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Incidence and Clinical Features of Cerebrovascular Disease Among HIV-Infected Adults in the Southeastern United States

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Abstract

With aging of the HIV-infected population, non-AIDS conditions such as cardiovascular disease (CVD) now account for substantial mortality and morbidity. While myocardial infarction is the major outcome of interest in the field of HIV and CVD, cerebrovascular disease remains understudied, especially in the Southeastern United States. We determined the incidence and clinical features of cerebrovascular events (CVE) in a large HIV clinical cohort in North Carolina (NC). A total of 2,515 HIV-infected adults contributed a median of 4.5 years (IQR: 2.0, 7.8) of follow-up. Fifty-three CVEs were adjudicated for an incidence rate of 3.87 per 1,000 person-years (95% CI: 2.90, 5.06). The ischemic stroke incidence was 2.26 per 1,000 person-years (95% CI: 1.53, 3.21), approximately 1.5 times the rate of a population-based cohort in NC. At the time of CVE, the median age was 48 years (IQR: 42, 55). Of ischemic strokes 76% resulted from large artery atherosclerosis or small vessel (lacunar) disease. In multivariable analyses, age, hypertension, dyslipidemia, recent $CD4^+$ cell count ≤ 200 cells/mm^3, and recent HIV RNA >400 copies/ml were associated with an increased risk of CVE. Antiretroviral therapy (ART) was not associated with the risk of CVE. We concluded that in the post-ART era, HIV-infected individuals appear to be at moderately increased risk of stroke. Prevention of CVEs in this population will require modification of traditional CVD risk factors and early, effective treatment of HIV infection.

Introduction

Due to the success of antiretroviral therapy (ART), the life expectancy among HIV-infected individuals has increased and AIDS-related causes of death, namely opportunistic infections (OI) and AIDS-defining cancers, have become less common. With aging of the HIV-infected population, non-AIDS conditions such as cardiovascular disease (CVD) now account for substantial mortality and morbidity.[1,2] For example, compared to their uninfected counterparts, HIV-infected adults appear to be at increased risk of myocardial infarction (MI) and may experience MI at a younger age.[3] Multiple factors may contribute to a high CVD risk among HIV-infected persons. Among HIV-infected persons, the vasculature may be damaged by HIV itself through both generalized inflammation as well as by direct infection and activation of T cells and macrophages in the vascular lining.[4,5] Moreover, among HIV-infected adults in the US, there is a high prevalence of traditional CVD risk factors such as smoking, hypertension, and dyslipidemia.[3] It is likely that ART also plays a role in increasing CVD risk, because although it effectively suppresses viral replication and decreases inflammation, some antiretroviral agents predispose to diabetes and dyslipidemia resulting in an increased CVD risk factor profile.[6,7]

While MI has been the major outcome of interest in the field of HIV and CVD, cerebrovascular disease has remained relatively understudied. In the setting of HIV infection, cerebrovascular events (CVE) (including ischemic strokes, hemorrhagic strokes, and transient ischemic attacks) have diverse etiologies.[8–10] In the pre-ART era, strokes related to central nervous system (CNS) OIs made the independent association of HIV infection and CVEs difficult to establish.[11] As the incidence of CNS OIs decreased with ART, CVEs were expected to become less frequent.[12] Instead from 1997 to 2006, the proportion of HIV-infected persons who experience a stroke has increased.[13] Recently, relying on administrative databases in Europe[14] and an urban center in the US,[15] two studies found high stroke incidence rates among

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individuals known to be HIV-infected, compared to the general population.

North Carolina (NC) is located in the Southeastern US, which has been coined the "stroke belt" due to historically high rates of stroke-related mortality.[16] More recently the region was recognized to have the country's highest rates of new HIV infections.[17] In this study we evaluated CVEs from 1999 to 2010 among HIV-infected patients participating in the University of North Carolina (UNC) Center for AIDS Research HIV Clinical Cohort (UCHCC) study. We estimated CVE incidence rates, assessed the types and mechanisms of events, and identified both traditional and HIV-specific risk factors.

Materials and Methods

Study population

All patients who received HIV primary care from 1999 to 2010 and enrolled in the UCHCC were included. As the major public hospital in central NC, UNC provides care for HIV-infected individuals from throughout the state, regardless of socioeconomic or insurance status. The UCHCC study and procedures have been described previously.[18] Briefly, the UCHCC includes demographic, clinical, and laboratory data on all participants from electronic institutional records or standardized medical record reviews. Dates of death are ascertained using the NC vital records death certificates and/or family report. For this study we excluded patients with a known history of cerebrovascular disease at HIV care initiation.

Adjudication of cerebrovascular events

As part of standardized medical record reviews that take place every 6 months for the UCHCC, CVEs were recorded in the database. For this study, each recorded CVE was adjudicated by three clinicians (M.J.V., S.W., and D.Y.H.) using paper and electronic medical records. Two blinded adjudicators (M.J.V. and S.W.) used the WHO MONICA[19] and the American Heart Association criteria[20] to confirm each CVE. Disagreements between reviewers were resolved by a vascular neurologist (D.Y.H.). Events that occurred in the setting of organic brain lesions such as tumors, parasitic infections, or progressive multifocal leukoencephalopathy were not classified as CVEs.

Confirmed CVEs were categorized as ischemic strokes, subarachnoid hemorrhages, intracranial hemorrhages, or transient ischemic attacks (TIAs). Both 28-day and 12-month mortality were recorded. For each ischemic stroke, two stroke specialists (S.W. and D.Y.H.) determined its probable mechanism using the TOAST criteria.[21] To categorize the TOAST mechanism (into large artery atherosclerosis, small vessel disease, cardioembolic, other, or unable to classify), stroke specialists reviewed CT and MRI/MRA reports (and images when available), echocardiograms, carotid ultrasounds, lumbar puncture results, and hypercoagulable tests.

An HIV-uninfected cohort at UNC was unavailable for comparison; therefore, we compared our ischemic stroke rate with published results from the NC site of the Atherosclerosis Risk in Communities (ARIC) cohort.[22] The ARIC cohort is a population-based CVD study with one of four study sites in central NC.

Study measures

Hypertension, diabetes, and hyperlipidemia were defined either by clinician diagnosis or by the prescription of antihypertensive, glucose-lowering, or cholesterol-lowering medications, respectively. Creatinine clearance (Crcl) was calculated using the MDRD formula[23] and chronic kidney disease was defined as Crcl ≤ 60 for greater than 3 months.[24] Coronary artery disease was defined by physician diagnosis. Coinfection with hepatitis C virus (HCV) and hepatitis B virus (HBV) were defined by positive HCV antibody and HBV surface antigen, respectively. Known behavioral risk factors for CVE (smoking, intravenous (IV) drug use, cocaine, and alcohol abuse) were recorded when reported by the provider and dichotomized to "ever" or "never."

$CD4^+$ cell count and HIV RNA level were measured as necessary for routine clinical care. $CD4^+$ cell count nadir was defined as the lowest recorded count during follow-up. To minimize the impact of having an event on the measurement of HIV-specific laboratory tests, the most recent $CD4^+$ cell count and HIV RNA level were defined as the most proximal measurements at least 7 days prior to the event or censor date.

Statistical analysis

Descriptive statistics were used to examine the distribution of demographics, comorbidities, and HIV-specific factors stratified by whether a patient experienced a CVE. Follow-up was defined as the time from entry into the cohort (at entry to care at the infectious diseases clinic or January 1, 1999) to the date of first CVE, death, or loss to follow-up (LTFU). The incidence of CVE was calculated as the number of confirmed events divided by the total contributed person-years of follow-up. LTFU was defined as absence from the clinic for 24 months. Participants remaining in care and event-free were administratively censored on December 31, 2010.

The duration of ART was quantified using prescription start and stop dates. We determined the impact of any current ART on CVE risk and assessed the association of current protease inhibitor (PI) use with CVE. In the analysis of CVE rate in persons receiving PI versus nonnucleoside reverse transcriptase inhibitor (NNRTI)-containing regimens, we excluded patients who received neither or both PI and NNRTI-containing regimens during their follow-up.

To identify independent factors associated with having a CVE, covariates examined in multivariable analyses using a Poisson model included traditional stroke risk factors as well as those factors found to have p value ≤ 0.2 on bivariable analyses. Statistical significance was determined using two-tailed tests with $p < 0.05$ considered significant. Statistical analyses were performed using STATA software (Version 11, StataCorp, College Station, TX). This study received approval from the UNC institutional review board.

Results

Study population

Of the 2,574 HIV-infected patients who met our study inclusion criteria, we excluded 59 (2%) with prevalent cerebrovascular disease at baseline. The median age at the start of follow-up was 39 years (IQR: 32, 45); 70% were men and 58%

Table 1. Characteristics of the HIV Clinical Cohort and of Cohort Participants Who Experienced an Incident Cerebrovascular Event

	All cohort participants (n = 2515)	*Participants who experienced an incident CVE (n = 53)*
Age at baseline in years, *n* (%)		
< 40	1,349 (54)	18 (34)
40–50	841 (33)	19 (36)
> 50	325 (13)	16 (30)
Age at time of event, median years (IQR)	NA	48 (42–55)
Male sex, *n* (%)	1,724 (70)	32 (60)
Race/ethnicity, *n* (%)		
Black	1,458 (58)	34 (64)
White	806 (32)	16 (30)
Other[a]	251 (10)	3 (6)
HIV risk factor, *n* (%)		
MSM	1,017 (40)	11 (21)
IVDU	339 (14)	14 (26)
Heterosexual sex	1,409 (56)	35 (66)
Hepatitis B coinfection, *n* (%)	119 (4.7)	4 (8)
Hepatitis C coinfection, *n* (%)	405 (16)	16 (30)
$CD4^+$ cell count nadir, median cells/mm^3 (IQR)	235 (69–407)	121 (43–300)
Most recent $CD4^+$ cell count, median cells/mm^3 (IQR)	466 (260–700)	267 (96–530)
Baseline HIV RNA > 400 copies/ml, *n* (%)	1,787 (73)	42 (79)
Most recent HIV RNA, > 400 copies/ml, *n* (%)	992 (40)	30 (57)
Antiretroviral therapy use, *n* (%)	2,239 (89)	50 (94)
Duration of follow-up, median years (IQR)	4.5 (2.5–7.9)	3.3 (1.9–6.7)
Entered cohort since 1999, *n* (%)	1,840 (73)	23 (43)

[a]Hispanic (5%), American Indian (2%), and unknown (3%).
CVE, cerebrovascular event; IQR, interquartile range; MSM, men who have sex with men; IVDU, intravenous drug use.

were black (Table 1). At baseline the median $CD4^+$ cell count was 351 cells/mm^3 (IQR: 144, 569), 46% had received ART, and 27% had HIV RNA levels below 400 copies/ml.

The median duration of follow-up was 4.5 years (IQR: 2.0, 7.8) with patients contributing a total of 13,708 person-years of follow-up. While under observation, 275 (11%) patients died, 921 (37%) were lost to follow-up, and 1,266 (50%) remained in care and event-free.

Cerebrovascular event rate and mechanisms

Fifty-three CVEs were confirmed during adjudication, resulting in an incidence rate of 3.87 events per 1,000 person-years (95% CI: 2.90, 5.06). The median age at time of CVE was 48 years (IQR: 42, 55) (Table 1). Ischemic strokes ($n = 31$) were the most common type of CVE (Table 2) at an incidence of 2.26 per 1,000 person-years (95% CI: 1.53, 3.21).

Retrospective TOAST categorization of observed ischemic strokes determined that 76% were caused by large artery atherosclerosis or small vessel (lacunar) occlusion (Table 2). Only one ischemic stroke occurred as a result of a possible OI. In that case, a 35-year-old man with a $CD4^+$ cell count of 1 cell/mm^3 and HIV RNA of 750,000 copies/ml presented with stroke symptoms. White matter lesions found on imaging were suspicious for a CNS OI. However, the patient died before the etiology of the lesions could be identified. In three ischemic strokes (10%), we could not identify the mechanism. Two patients (4%) died within 28 days of their event (one from a massive ICH and one from anoxic brain injury due to cardiogenic shock). The 12-month mortality rate was 15% overall (ranging from 0% for TIA to 50% for ICH).

Evaluation of risk factors

In bivariable analyses, demographic and HIV clinical and treatment characteristics, as well as comorbid conditions were

Table 2. Types of Cerebrovascular Events ($N = 53$) and Mechanisms of Ischemic Stroke ($N = 31$) Among HIV -Infected Individuals

	n *(%)*
Type of event	
Ischemic stroke	31 (58)
Transient ischemic attack	12 (23)
Intracerebral hemorrhage	9 (17)
Unable to determine	1 (2)
Mechanisms of ischemic strokes[a]	
Large artery atherosclerosis	13 (42)
Small vessel (lacunar) occlusion	11 (35)
Cardioembolism	1 (3)
Stroke of other determined etiology[b]	3 (10)
Stroke of undetermined etiology[c]	3 (10)

[a]Using TOAST criteria.[21]
[b]Other determined etiologies included cocaine-induced vasospasm, stump syndrome, and white matter lesions suspected but not confirmed to be caused by a CNS OI.
[c]Insufficient records available or incomplete work-up.

Table 3. Demographic Characteristics, Traditional Cardiovascular Disease Risk Factors, and HIV-Specific Factors Associated with Cerebrovascular Events

Totals	*No. events/ No. PYs*[a] *53/13,708*	*Incidence rate, No. events per 1,000 PYs 3.87*	*Incidence rate ratio (95% CI)*	p
Demographics				
Age at baseline in years				
>50	16/1,461	10.95	2.15 (1.53, 3.01)	<0.01
40–50	19/4,723	4.02	0.92 (0.80, 1.04)	
<40	18/7,577	2.38	Referent	
Female sex	21/4,169	5.04	1.51 (0.87, 2.62)	0.14
Black race (vs. other)[b]	34/7,924	4.29	1.32 (0.75, 2.31)	0.34
Comorbidities				
Hypertension	37/7,358	5.03	3.01 (1.67, 5.41)	<0.01
Diabetes	11/1,976	5.57	2.00 (1.03, 3.88)	0.04
Dyslipidemia	26/5,269	4.93	2.56 (1.49, 4.38)	<0.01
Chronic kidney disease	11/2,718	4.05	1.45 (0.75, 2.82)	0.27
Coronary artery disease	6/751	7.99	4.51 (1.21, 16.75)	0.03
Hepatitis C coinfection	16/2,384	6.71	2.15 (1.20, 3.87)	0.01
Hepatitis B coinfection	4/819	4.88	1.82 (0.66, 5.05)	0.25
HIV-specific factors				
CD4 nadir ≤200 cells/mm^3	31/7,136	4.34	1.31 (0.76, 2.26)	0.34
Most recent CD4 ≤200 cells/mm^3	20/2,148	9.31	3.36 (1.92, 5.88)	<0.01
Most recent HIV RNA >400 copies/mL	30/4,291	6.99	2.83 (1.64, 4.87)	<0.01
Antiretroviral therapy use	50/12,934	3.86	2.13 (0.67, 6.84)	0.20
PI vs. NNRTI use[c]	21/6,855	3.06	1.46 (0.52, 4.08)	0.47

[a]PY, person-year.
[b]There was no difference in CVE rate between other race/ethnicities.
[c]PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; analysis included only patients who received solely PI-based ($N=1164$) or NNRTI-based ($N=795$) regimens.

associated with increased CVE incidence rates (Table 3). Specifically, older patients and those with lower CD4$^+$ cell counts, detectable HIV RNA levels, hypertension, diabetes, dyslipidemia, coronary artery disease, and HCV coinfection were all at greater CVE risk. While CD4$^+$ cell count nadir ≤200 cells/mm^3 was not associated with CVE (IRR 1.31, 95% CI: 0.76, 2.26), most recent CD4$^+$ cell count ≤200 cells/mm^3 was associated with a 3-fold increased rate of CVE (IRR 3.36, 95% CI: 1.92, 5.88). Overall, current ART was not associated with increased risk (Table 3). Current receipt of PI-containing regimens (in 1,164 patients), when compared to NNRTI-containing ART (in 795 patients), did not increase the rate of events (IRR 1.46, 95% CI: 0.52, 4.08). During follow-up, 40% of patients reported smoking; however, smoking did not increase CVE risk. Similarly, IV drug use, alcohol abuse/dependency, or cocaine use showed no association with CVE risk.

Age, hypertension, dyslipidemia, recent CD4$^+$ cell count ≤200 cells/mm^3, and recent detectable HIV RNA level were independently associated with CVE (all $p<0.05$) (Table 4).

Table 4. Factors Independently Associated with Risk of Cerebrovascular Events Among HIV-Infected Individuals

	Full model[a] *IRR (95% CI)*	p	*Final model*[b] *IRR (95% CI)*	p
Age (per 10 year increase)	1.78 (1.25, 2.55)	<0.01	1.72 (1.29, 2.28)	<0.01
Female sex	1.69 (0.82, 3.48)	0.16		
Black race	0.89 (0.46, 1.74)	0.73		
Hypertension	1.96 (0.99, 3.99)	0.05	2.04 (1.08, 3.87)	0.03
Diabetes	0.95 (0.42, 2.18)	0.91		
Dyslipidemia	3.02 (1.48, 6.17)	<0.01	2.94 (1.63, 5.32)	<0.01
Coronary artery disease	2.51 (0.62, 10.17)	0.20		
Tobacco smoking	0.81 (0.40, 1.65)	0.56		
Hepatitis C coinfection	1.81 (0.85, 3.84)	0.12		
Most recent CD4 <200 cells/mm^3	2.83 (1.27, 6.33)	0.01	2.69 (1.47, 4.91)	<0.01
Most recent HIV RNA >400 copies/mL	3.97 (1.90, 8.31)	<0.01	3.56 (1.94, 6.53)	<0.01
Antiretroviral therapy use	4.16 (0.80, 21.65)	0.09		

[a]Risk factors in the full Poisson regression model were selected *a priori* or after bivariable analyses.
[b]Full model was reduced based on $p>0.05$ to reach the final model.

Independent of age, dyslipidemia, $CD4^+$ cell count, and HIV RNA level, patients with hypertension had twice the rate of CVE (IRR 2.04, 95% CI: 1.08, 3.87). Having a detectable HIV RNA level at the most recent measurement was associated with more than a 3-fold increased rate of CVE (IRR 3.56, 95% CI: 1.94, 6.53), independent of age, hypertension, dyslipidemia, and $CD4^+$ cell count. In a sensitivity analysis that restricted the sample to patients with a viral load measurement within 90 days of the event, censoring, or death, the incidence rate ratio increased to 4.81. Exclusion of patients who entered care at UNC prior to the cohort inception (27%) from the analysis did not change the results.

Discussion

Among HIV-infected adults receiving care at the UNC Hospital, we estimated the overall incidence of CVE at 3.87 per 1,000 person-years and the incidence of ischemic strokes at 2.26 per 1,000 person-years. At the time of CVE, patients had a median age of 48 years. Both traditional CVD risk factors (hypertension and dyslipidemia) and HIV-specific factors (recent $CD4^+$ cell count and HIV viral load) were associated with the risk of CVE. Our cohort study is the first to investigate the clinical epidemiology of CVE among HIV-infected persons living in the Southeastern United States.

Stroke incidence rates among HIV-infected adults in NC are slightly different from other HIV-infected populations. In Europe, HIV-infected adults have a slightly lower CVE incidence than we recorded, consistent with lower rates seen in the general population of Europe compared to the US.[14,25–27] Among HIV-infected populations in the US, two studies reported somewhat higher incidence rates than seen in our cohort. The Veterans Aging Cohort Study (VACS) reported a stroke rate of 2.93 per 1,000 person-years in HIV monoinfected and 6.99 per 1,000 person-years in HIV/HCV coinfected patients.[28] The VACS consists of military veterans who have a high prevalence of comorbidities and behavioral risk factors that have been associated with stroke. Partners Healthcare in Boston, which utilized a large administrative database, estimated the incidence of ischemic strokes at 5.27 per 1,000 person-years.[15] Administrative cohorts that rely on ICD-9 codes are valuable in the study of rare events but can be prone to low specificity.[29] Therefore, in the Boston study, a clinician reviewed events to improve the accuracy of their estimate.[14,15]

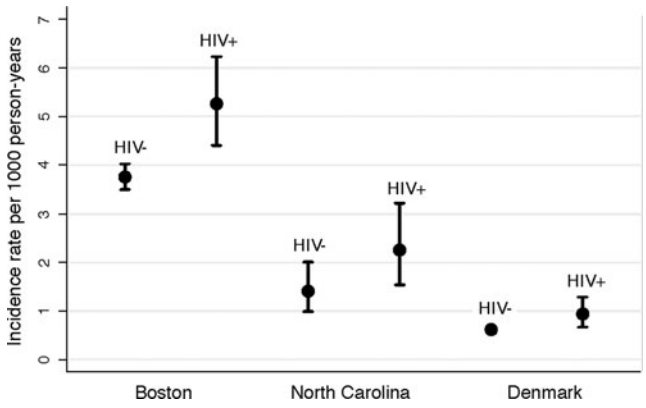

FIG 1. Ischemic stroke rates in HIV-infected and comparison cohorts from a Boston-area health care system (left),[15] from NC [in the UNC Center for AIDS Research HIV Clinical Cohort (UCHCC) and Atherosclerosis Risk in Communities (ARIC) Cohort] (center),[29] and from a Danish nationwide population-based cohort (right).[14]

In addition to variability in CVE rates by population, CVE incidence appears to vary by HIV status. In Denmark and Boston, HIV-infected individuals had approximately 1.5 times the rate of CVE compared to the general population (Fig. 1).[14,15] One limitation to our study was our inability to directly compare our stroke rates to an HIV-uninfected cohort at our institution. However, we compared our results to the NC site of the ARIC cohort, whose demographically mixed population is representative of NC. In NC, individuals aged 45–84 years old (followed from 1987 to 1995) had an age-adjusted incidence of ischemic strokes of 1.41 per 1,000 person-years (95% CI: 0.99, 2.01),[22] approximately two-thirds the rate seen in our cohort. Participants aged 45–54 across all sites of the ARIC cohort from 1987 to 2001 had a rate of ischemic stroke of 1.18 per 1,000 person-years,[30] approximately one-third the rate seen in 40–50 year olds in our cohort. Because of differences in the timing, design, and adjudication between ARIC and our study, we cannot be certain that the difference in CVE rates is due to HIV infection. However, our results, in conjunction with two recently published studies,[14,15] suggest that HIV-infected individuals may be at increased risk of CVE. The fact that a low CD4 cell count and detectable plasma HIV RNA level were associated with stroke in the multivariable analysis supports the plausibility of this relationship.

Among patients who experienced a CVE, ICH accounted for approximately 20% of events, which compares to 10% reported in the general population.[30] However, the 28-day mortality after hemorrhagic stroke was only 7.7% in this study versus 37.5% in the ARIC cohort.[22] Consistent with the general population, the majority of ischemic strokes in this study resulted from large artery atherosclerosis and small vessel disease (Table 2). We observed a very small number of events caused by CNS OIs, which is similar to other HIV studies done after ART became widely available in the United States and Europe.[9,26] We did not identify any cases of HIV-associated vasculopathy, which is a poorly characterized condition that manifests as fusiform intracranial aneurysmal disease in HIV-infected persons.[8] Although two stroke specialists participated in the adjudication process, we acknowledge the difficulty in accurate assignment of TOAST categorization, which is most accurate when utilized in prospective studies that have consistent and comprehensive diagnostic work-ups. Due to the retrospective nature of this study, diagnostic testing patterns were variable, and in some cases adjudicators relied on radiology reports when images were not available for review.

While we confirmed that among our HIV-infected cohort traditional risk factors are the key targets for prevention of CVD, viremia and immunosuppression should also be viewed as modifiable risk factors. Consistent with other observational studies,[31,32] viral load was associated with the risk of an event in our analysis. Systemic inflammation as a consequence of uncontrolled viremia, has been linked with cardiovascular events. In the SMART study, HIV-infected patients with high $CD4^+$ cell counts randomized to a viremia permissive strategy had an increased risk of CVD compared to those who were virologically suppressed.[33] Recently in an observational cohort of ART-treated patients, episodes of high-level viremia predicted cardiovascular events.[34] In light of emerging evidence regarding the harm of uncontrolled

viremia, HIV treatment guidelines in the US now support initiating ART earlier in the course of HIV infection.[35] Further investigation should evaluate the role of virologic suppression in the prevention of CVD.

While ART-induced virologic suppression could modify the risk of CVD, certain antiretroviral agents have been linked with an increased risk of MI.[25,36] This association has not been established for ART and stroke. One of the strengths of this study was our ability to utilize both the duration and timing of ART exposure in our Poisson models. Overall, we did not find a significant association between ART use and risk of CVE. PIs can increase the CVD risk profile by predisposing patients to major CVD risk factors including hyperglycemia, dyslipidemia, and metabolic syndrome.[6,37] We compared patients who received PI versus NNRTI-based regimens (which were protective for CVE in a prior study[15]) and found that in our study population, PI exposure did not predict increased the risk of CVE. The lack of association between PI exposure and CVE has been previously reported[15] and may be due to differences in the pathogenesis of MI and CVE in HIV-infected individuals.

The major strength of this study was the use of a large clinical cohort study located in the Southeastern US with comprehensive patient data coupled with systematic event adjudications by our clinical and research team. We captured events that presented to both the inpatient and outpatient setting as well as events initially managed at outside hospitals. This minimized the chance of underestimating the event rate. Because stroke and other non-AIDS conditions can be inaccurately coded in the medical record,[29,38,39] we confirmed each event with at least two blinded adjudicators and utilized stroke specialists. While we identified and adjudicated all events that occurred during follow-up, LTFU was quite high (37%) and could have affected our observed incidence rate. Although patients in UCHCC are demographically similar to HIV-infected individuals receiving care in NC, as a public and tertiary care medical facility, UNC may provide care disproportionately to HIV patients with lower income and more advanced disease compared to the HIV-infected population in NC. Because low SES and advanced HIV disease have been associated with CVE, our observed incidence rate may not be generalizable to all North Carolinians living with HIV/AIDS.

In summary, CVEs are uncommon but potentially life-threatening events for which persons living with HIV infection may be at modestly increased risk. In the post-ART era, the mechanisms and risk factors for CVE among HIV-infected adults appear to mirror those of the general population. Modification of traditional risk factors should be a focus of CVD prevention in HIV clinics. ART does not appear to increase the risk of CVE; instead, early ART and viral suppression may be an adjunctive approach to prevention.

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Author Disclosure Statement

No competing financial interests exist.

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