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AIDS/HIV Infection and Cerebrovascular Disease

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The occurrence of cerebrovascular disease in patients with human immunodeficiency virus (HIV) infection has been reported mainly in advanced stages of the disease and was generally associated with nonbacterial thrombotic endocarditis, opportunistic infections, or tumors, although in recent series a large number of cryptogenic strokes were found, probably related to HIV vasculopathy. Recently a population-based study reported a strong association between acquired immunodeficiency syndrome (AIDS) and both ischemic stroke and intracerebral hemorrhage, with an incidence of 0.2% per year. However, with the advent of highly active retroviral therapy (HAART)-causing immune restoration in HAART-treated patients and avoiding early death and leading to a lengthening of the disease free-survival, an older population was created, which is at higher risk for stroke. Furthermore, recent evidence suggests that accelerated atherosclerosis may be a potential risk for stroke in these patients as it accompanies dyslipidemia and insulin resistance that were found to be more frequent among patients in the HAART regimen. The relationship of HIV infection and stroke is undergoing remarkable changes and epidemiological studies should be performed on aging HIV populations to state the impact of this new information on the incidence of cerebrovascular disease in HIV-infected patients and to identify factors that are associated with its occurrence.
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Although neurological complications of human immunodeficiency virus (HIV) infection are common,[1] the presence of cerebrovascular disease in HIV patients has been seldom reported.[2] The use of prophylaxis against opportunistic infections and the introduction of a new anti-retroviral therapeutic regimen have led to reduced morbidity and mortality in those patients infected with HIV.[3] Furthermore, the introduction of highly active retroviral therapy (HAART), with an immune restoration in HAART-treated patients, has led to a 50% decline in acquired immunodeficiency syndrome (AIDS) death rate, decreased maternal–fetal transmission rates, lower incidence rates of opportunistic infections, and a 40 to 50% decrease in the incidence of HIV-associated dementia.[4,5] This new reality probably will change the incidence of strokes among AIDS patients, since stroke usually occurs in the later stages of the disease and is mainly due to nonbacterial thrombotic endocarditis, opportunistic infections, or neoplasm, although iatrogenic causes or associated risk factors, such as intravenous drug abuse (IVDA), or a direct relation to HIV itself due to an immunological and metabolic response to HIV has been reported.[2]

This article will review available data on the association between stroke and AIDS/HIV infection based on published clinical and autopsy series, the mechanism of ischemic and hemorrhagic strokes in HIV-infected/AIDS patients, and the impact and risks of HAART regimen.

Clinical Series

Several reports are available on the association between HIV infection or AIDS and cerebrovascular events.[2,6-29] Most of these reports describe cardioembolism, opportunistic infections, neoplasms, or inflammatory mechanisms to be the underlying cause of stroke. In some cases, a possible event was attributed to a migraine aura,[18] supposed to be induced by the presence of anticardiolipin antibodies[13,16] or caused by an HIV-associated vasculitis or vasculopathy.[28] The reported rate of stroke occurrence varies between 0.5 and 5% in different clinical series.[6-12,28,29]

In a review by Pinto,[2] a Medline research was performed between 1976 and 1994 and six clinical series were described. Half of the studies were prospective; data were un-

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controlled, and most of the series included predominantly cases in "advanced stage of disease," although staging was not defined. A total of 1885 cases of AIDS, AIDS-related complex, or patients with HIV infection was identified. Twenty-five patients (1.3%) had a stroke syndrome. Ischemic stroke (IS) was more common than intracerebral hemorrhage (ICH) (19 of 28 cases [68%] versus 9 of 28 cases [32%]). The majority of patients were homosexual men or patients with history of IVDA. Intracerebral hemorrhages were usually associated with thrombocytopenia, primary central nervous system (CNS) lymphoma, or metastatic Kaposi sarcoma. ISs were generally due to nonbacterial thrombotic endocarditis or concomitant opportunistic infections. Hematological conditions and cerebral vasculitis were reported in only a few cases, although an unknown etiology was more frequent in a recent series of IS patients, with an HIV-related vasculitis being suggested.[11,12,28] Due to limitations of the data, at that time it was not clear whether there was an association between AIDS and stroke.

Recently, Cole and coworkers[29] reported a population-based study of AIDS-associated stroke, with an incidence of both IS and ICH in patients with AIDS of 0.2% per year. If identifiable causes for either disorders were excluded, the incidence of IS and ICH in AIDS patients was 0.14 and 0.11% per year, respectively. The adjusted relative risk (RR) for both IS and ICH were significantly increased at 9.1 (95% confidence intervals (CI), 3.4 to 24.6) for IS and 12.7 (95% CI, 4 to 40) for ICH, with a combined adjusted RR of 10.4. Only AIDS patients were included (according to the 1987 Center for Disease Control (CDC) definitions of AIDS[30]), whereas HIV-positive patients (10 with IS and 5 with ICH) were included in the non-AIDS stroke group. Although underreporting of AIDS and stroke among the AIDS patients study population was a potential confounder, it is unlikely that these or other confounders would have significantly changed the authors' results. Despite the absence of CD4+ T-lymphocytes counts or other measures of immunological function, the study population was collected before HAART regimen was available, so all included patients had a profound immunosuppression. This population-based study found that AIDS is strongly associated with both IS and ICH. However, due to the small number of females, these results should not be extended to them.

This association has been already suggested by some previous studies. Over a 5-year period, Engstrom and coworkers,[12] in a retrospective clinical series of 1600 AIDS patients, recorded 12 IS (0.75%) cases that were compared with the annual incidence of IS among young adults (aged 35 to 45 years) and were higher than expected (0.0025%).[31] Mocham and coworkers,[27] in a prospective analysis of 35 hospital-based black South-Africans heterosexual HIV-infected patients, free of drug abuse and retroviral therapy, found 33 patients with IS and 2 with ICH, with a mean age of 32 years. Stroke was the first manifestation of the disease in 20 patients (57%). Coagulopathy, predominantly due to protein S deficiency, was the principal etiology, followed by meningitis and cardioembolism. In two patients, a vasculitic process of small vessels, not associated with an opportunistic infection, was found, and five patients had a cryptogenic stroke. A distinction between HIV-infected patients and AIDS patients was not found and respective stroke etiologies in each group are unknown. Fourteen patients had AIDS on the basis of CD4+ T-cells criteria (CD4+ T cells <200 mm^3). Evers and coworkers,[28] in a prospective cohort study, conducted for 9 years (1993 to 2001) on 772 consecutive HIV-infected patients, 639 of them younger than 46 years, found 15 patients with acute cerebrovascular disease, a prevalence rate of 1.9%. Six patients had a transient ischemic attack (TIA) with a prevalence of 0.8% and nine had an IS, with a prevalence of 1.2%. Ten of these patients were less than 46 years old with a rate of 1.6%, higher than reported for non-HIV patients.[32] When compared with the average annual incidence rate of TIA or IS among the non-HIV population from the same region, the HIV clinical cohort rate was about five times higher.[33] IS patients were older, with lower CD4+ T-lymphocytes counts, and in a more advanced stage of disease according to CDC classification. In 10 patients no etiology was found and stroke was considered cryptogenic. Dividing the cohort into two groups, with stroke occurring before and after 1997 when HAART regimen became available, there was no difference in the incidence rate of stroke, yet the number of patients was small. Some bias and confounders could be found in the present study, such as an increased rate of focal neurological symptoms among the cohort patients, underreporting of TIA, not all patients were fully investigated, and migraine aura or focal seizures could had been confused with TIA. Nevertheless there was an increased rate of ischemic vascular events in HIV-infected patients and in some cases an HIV-associated vasculitis or vasculopathy was assumed to be the underlying etiology of the event.

In two retrospective case-control studies, an association between HIV infection and stroke was not established.[21,25] Qureshi and coworkers[21] evaluated the relationship between HIV infection and stroke in young patients less than 45 admitted between 1990 and 1994. They analyzed 236 stroke patients, 113 with a known HIV status, 85% of them being African Americans, of whom 25 were HIV-positive (10 with AIDS). HIV-tested patients were more likely to be younger, cocaine users, with an IS, and had less arterial hypertension; HIV-untested patients were more likely to die during hospitalization. When compared with age- and sex-matched controls admitted due to status asthmaticus with known HIV serology, and after adjusting for other known cerebrovascular risk factors, there was an increased risk of stroke among HIV-infected patients (odds ratio (OR) = 2.3; 95% CI, 1.0 to 5.3; $P = 0.05$), particularly with IS (OR = 3.4; 95% CI, 1.1 to 8.9; $P = 0.03$). However, after excluding patients with IS due to meningitis or protein S deficiency (11 cases), the association between HIV infection and IS was not statistically significant, suggesting that the excessive risk could be due to these two underlying causes. Hoffmann and coworkers,[25] in a population of black HIV-infected patients from the Durban Stroke Data Bank, free of drug abuse and opportunistic infections, compared with age- and sex-matched controls, found no significant overall increased of stroke rate among HIV stroke patients (16%). However, there was a higher rate of large-vessel cryptogenic IS among the HIV-infected cohort

(91% among cases and 36% among controls). The authors suggested that the presence of a coexistent prothrombotic state could have been responsible for this finding. Evidence of a direct effect of HIV infection or immunosuppression on the risk of stroke was not found.

It is important to note that, except for the Evers and coworkers' study,[28] all of the others were conducted before the introduction of protease inhibitors (PIs) and subsequent antiretroviral combination drug regimens (HAART). This new therapy, leading to a lengthening of the disease-free survival, created an older population that is at higher risk for stroke. In addition, recent evidence suggests that a potential risk of accelerated atherosclerosis that may accompany dyslipidemia and insulin resistance is more frequent among patients in the HAART regimen, which could lead to a higher risk for stroke in the AIDS population.[34]

Autopsy Series

According to Pinto's review paper,[2] the proportion of AIDS cases with findings of cerebrovascular disease (CVD) on neuropathological examinations was much higher than in clinical series, with a 39% of CVD findings (98 among 251 patients), and a prevalence rate from 4 to 34%.[16,35-44] A higher ratio of ischemic to hemorrhagic cases was observed (72 among 98 patients with IS [73%] and 12 among 98 with ICH [12%]). As in the clinical series, the majority of patients were homosexual men or IVDA. These autopsy findings were not associated with acute CVD before death and the majority of studies do not distinguish between asymptomatic findings or those with a history of IS. More recently the Edinburgh HIV autopsy cohort[45] described the neuropathological findings among HIV patients with a full neuropathological postmortem examination, after excluding patients with CNS pathology or normal brain. Out of 183 patients, of whom 44 (24%) were pre-AIDS patients, 26 were included; in 10 of those IS was observed (5.5% of the overall population; 7% of the AIDS patients). All were advanced AIDS cases who died before the HAART regimen was introduced. Only one patient had a TIA and another had an asymptomatic basal ganglia infarct on CT scan. All others were asymptomatic for CVD. All cases had multiple ischemic infarcts on neuropathological examination, and a nonvasculitic vasculopathy was found, yet it was not associated with virus load. The authors concluded that cerebral infarcts in HIV-infected patients are not common in the absence of CNS opportunistic infection, lymphoma, or embolic sources. Each of those underlying conditions leading to stroke should be excluded before assuming that the cause is HIV itself—as a result of a vasculopathy or some other yet unrecognized pathogenic mechanism. Previous series have also described a mural thickening of small vessels in half the patients and multiple subclinical infarcts.[42] A vasculopathy mediated primarily by HIV was thought to be responsible for 40% of IS in another autopsy study.[16]

Table 1 Potential Causes of Ischemic Stroke in AIDS/HIV-Infected Patients

Cardioembolic
Nonbacterial thrombotic endocarditis (with and without IVDA)
Infective endocarditis (IVDA)
HIV myocarditis with thrombus
Myxoid valvular degeneration
Mural thrombus
Dilated cardiomyopathy
Cerebral opportunistic vasculitis/vasculopathy
Opportunistic infections
Cytomegalovirus
Mycobacterium tuberculosis
Varicella-Zoster virus
Syphilis
Cryptococcosis
Mucormycosis
Aspergillosis
Candida albicans
Toxoplasmosis
Coccidioidomycosis
Trypanosomiasis
Cerebral opportunistic neoplasm
Lymphoma
Prothrombotic states
Protein S deficiency
Antiphospholipid antibodies
Disseminated intravascular coagulation
Intravenous drug abuse
Cocaine
Heroin
HIV-related vasculitis/vasculopathy
Impaired vasoreactivity
Impaired vascular bed-specific homeostasis
Accelerated atherosclerosis with protease inhibitors
Dyslipidemia, insulin resistance
Endothelial dysfunction
Cryptogenic

Ischemic Stroke in HIV-Infected Patients

As previously reported in clinical, radiological, and pathological series, there is an increased risk of IS in AIDS patients. There are several potential causes for IS in HIV-infected patients (Table 1).[3] Data are not available to determine whether risk factors for HIV infection influence the etiology and frequency of CVD. The most frequently reported causes are cardioembolism or opportunistic diseases of the CNS,[2,8-12,44] followed by hemostatic abnormalities, especially protein S deficiency.[21,27] Ischemic strokes in IVDA have been rarely reported, except when associated with endocarditis.[2,44] Other possibilities were vasculitis, vasospasm, or foreign body embolism. Therefore, a higher rate of stroke was to be expected in HIV-infected/AIDS patients with an actual history of IVDA compared with the age-matched sample from the general population. Ischemic stroke has been classified as cryptogenic in several clinical series.[2,8,11,12,16,25,28] Recently

the use of PIs has been associated with an increased risk of vascular events including stroke.[26]

Cardiac disease is frequent in HIV-infected/AIDS patients and usually has been reported as the principal cause of embolic stroke. The most common cardiac lesions are nonbacterial thrombotic endocarditis and infectious endocarditis, both associated or not with IVDA. Dilated myocardiopathy, mural thrombi, myxomatous degeneration of valves, and HIV myocarditis have also been described.

Several opportunistic infections have been associated with stroke in HIV-infected/AIDS patients (Table 1). These causes are usually present in the advanced stage of the disease and thus with the introduction of prophylactic therapy for opportunistic infections and the current use of HAART regimen; their incidence will probably decrease dramatically, although thus far no data exist to confirm this assumption.

A variety of hemostatic abnormalities has been reported in HIV-infected patients with IS. The most consistently described prothrombotic state has been protein S deficiency, but antiphospholipid antibodies had also been found.[11] A disseminated intravascular coagulation can cause IS in terminally ill patients due to dehydration.[39,44] An unrecognized prothrombotic state has been suspected responsible for the high incidence of "cryptogenic strokes," but no data supported this evidence.[46] Other forms of hypercoagulability have been seen in HIV patients, but no data exist to confirm that their frequency is higher than in the general population.[46]

As previously discussed, IVDA has been rarely associated with IS in HIV-infected/AIDS patients, even though the active use of cocaine and heroin increase the risk of stroke. While in heroin users stroke usually occurred after reintroduction of the drug, suggesting an immunological mechanism, in cocaine users the mechanism of ischemia is unclear.[47]

As a result of recent clinical series, an HIV-related vasculopathy has been recently suggested as the mechanism of stroke in HIV/AIDS patients who are free of other risk factors for these vascular changes. A case of recurrent stroke in HIV patients with isolated central nervous system angiitis in the absence of an opportunistic cause had been described.[48] Those findings were already reported in autopsy series and the most relevant data are provided by the Edinburgh Autopsy Cohort Study,[45] where the presence of an asymptomatic vasculopathy characterized by small-vessels wall thickening, perivascular space dilation, rarefaction, and pigment deposition with vessel wall mineralization, and occasional perivascular inflammatory cells infiltrates, was found, without definitive evidence of vasculitis. These vascular changes were similar to those found in elderly patients with vascular risk factors and cerebral atherosclerosis, although the Edinburgh cases were young patients, free of vascular risk factors. We should not forget, however, that all autopsy findings were not associated with acute CVD. Abnormalities of cerebral perfusion have been documented in asymptomatic HIV patients using ^{113}Xe single-photon emission computed tomography[49] and confirmed in a transcranial Doppler study when reduced baseline blood flow velocity was found after acetazolamide injection when compared with controls, suggesting alterations of cerebral resistance at the arteriolar level.[50] Those findings suggest that a CNS vasculopathy is present in HIV-infected patients without symptoms of cerebrovascular disease and that the disorder is confined to small cerebral arterioles or at least to the peripheral vascular bed, the same vessels showing pathological changes in the autopsy series discussed above. This vasculopathy could be due to direct infection of the vessel walls by HIV.[45] However, the clinical relevance of HIV-related vasculopathy is still a matter of debate.

Figure 1 illustrates the MRI findings of a 59-year-old male with an acute stroke and previously unidentified AIDS disease.

Intracerebral Hemorrhage in HIV-Infected Patients

The causes for ICH in HIV-infected patients are listed in Table 2.[2,6-8,23] The mortality tends to be higher and ICH is a later complication of HIV infection, generally with CD4+ T-lymphocytes cells below 200 mm^3.[23] From previous studies it was unclear whether hemorrhagic stroke was more frequent in the HIV-infected population,[2,21] although some authors have suggested that this was the case,[23] with a 1% incidence, higher than expected in young adults. Cole and coworkers[29] in the first population case-based study found an incidence of 0.11% per year for ICH with an adjusted RR of 12.7% (95% CI, 4 to 40), confirming that AIDS is strongly associated with ICH. This incidence may decline with the HAART regimen and the subsequent decrease in the principal conditions conferring an increased risk of ICH.

HAART Regimen and HIV-Infected/AIDS Patients

Clinical atherosclerotic disease was not frequently reported in HIV-infected/AIDS patients in the pre-PIs era, although this low incidence of atherosclerosis may have been related to the reduced live expectancy.[51] With the introduction of PIs and HAART regimen, a clear reduction of comorbid conditions, including opportunistic infections, and premature mortality occurred. This could account for a growing prevalence of atherosclerosis in HIV-infected patients as they get older and as underlying pro-atherosclerotic effects of the HIV infection itself become evident.[52-54]

Though inconclusive at this time, data have suggested that HAART regimen is associated with an increased incidence of metabolic changes—dyslipidemia, insulin resistance—and somatic—lipodystrophy/lipoatrophy—compared with the general population, which is associated with an increased risk of cardiovascular disease, mainly coronary artery disease and stroke.[34] Treatment with PIs has been associated with severe premature atherosclerotic vascular disease, albeit mostly on the basis of anecdotal evidence.[55-58] Marked lipid abnormalities may be present in 24 to 64% of patients treated

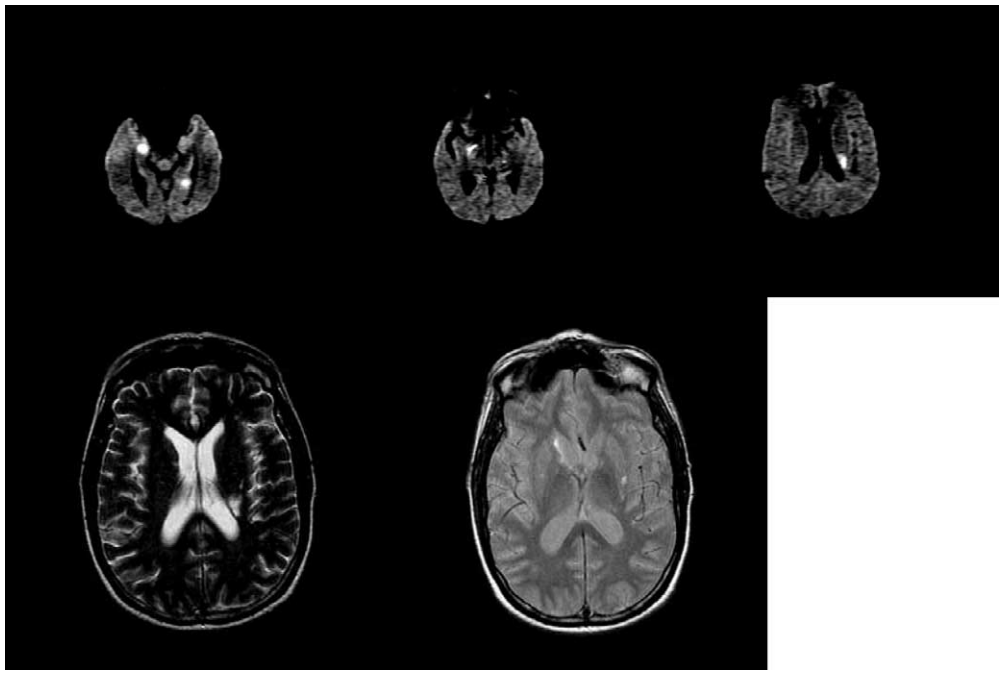

Figure 1 A 59-year-old man, without known vascular and HIV risk factors, was admitted to the hospital for acute onset of left hemiparesis. Diagnostic work-up revealed HIV1+ and AIDS disease criteria were found to be present. His brain MRI showed multiple ischemic lesions (axial diffusion, T2-weighted, and flair scans).

with PIs[55,59,60] and the largest published study has shown an average increase in the total cholesterol and serum triglyceride levels of 28 and 96%, respectively, when compared with pretreatment levels and matched PI-naïve HIV-infected controls.[51]

Myocardial infarction has been the most frequent vascular event, but stroke also can occur.[26] Studies published before HAART therapy showed that subclinical echocardiographic abnormalities independently predict adverse outcomes and identify high-risk groups to target for early intervention or therapy.[61] However, contrasting opinion still exists about the incidence of coronary artery disease among HIV-infected patients receiving PIs including HAART.[62,63] Nevertheless for HIV patients on HAART regimen it may be important to evaluate traditional cardiovascular risk factors and to try to intervene in those that can be modified.[34]

Table 2 Potential Causes of Intracerebral Hemorrhage in AIDS/HIV-Infected Patients

Opportunistic infection
Mycobacterium tuberculosis
Toxoplasmosis
Opportunistic neoplasm
Lymphoma
Metastatic Kaposi sarcoma
Prothrombotic states
Disseminated intravascular coagulation
Thrombocytopenia
Vascular
Mycotic aneurysm (IVDA)

Whether any particular PI drug or a combination of PI agents is more atherogenic remains unclear and, although studies have preferentially implicated different PIs (most frequently ritonavir), all available PIs induced potentially atherogenic metabolic derangements.[60,64,65] However, while the association between PIs and dyslipidemia is well defined, the risk of clinically relevant premature atherosclerosis remains to be established.[65] Fibric acid derivatives and statins can lower HAART-associated increases in dyslipidemia, although further data are needed on interactions between statins and PIs, as most statins are metabolized through the CYP3A4 pathway, inhibited by PIs. The statin that is least influenced by the CYP3A4 pathway is pravastatin.[34] Compared with the general population, HIV-infected patients receiving HAART regimens are at higher risk of developing hypertension. Calcium channel blockers and ACE inhibitors are the preferred therapy, although controlled clinical trials are lacking.[34] Moreover, HIV-infected patients, especially those with fat redistribution, may develop coagulation abnormalities, eg, increased levels of fibrinogen, plasminogen activator inhibitor-1, and tissue-type plasminogen activator antigen, and protein S deficiency.[66] Thrombocytosis following HAART therapy may also contribute to cardiovascular disease.[67]

We can conclude that some HAART regimens may promote a process of accelerated atherosclerosis, possibly associated with dyslipidemia and insulin resistance, and an increased risk of death by myocardial infarct and stroke. A careful laboratory and cardiac screening is warranted, especially in patients with underlying cardiovascular disease risk factors.

Conclusions

There is now clear evidence that stroke (IS and ICH) is strongly associated with AIDS. However, population-based studies with HIV-infected patients without AIDS criteria are lacking. The most common causes for IS are cardioembolism and opportunistic infections, although in recent series a large number of cryptogenic strokes were found, probably related to HIV vasculopathy. This entity is confined to small cerebral vessels and is probably due to direct HIV infection of the vessel walls. In black populations series, the most frequent stroke etiologies are meningitis and proteins S deficiency, so both these causes should be excluded. ICH is usually due to opportunistic neoplasm or infection and thrombocytopenia and is less frequent than IS. The introduction of HAART regimen had led to reduced morbidity and mortality of those infected with HIV. Although the association between PIs and dyslipidemia is well defined, the risk of clinically relevant premature atherosclerosis remains to be established.

The relationship of HIV infection and stroke is undergoing remarkable changes, as the prognosis of HIV infection is changing with an increased survival rate of patients, immune restoration in HAART-treated patients, and lower incidence rates of opportunistic infections. However metabolic effects of the drugs used for treatment and older age with underlying traditional risk factors might lead to an increased incidence of ischemic strokes, due to possible accelerated atherosclerosis in patients treated with HAART. Furthermore, HIV-related vasculopathy, more frequent in recent series, should not be forgotten, yet its clinical relevance is still to be established. Epidemiological studies should be performed on aging HIV populations to state the impact of these new data on the incidence of cardiovascular diseases and stroke predominantly in HIV-infected patients.

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