density lipoprotein (LDL) levels as well as inflammation. Studies have shown that statins can reduce the levels of certain inflammatory markers in PLWH 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 PLWH with stroke, with consideration of ART drug interactions when selecting a statin.

Few studies have evaluated the management of hypertension in PLWH for secondary prevention of stroke. At this time, the blood pressure goals remain the same as for the general population. Since 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 PLWH[45]. Furthermore, hemoglobin A1C, a common screening tool for diagnosis of diabetes, has been shown to underestimate glycemia in PLWH[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, PLWH 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 PLWH ranges from 47–71% and is the strongest risk factor for predicting CVD events[81]. However, one study showed that PLWH are less likely to receive smoking cessation counseling from their HIV providers compared to 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 PLWH[83].

F. Future directions

As PLWH 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 PLWH 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.

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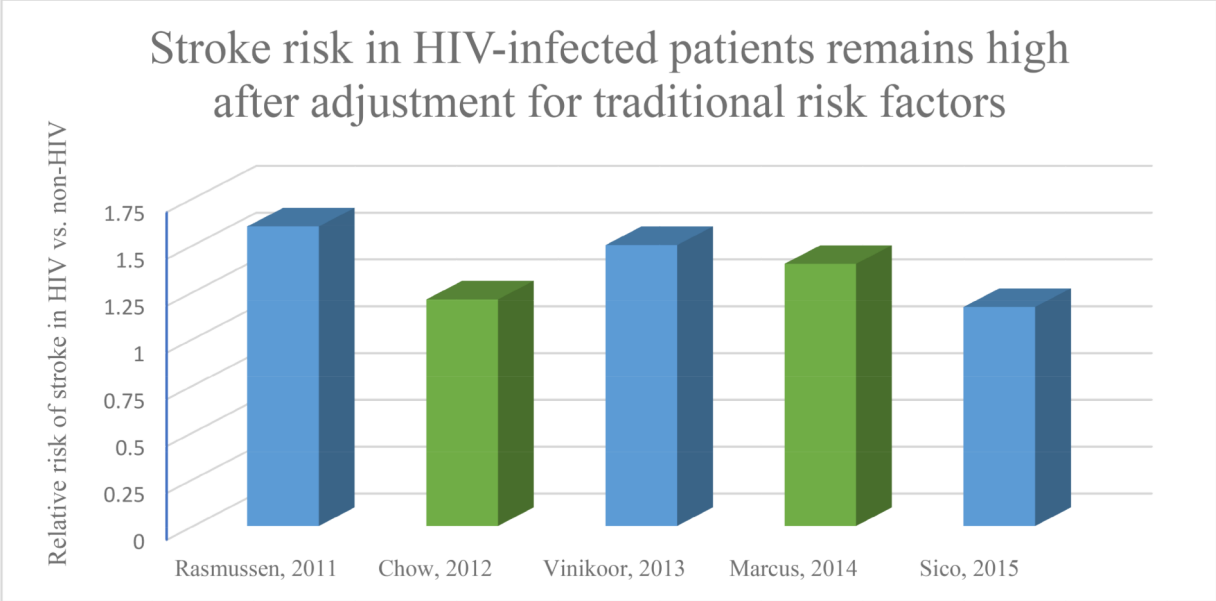

Figure 1.

Studies demonstrating the increased relative risk of stroke in patients with HIV compared to patients without HIV. All *p*-values were < 0.05.

Table 1.

A summary of 7 studies that reported etiology of ischemic stroke in PLWH.

Etiology of ischemic stroke in persons living with HIV								
Study	**Sample Population**	**LAA**	**Cardio- embolism**	**SVD**	**Infectious**	**Coagulopathy**	**Other**	**Cryptogenic/ Unknown**
Gutierrez[1] (2018) *New York City, USA*	**N**=115 **CD4**: 312 **ART use**: 64%	22%	8%	17%	16%	6%	10%	21%
Chow[2] (2014, 2017) *San Francisco, USA*	**N**=60 **CD4**: 276 **ART use**: 65%	23%	17%	20%	12%	3%	2%	23%
Benjamin[3] (2017) *Blantyre, Malawi*	**N**=64 **CD4**: unknown **ART use**: 40%	11%	6%	2%	25%	9%	27%	20%
Silva-Pinto[4] (2016) *Porto, Portugal*	**N**=23 **CD4**: 274 **ART use**: 71%	17%	17%	30%	5%	0%	5%	26%
Vinikoor[5] (2013) *North Carolina, USA*	**N**=31 **CD4**: 267 **ART use**: 94%	42%	3%	35%	3%	0%	6%	10%
Corral[6] (2009) *Madrid, Spain*	**N**=25 **CD4 (mean)**: 355 **VL<50copies/ml**: 48%	24%	8%	24%	4%	0%	8%	32%
Ortiz[7] (2007) *Miami, USA*	**N**=77 **CD4 (mean)**: 113 **ART use**: 37%	13%	19%	19%	0%	9%	14%	25%

ART use; percentage of ART use was used as a surrogate marker of viral load suppression in most of the studies.

CD4; median CD4 count of the cohort, unless stated otherwise

LAA; large artery atherosclerosis

N; number of HIV-infected patients with ischemic stroke in the cohort

SVD; small vessel disease

VL; HIV viral load

Infectious; infectious etiologies included (in order of higher prevalence to low): VZV[1,3], bacterial endocarditis[1,2,4], tuberculosis[3,6], syphilis[1,3], undifferentiated meningitis[2], cryptococcosis[1], toxoplasmosis[1], bacterial meningitis[1], mucormycosis[1], unidentified opportunistic infection[5].

Other; other etiologies included (in order of higher prevalence to low): vasculitis[3,6,7], cocaine use[1,4,5,6], non-atherosclerotic vasculopathy[3], multiple etiologies[3,7], arterial dissection[1,7], medication use[1], sickle cell crisis[1], carcinomatous meningitis[2], stump syndrome[5].

Cryptogenic/unknown; no etiology for stroke was found

Table 2.

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.

DIAGNOSTIC EVALUATION FOR A PATIENT WITH HIV AND STROKE

History
- Assess for vascular risk factors (HTN, dyslipidemia, diabetes, smoking, or prior TIA or stroke)
- **Previous opportunistic infection**
- Recent infections (esp. varicella zoster)
- History/symptoms of syphilis
- **History/symptoms of TB**
- Smoking and drug history
- Sexual history

Physical exam
- Skin changes (i.e. rash)
- Neurological manifestations of syphilis
- Signs of a systemic infection

Procedures
- ECG
- ***Lumbar puncture for cell count, protein, glucose, and other infectious work-up when indicated***

Bloodwork
- Complete blood cell count
- **CD4 count**
- **HIV viral load**
- BUN, creatinine, electrolytes, glucose
- Cholesterol panel
- ***ESR, CRP, ANA, ANCA***
- ***Coagulation screen for antiphospholipid antibodies***
- Treponemal test for syphilis (FTA-ABS, TPPA, EIA)
- ***Toxoplasma IgG (if no prior documentation)***
- ***Bacterial blood culture***
- ***Other infectious serologies, when indicated***

Imaging
- Brain imaging
- Imaging of intracranial/extracranial vasculature
- Chest X-ray
- Echocardiogram with bubble study
- Cardiac rhythm monitoring