International **J**ournal of **M**edical **R**eviews

Systematic Review Article

Human Immunodeficiency Virus (HIV) and Stroke Events: A Systematic Review and Meta-Analysis

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Abstract

Stroke is a very disabling state that affects a considerable number of people around the world and it has been associated with human immunodeficiency (HIV) infection. However, there is no comprehensive review article in the literature that well investigates this critical topic. So, we performed this systematic review using Pubmed search. From 655 studies found at the initial search using broad Mesh terms and after exclusion studies of unrelated topics or out of criteria, 39 studies have been left and reviewed. During over 1.2 million person-years of follow up, a broad spectrum of incidence rate of stroke events has been reported by different authors from 0.73/1000 to 5.27/1000 person years of follow up in different cohort studies. About the anatomical regions of the brain which are complicated by HIV infection, circle of Willis and basal structures including basal ganglia and thalamus seem to be more affected. The range of risk factors which have been associated with stroke events in HIV infected patients is too much wide and includes controversy: younger age, gender, hemorrhagic (*vs.* ischemic) stroke, antiretroviral therapy are the major factors with controversial factors associated with higher or lower stroke events in HIV infected individuals.on the other hand there were factors constantly reported as risk factors of higher stroke events in HIV positive patients which included CD4 cell counts, having AIDS, diabetes, being smoker, and not having arterial hypertension. Future controlled studies with large study populations can better clarify these risk factors.

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Submission Date: 15/12/2013
Accepted Date: 10/01/2014

Keywords: Human, Immunodeficiency, Virus, Stroke, Events

Introduction

Stroke is a very disabling state that affects a considerable number of people around the world and it is usually considered as a leading cause of adult disability in the industrialized countries [1]. In countries of lower financial strength as well, the incidence of stroke has recently increased substantially, and besides the increasing rate of the prevalence of vascular risk factors and ageing as the main contributing factors, infectious causes of stroke are also apparently play major roles in this risk enhancement [2,3].

Human immunodeficiency virus (HIV) infection is a global concern that complicates a large number of individuals around the world; and it is associated with a wide range of morbidities which can affect several human organs. Cardiovascular system is one of the major body systems that have been reportedly broadly affected by HIV infection which might lead to tragic consequences [4-6]. HIV infection has been strongly associated with ischemic stroke, especially in the younger age population [7]. Despite the overall decrease in the rate of stroke hospitalizations in the general population during the last decade, stroke hospitalization has substantially increased [6].

Epidemiological studies have revealed that HIV-associated stroke is not associated with conventional risk factor profile (e.g. hypertension, diabetes, hyperlipidemia, older age, and smoking) that is usually observed in HIV-negative stroke population [7,8]. Besides the HIV infection itself, antiretroviral therapy which is usually employed to manage the infection has been reported as a significant risk factor for cerebrovascular events [9]. Among the agents used for this purpose, some particular antiretroviral agents such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors have been more frequently accused as the players of the major roles in this risk enhancement due to their implications in the development of the metabolic syndrome, accelerated atherosclerosis and an increased risk for ischemic stroke. All of the above-mentioned facts about the risk profile disparity between HIV infected and non-infected stroke patients highlight the importance of a better understanding of stroke events happening in HIV infected individuals, which might be able to help us to prevent more effectively. In this systematic review article, we aim to review the existing literature to find studies on stroke events happening in HIV-positive individuals to represent a comprehensive view on the subject based on the current knowledge.

Methods

To conduct our systematic review, the primary search was done using the terms *"HIV*" and "*stroke*" as the keywords within the time-span of 1990-2013. A repeat of the study using "*CVA*" instead of "*stroke*" did not change the results. Again, the literature search using the term "*AIDS*" and "*Acquired immunodeficiency syndrome*" replacing the

keyword "HIV" added 24 new found studies to our initially found reports. The literature search was performed using the Pubmed database, which we believe provides relatively the largest published data of the most relevant studies in the fields of microbiology and neurology. We also tried to boost our search searching the citations of the found articles to find potential reports which have not been indexed in Pubmed or have not been retrieved through Pubmed search. In our search, overall, 655 studies were found upon a search of the literature by Pubmed using the keywords *Human immunodeficiency virus* and *stroke*. Then the found titles were screened to find appropriate studies associated with our systematic review. A majority of the studies, despite the keywords used to finding them were not associated with our review. For example, using keywords *AIDS* and *stroke*, most of the found studies were related to stroke rehabilitation using instrumental aids! Or in several of them, stroke was reported only as one of the events that were finally analyzed as a larger definition terminology of cardiovascular disease; but due to the subspecific value of our search, we "only" included studies that had investigated stroke events separately in their analyses. Finally, 39 studies have been remained, and reviewed according to the following categorization of the research: Prevalence of stroke in HIV infected patients, stroke in the young/children with HIV infection, HIV+ vs. HIV negative and stroke, pathology of stroke events in HIV positive patients, risk factors associated with stroke events in HIV infection.

Statistical analyses

The meta-analysis has been performed using software Stata v.9.0 (Stata corp, TX, USA).

Prevalence of stroke in HIV infected patients: As stated before, the prevalence of stroke events is believed to be augmented in HIV positive patients, and this risk enhancement is independent from the conventional risk factors that commonly found in the general population as associated with a higher risk of developing stroke events. However, to provide scientific evidence for this general presumption, we need to have epidemiological data that suggests a significantly higher prevalence of stroke events happening in HIV infected patients compared to the general population. Therefore, in this section, we review the existing published studies in the current literature that investigated the prevalence of stroke events in the HIV infected patients. In a cohort of 2515 HIV positive patients who were under follow for a median duration of 4.5 (2-7.8) years in the North Carolina, USA, the rate of ischemic stroke in the HIV positive patients was about 1.5 times larger than the rate of it in the general population of the same area [10]. In a prospective cohort of over 49,000 HIV+ patients from different countries, who followed for between 4-16 years in different cohorts, 258 stroke events happened, which rises the incidence rate to 1.3/1000 (95%CI: 1.1 to 1.4) person years [11]. A prospective cohort of 232 patients followed for a mean±SD of 782±308 days, Parruti et al. [12] showed that 19 patients (9.5%) experienced at least 1 vascular event; 6% of them died due to such events. another large prospective cohort study of about 4,300 HIV infected individuals followed for a mean±SD rate of 5.9±4.1 years, revealed an incidence rate of 5.27 per 1000 person-years for ischemic stroke, representing one of the highest rates reported in the literature [13]. A retrospective cohort of 7,053 HIV+ patients followed for 138,704 person years reported 29 incident cases of hemorrhagic stroke in this cohort [14]. A cross-sectional study of 583 HIV+ men showed that 3 of them had a history of stroke after their HIV test positivity, whose HIV duration was 194.5 (157.5–249) months [15]. In a retrospective cohort of 8,444 HIV positive patients with a median duration of over 15 years of infection, 39 stroke events have been detected [16]. But in a retrospective cohort of over 19 thousand veterans under 76,376 patient-years of follow up, a total of 868 CVA were diagnosed, which comprised the rate of CVA to 11.68 (95% CI, 10.93–12.48) per 1000 person years of observation [17]. Table 1 summarizes data of the studies investigating the prevalence of stroke events in the HIV positive adult populations.

Stroke in the young/children with HIV infection: Stroke is usually happens in individuals of more advanced ages, and is a very rare condition in children in the general population. However, in HIV infected population, observing stroke events in HIV positive patients is not rare. In a cross-sectional study on 179 pediatric patients with HIV infection, 8 patients were found to have clinical evidence to have acute stroke, and imaging study of them was confirmatory in all of them. Another cross-sectional study on 567 HIV infected patients who got the infection in the childhood and mostly in their childhood age (median: 5.5 years) at the time of analysis, Patsalides et al. [30] reported that from the 426 patients (75%) who were evaluated with neuroimaging studies, 11(2.6%) children were found to have cerebrovascular lesions, with only one of them having clinical neurologic symptoms associated with the imaging-detected lesion. A retrospective cohort study of 380 HIV positive children showed that 4(1%) had neuroimaging evidence of cerebral infarcts [31]. Another longitudinal study of 68 HIV infected children for a 4.5 years follow up, 4(6%) represented clinical evidence of stroke; and from 25 children who died through the follow up period (including 3 of the 4 patients with clinical diagnosis of stroke), autopsy analysis revealed 6(24%) having pathological evidence of cerebral stroke [32]. Table 2 summarizes studies investigating the prevalence of stroke events in children with HIV infection.

HIV+ vs. HIV negative and stroke: In the previous sections, we reviewed studies investigating the prevalence of stroke events in adult and pediatric HIV infected patients. However, only providing the incidence of stroke events in any population does not prove that the mentioned population is at an increased risk of developing it, even if the reported incidence is higher than the general population, because the patients might have different demographic features which may put them at an elevated danger. So, for this purpose, we need to conduct controlled studies in which the controls have similar characters to the cases. So, in the current section, we review prospective cohort studies which compared the incidence of stroke events in HIV positive patients with that in the HIV negative controls. Mateen et al. [34] in a prospective cohort started from 1996 to 2011, investigated 3945 (1776 HIV+) individuals, but found no

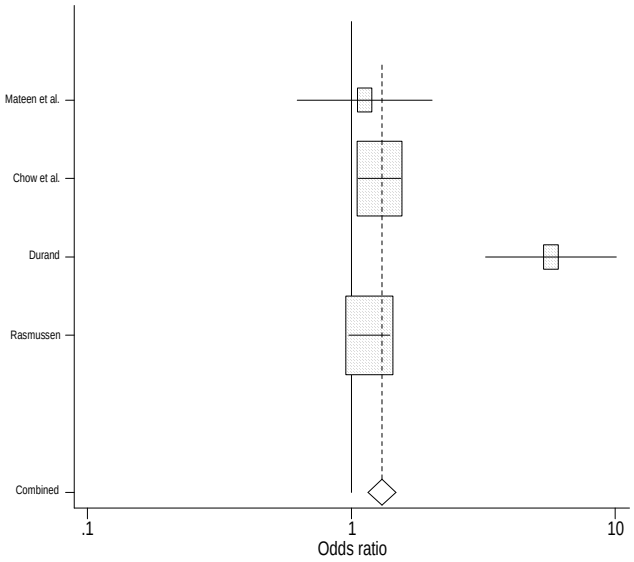
Table 1. Incidence of stroke events in adult HIV population

Study	Population	Methodology	Stroke determinant	Major findings
[10]	2515 HIV+ adults	Cohort of a median of 4.5 years (IQR: 2.0, 7.8) of follow-up	Clinical	Fifty-three CVEs were adjudicated for an incidence rate of 3.87 per 1,000 person-years (PY) (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.
[11]	>49,000 HIV+	Prospective cohort; follow up: 4-16 years; 201,925 PY	Clinical	258 stroke events (1.3/1000 (95%CI: 1.1 to 1.4) PYs of follow up) stroke.
[12]	232 HIV+	Prospective cohort; mean follow-up was 782±308 days.	Clinical	Nineteen patients (9.5%) had ≥1 vascular event; 12 (6.0%) died due to such events (n = 4) or any cause.
[13]	36,731:4,308 HIV+; 32,423 HIV-	Prospective cohort; 5.9(4.1) vs. 6.4(4.7) years	Clinical	The incidence rate of ischemic stroke was 5.27 per 1000 person-years in HIV-infected individuals.
[14]	7,053 HIV+	Retrospective cohort/138,704 PYs follow	Clinical	There were 29 incident intracranial hemorrhages in HIV-positive.
[15]	583 HIV+ men receiving ART	Cross-sectional observational	Clinical	3 cases with a history of stroke with HIV duration of 194.5 (157.5–249) months.
[17]	19,424 HIV+	Retrospective cohort; 76,376 patient-years of follow, (median duration, 3.93 years)	Clinical	A total of 868 CVA were diagnosed. Rate of CVA was 11.68 (95% CI, 10.93–12.48) per 1000 PY of observation.
[18]	FULLTEXT322 HIV+ adults	Retrospective cohort	Clinical	History of stroke was available in 11(3.4%) of HIV+ patients.
[9]	2,012 HIV+ under HAART	Retrospective cohort; a total follow-up of 13,228 patients/year.	Clinical	27 stroke events in 25 HIV+ patients. Incidence: 189 events (166 strokes) per 100,000 patients/year.
[19]	705 HIV+ hospitalized	Retrospective observational; over 5 years of follow up	Clinical	Stroke 19 (12.7%); stroke patients' CD4+ count, (mean 120, median 30, range 15-394/cmm)
[20]	23,468 HIV+	Prospective cohort; 36,145 PYs of follow up	Clinical	41 strokes happened in 39 (38 first event) patients, of which 7 (18.4%) were hemorrhagic and 29 were infarctions. The incidence of first CCVE was 5.7 per 1000 PYs (95% CI, 5.0–6.5).
[21]	772 HIV+	Cohort	Clinical	A total prevalence of 1.9% for TIA (0.8%) and stroke (1.2%) was calculated resulting in an annual incidence rate of 216 per 100000.
[22]	183 autopsy from HIV+	Cross-sectional	Pathology	Ten (5.5%) cases fulfilled the inclusion criteria and demonstrated similar hypoxic-ischemic lesions.
[23]	71 HIV+ patients who had undergone brain MRI for any reason	Retrospective observational	MRI	13 patients had ischemic lesions (22 lesions totally)
[24]	748 HIV+	Retrospective cohort (10 years period)	Clinical	Seven cases with recurrent transient neurological deficits were identified
[25]	104 HIV+	Cross-sectional	Clinical	Acute onset hemiplegia, believed to be due to stroke, was present in four (4%) of the HIV-1-seropositive patients.
[26]	5031 HIV+ (>16yr) follow up: 40,386 PY	Retrospective cohort	Clinical	140 HIV+ patients experience CVE. While in 1082 HIV- controls.
[27]	49,734 HIV+	303,118 person years follow up	Clinical	523 strokes happened.
[28]	49,737 HIV+	Prospective cohort of 234,818 PYFU	Clinical	There were 78 sudden deaths (0.33/1000 PYFU; 95% CI, .26–.41) and 172 nonhemorrhagic strokes (0.73/1000 PYFU; 95% CI, .62–.84).
[6]	Yearly reports (year 2006: 926,997 weighted total number of strokes	Retrospective cohort	clinic	1,425 (0/15%) cases of stroke were HIV positive. Actual numbers of overall US stroke hospitalizations lessened 7% (998,739 in 1997 to 926,997 in 2006), while actual numbers of stroke hospitalizations with coexisting HIV infection rose 60% (888 to 1,425, respectively).
[29]	113: 25 HIV+; 88 HIV-			Among patients with stroke, cerebral infarction was more frequent in HIV-infected patients than in HIV-seronegative patients (20 [80%] of 25 vs 48 [56%] of 88, P = .04).

Table 2. Pediatric HIV infection and incident stroke events

Study	Population	Methodology	Stroke determinant	Major findings
[33]	179 pediatric HIV+	Cross-sectional	brain CT, MRI, and MRA	Eight PHIV patients with clinical findings of acute stroke referred to the neuroimaging were identified. CT and MRI findings of infarction were found in all (8/8) patients.
[30]	567 HIV+ children getting the infection in childhood	Cross-sectional	Imaging	Eleven children (2.6%) were found to have cerebrovascular lesions. Only one had focal neurologic symptoms at the time of diagnosis. 27 infarctions were found in eight patients.
[31]	380 HIV+ children	10 years follow up of those with positive radiological findings of cerebral infarcts. Retrospective cohort	Imaging	4 patients were confirmed as having cerebral infarcts.
[32]	68 HIV+ children	Longitudinal study of 4.5 years period	Clinical/Pathology	4 out of 68 children (6%) in a longitudinal study of neurological complications of human immunodeficiency virus (HIV) infection had clinical and/or neuroradiological evidence of stroke, yielding a clinical incidence of stroke in this population of 1.3% per year. During this period, 32 subjects died, and permission for autopsy was granted in 18 of the patients, including 3 of 4 who had clinical evidence of stroke. The prevalence of cerebrovascular pathological features in our consecutive autopsy series was higher than the clinical incidence. At autopsy cerebrovascular disease was documented in 6 (24%) of 25 children with HIV infection, including all 3 children who had clinical evidence of stroke. Four patients had intracerebral hemorrhages, 6 patients had nonhemorrhagic infarcts, and 3 had both. Hemorrhage was catastrophic in 1 child and clinically silent in 3 children, all of whom had immune thrombocytopenia.

Figure 1. Forest plot of meta analysis of studies investing the impact of HIV infection on stroke events



Study	RR	95% CI Lower	Upper
[34]	1.12	0.62	2.02
[13]	1.28	1.06	1.54
[14]	5.71	3.23	10.10
[26]	1.17	0.98	1.40

Heterogeneity chi-squared = 27.71; p = 0.000; I-squared (variation in RR attributable to heterogeneity) = 89.2%; test of RR=1; z=4.25; p = 0.000

significant difference between HIV positive and negative people in the development of stroke (22 cases vs. 23 controls developed stroke events during the follow up). Chow et al. [13], however, studied a larger population of 36,731 individuals and showed that stroke events were significantly more frequent in the HIV infected patients than non-infected controls (132/4308 vs. 782/32,423, respectively). Similar findings have been reported by Durand et al. [14] on the prevalence of hemorrhagic stroke in their study showing that the event was observed in 29/7,053 HIV positive patients compared to 20/27,681 HIV negative individuals; and finally in the last study, Rasmussen et al. [26] investigating over 50 thousand people found that 140 out of 5,031 HIV positive patients versus 1,082 of 45,279 HIV negative controls represented stroke events, which showed an increased risk of stroke for HIV infection. Figure 1 shows the forest plot of a meta-analysis of the mentioned studies.

Pathology of stroke events in HIV positive patients: In the previous sections, we showed that the incidence of stroke events is increased in HIV infected patients. Nevertheless, for a better understanding of the cerebrovascular burden of stroke events complicating HIV infected individuals, we need to know the pathology of this complication. Izbudak et al. [33] investigating 179 pediatric HIV positive patients from whom 8 had a history of stroke, reported that basal ganglia-thalami infarction was the most frequent anatomical location of brain which was complicated by stroke [33]. MR angiographic evaluation of the cerebral arteries in 6 of these patients revealed that segmental occlusion, narrowing and/or dilatation in the circle of Willis was found in all of the six, and fusiform aneurysms were detected in three (50%) and a saccular aneurysm in one patient [33]. A prospective cohort of about 23,500 people with reported that during over 36 thousand person-years of follow up, 41 stroke events happened in 39 patients of which 7 (18%) were hemorrhagic and 29 were infarction [20]. In a series of 183 autopsies from HIV+ patients, 10 cases were found to have stroke lesions, in 2 of whom, there was an apparent clustering of lesions in superficial cortical layers 2 and 3, whereas in others, there was an apparent preference for deeper cortical layers [22]; with less frequency, lesions were detected in the thalamus (4 cases), cerebellum (2 cases), and brain stem (1 case), and parietal cortex (1 case) [22]. There was no evidence of large hemispheric or regional vessel territory infarction, wedge-shaped cortical infarction, or intracerebral or subarachnoid hemorrhage in any of the patients [22]. However, neuroimaging study of 71 alive HIV+ patients revealed completely different results with 13 patients having ischemic lesions from whom one represented occlusion of the middle cerebral artery, another had infarction of the posterior middle cerebral artery territory, and five had infarction in the vertebrobasilar territory) [23]. A retrospective cohort study of 10 years follow up, 7 out of 748 HIV positive patients (1%) represented clinical evidence of a stroke attack, but none of them had neuroimaging evidence of cerebral infarction [24]. In a cohort of 68 children with HIV infection, 32 patients died and autopsy examination revealed that cerebrovascular pathological features was available in 6 (24%) of 25 children, including all 3 children who had clinical evidence of stroke [32]. Four patients had intracerebral hemorrhages, 6 patients had nonhemorrhagic infarcts, and 3 had both [32].

Table 3. Stroke events in HIV+ vs. HIV negative individuals

Study	Population	Methodology	Major findings
[34]	3945: 1776 HIV+; 2083 HIV-(86 new infection)	Prospective cohort	Stroke events were found in 23 HIV negative vs. 22 HIV positive patients (p>0.6)
[13]	36,731:4,308 HIV+; 32,423 HIV-	Prospective cohort; 5.9(4.1) vs. 6.4(4.7) years	132 stroke events happened in HIV infected cases vs. 782 events among the controls. The incidence rate of ischemic stroke was 5.27 per 1000 person-years in HIV-infected compared with 3.75 in non-HIV-infected patients, with an unadjusted HR of 1.40 [95% confidence interval (CI): 1.17 to 1.69, P < 0.001]. HIV remained an independent predictor of stroke after controlling for demographics and stroke risk factors (HR: 1.21, 95% CI: 1.01 to 1.46, P = 0.043).
[14]	7,053 HIV+; 27,681 HIV-	Retrospective cohort/138,704 person years follow	There were 49 incident intracranial hemorrhages, 29 in HIV-positive and 20 in HIV-negative individuals. The adjusted hazard ratio for intracranial hemorrhage in HIV-positive compared to HIV-negative patients was 3.28 (95% confidence interval [CI] 1.75-6.12). The effect was reduced to 1.99 (95% CI 0.92-4.31) in the absence of AIDS-defining conditions, and increased to 7.64 (95% CI 3.78-15.43) in subjects with AIDS-defining conditions. Hepatitis C infection, illicit drug or alcohol abuse, intracranial lesions, and coagulopathy were all strongly associated with intracranial hemorrhage (all P < .001). In the case control study, 29 cases of ICH in HIV-positive individuals were matched to 228 HIV-positive controls. None of the antiretroviral classes were associated with an increase in the odds ratio of intracranial hemorrhage.
[26]	5031 HIV+ (>16yr) follow up: 40,386 person years. Controls: 45,279: follow up: 470,248 person years	Retrospective cohort	140 HIV+ patients experience CVE. While in 1082 HIV- controls.

Risk factors associated with stroke events in HIV infection: Besides having evidence suggestive of a promoting role for HIV infection in inducing stroke events, we need to investigate whether there are risk factors predicting this risk enhancement in this patient population. For this reason, the most powerful method of evaluating potential effects of any factor is to investigate its differential effectiveness in HIV-positive versus –negative patients. Nevertheless, due to the shortage of the number of controlled studies in this topic, herein, we review all the available data derived from any study by any methodology, and will let readers to decide on the value of the findings from each study.

Table 5 summarizes data of studies investigating different risk factors associated with A large controlled prospective cohort study of 4,308 HIV infected patients versus 36,731 uninfected individuals revealed that the relative increase in stroke rates was significantly higher in younger HIV patients and in women. Among HIV patients, increased HIV RNA was a significant risk factor for stroke events [13]. Similar to this study, a cross-sectional study of 116 HIV infected individuals also corroborated that HIV positivity in younger individuals has a more significant role in the increase in the incidence of stroke events than that in older patients [39]; the same study suggested autoimmunity and metabolic syndrome as significant predictors of stroke events in HIV infected patients. Similarly, being of younger age group and not having arterial hypertension were significant predictors of stroke events in HIV infected patients in another cross-sectional study [40]. But a retrospective cohort study of about 8,500 HIV infected patients with a median follow up time of over 15 years, having older age was a risk factor of stroke in HIV infected patients [16]. Another controlled retrospective cohort of 7,053 HIV infected people versus 27,681 uninfected individuals demonstrated that HCV infection, illicit drug or alcohol abuse, intracranial lesions, and coagulopathy but none of the employed antiretroviral agents, were associated with an increase in the odds ratio of intracranial hemorrhage [14]. A large prospective cohort study of about 50 thousand HIV positive patients in univariate analysis, besides high BMI, being smoker having diabetes and receiving antiretroviral therapy, male gender was a significant predictor of stroke and/or sudden death events [28], but in another study, female gender was associated with a higher risk of HIV-related stroke [13]. On the other hand, a large retrospective cohort study of over 19 thousand HIV infected patients showed that use of tenofovir and abacavir were associated with a lower risk of CVA attacks [17]. Similarly, being under fewer duration of antiretroviral therapy was demonstrated as an independent risk factor for CVA events [9].

Conclusion

In this systematic review, after exclusion studies of unrelated topics or out of criteria, 39 studies have been left and reviewed. There were 8 prospective and 13 retrospective cohort studies and the remaining were cross-sectional or cross-sectional studies. During over 1.2 million person-years of follow up, a broad spectrum of incidence rate of stroke events has been reported by different authors from 0.73/1000 [28] to 5.27/1000 [13] person years of follow up in different cohort studies. About the anatomical regions of the brain which are complicated by HIV infection, circle of Willis and basal structures including basal ganglia and thalamus seem to be more affected. The range of risk factors which have been associated with stroke events in HIV infected patients is too much wide and includes controversy. For example younger age or male gender in some studies have been reported as significant factors associated with stroke events in HIV positive patients, in others, patients of older age or female gender are supposed to be at increased risks. Moreover, while in one study HIV positivity had been associated with hemorrhagic stroke events [14], in another one it was associated with a significantly less frequency [36]. Antiretroviral therapy also has the same story, while in one study longer duration of using these agents was associated with lower incident rates of stroke [17], in others it was assigned as a risk factor for higher stroke events [28]. However, there are factors that almost invariably were associated with higher stroke events in HIV infected patients which included lower CD4 cell counts, having AIDS, diabetes, being smoker, but not having arterial hypertension. Future controlled studies with large study populations can better clarify these risk factors.

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