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Clinical Report

Cerebrovascular disease in young, HIV-infected, black Africans in the KwaZulu Natal Province of South Africa

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The objective of this study was to elucidate the mechanisms of an ischemic stroke in a human immunodeficiency virus, type 1 (HIV)-infected population. Several clinical and autopsy studies have suggested an increased incidence of strokes in HIV-infected persons. These studies have been performed on diverse populations with numerous confounds for strokes, including, drug abuse and coexistent opportunistic infection. Because of these confounding factors, it has been difficult to assess whether a unique stroke propensity exists among HIV-infected persons. A retrospective case-controlled study was carried out of patients registered in the Durban Stroke Data Bank (DSDB) (*n*=1298) located in KwaZulu Natal province of South Africa. Sixteen per cent of all strokes in young (<50 year old) black Africans living in KwaZulu Natal province on the east coast of South Africa reported to the DSDB occurred in association with HIV infection. This HIV-infected population was free of drug abuse and relatively devoid of opportunistic infections. The incidence rate of HIV in this stroke population paralleled that of the young black population at large, suggesting no significant overall increased rate of stroke in association with HIV. However, when compared to strokes occurring in an age- and sex-matched, HIV-seronegative control population, the cryptogenic stroke was more common in the HIV-infected population. Although the incidence of rate of stroke appeared to be no higher among HIV-infected young black Africans in the KwaZulu province than among HIV-seronegative controls, the increased incidence of a large vessel cryptogenic stroke in the former suggests the presence of a co-existent prothromobotic state. *Journal of NeuroVirology* (2000) **6,** 229–236

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Introduction

In contradistinction to the common and well-described neurological syndromes associated with the human immunodeficiency virus, type 1 (HIV) disease, such as, AIDS dementia complex and peripheral neuropathy, cerebrovascular disease is, in general, poorly characterized and seldom reported in comprehensive surveys of the illness. Even in those case series of stroke and HIV reported to date, many patients had concomitant central nervous system infections or tumors or other risk factors for stroke (Pinto, 1996; Mizusawa *et al*, 1988; Engstrom *et al*, 1989; Berger *et al*, 1990; Baily and Mandal, 1995; Shah *et al*, 1996; Qureshi *et al*, 1997; Philippet *et al*, 1994; Park *et al*, 1990; Moriarty *et al*, 1994; Gillams *et al*, 1998; Roquer *et al*, 1998; Gam *et al*, 1994; Kieburtz *et al*, 1993; Santonja *et al*, 1998; Strobel *et al*, 1995). The association between stroke and HIV infection remains unclear with several different pathological mechanisms proposed (Berger *et al*, 1990). In an attempt to elucidate the problem, a recent review on the subject recommended more stringent case definition of both entities, attention to confounding factors such as IV drug abuse, and citation of the denominators of both populations (Berger *et al*, 1990). To the best of our knowledge, we present the

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largest series to date of clinically, well-characterized, young stroke patients with HIV infection. The patients were derived from the Durban Stroke Data Bank (DSDB, *n*=1298), an area with very high endemicity of HIV. HIV seropositivity point prevalence in the South African province of KwaZulu Natal for black antenatal women is currently 31.07% (Swanvelder *et al*, 1998). The figures for black men and women for the respective years of the study were 1992: 4.7%, 1993: 9.6%, 1994: 15.2%, 1995: 20.1%, 1996: 23.0%, and 1997: 27.4% (Swanvelder *et al*, 1998; York and Smith, 1998). All patients were young stroke victims, relatively free of other confounding cerebrovascular risk factors. HIV transmission was the consequence of heterosexual activity. None of the patients were drug abusers. A historical control group from the same stroke registry was used for comparison.

Results

Demographics
Within the DSDB (*n*=1298), over the period of July 1992 to July 1998 there were 729 males (56.2%), 972 whites (74.8%), 154 Asian Indians (11.9%), 151 blacks (11.6%) of which 106 (106/151; 70%) were young patients. Twenty-two patients (1.7%) were of mixed race or other race. The mean age of whites (61 years; s.d. $\pm$14.05) and blacks (41.5 years: s.d. $\pm$14.4) differed significantly. Overall there were 25 HIV positive patients with strokes, of which 24 were black and one was Asian Indian. Of the 24 (24/151; 16%) black patients with HIV seropositivity on ELISA confirmed by Western blot analysis only two were older than 49 years (52 and 53 years) and these were therefore excluded from further analysis. There were 13 men and nine women with a mean age 29.1 years (range 20–42 years). In the control group of black patients with the same gender distribution, the mean age was 31 years and age range 19–44 years (*t*-test, *P*=0.26 NS).

Clinical presentations
Presentation by gross arterial system involvement according to the OCSP classification revealed no significant differences in two groups examined. Neither the degree of neurological deficit (Canadian Neurological scale) nor the degree of disability (Rankin scale) on presentation was statistically significant between the HIV stroke group and control group. No statistically significant difference was noted in the number of patients presenting with seizures at the time of the stroke. Seizures were observed in 7/22 (31.8%) in the HIV stroke group compared to only 2/22 (9.1%) in the control group (*P*=0.13, Fisher's Exact Test).

Cognitive impairment
Patients from the HIV group more often had large scale network impairment such as frontal system syndromes (4/22; 18%) and aphasia (10/22; 45%) compared to the control group (frontal system syndrome 3/22; 14% and aphasia 8/22; 36%). The HIV group were also less likely to have normal cognitive examinations (5/22; 23%) compared to the control group (8/22; 36%). However none of these comparisons were statistically significant. The other syndromes delineated occurred too infrequently to allow for meaningful comparisons.

Neuroradiological investigation – brain parenchyma
All patients had parenchymal neuroimaging with either CT or MRI brain scans. MRI brain scans were performed in 20/22 (91%) of the patients in the HIV stroke group and 19/22 (86%) of the control group. No significant differences were found between the two groups when analyzed according to gross arterial involvement, i.e., anterior (middle and anterior cerebral artery) and posterior circulation (posterior cerebral artery, brainstem, cerebellum) and subcortical involvement (Table 1). No patient in either group had multiple infarcts on CT scan or MRI imaging.

Neuroradiological investigation – angiography
Angiography was performed in only 10 of the HIV stroke group and 19 of the control patients. Catheter angiography was performed in one patient in the HIV stroke group for an intracranial arterial aneurysm and in three patients in the control group (Takayasu's arteritis in two and TB-related arteritis in one). Eight (80%) of 10 patients in the HIV group demonstrated large vessel occlusion as depicted on MR or catheter angiography involving the internal carotid (*n*=4), middle cerebral artery (*n*=3) and posterior cerebral artery (*n*=1). None of the angio-

Table 1 MRI brain parenchymal findings

	Brain parenchymal lesions						
	Anterior circulation			*Posterior circulation*			
	MCA	*ACA*	*Subcort*	*PCA*	*BS*	*Cerebell*	P-*value*
HIV group	11	2	5	1	3	0	
Control group	7	1	10	1	3	1	NS*

*, Fisher's exact test; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; subcort, subcortical infarction; BS, brainstem infarction; cerebell, cerebellar infarction.

grams in the HIV group was normal; five (24%) of 21 in the control group were normal. This difference did not achieve statistical significance (Fisher's Exact test P=0.14). There was, however, a statistically significant difference between the HIV and control group with respect to large vessel occlusions and other vasculopathic or normal findings (Table 2).

Sonography
Duplex Doppler studies of the cervicocephalic arteries and echocardiography were performed in all patients in the control group and HIV group except for one patient in the latter group who died during the first week of study due to presumed disseminated cryptococcosis. Duplex sonography of the carotid and vertebral arteries was normal in 16/21 (76%). The abnormalities included internal carotid artery occlusions in four patients and high resistance, low velocity signals in one patient. Echocardiography was abnormal in two patients, one with aortic valvular disease and another who had both mitral and aortic valve disease as a consequence of infective endocarditis.

Cerebrospinal fluid analysis
CSF was examined in 14/21 (67%) patients. Lumbar puncture was relatively contraindicated in seven patients due to the risk of brain herniation from a large hemispheric infarct (6) and or toxoplasma mass lesion (1). The patient with superior sagittal sinus thrombosis also did not have a CSF analysis. Significant CSF abnormalities were noted in only one patient (TG 22 BF) who had a positive cryptococcal antigen, CSF pleocytosis, elevated protein and low glucose.

Competing causes of a stroke and opportunistic infections
Causes of a stroke were unique to both groups. In the HIV group, three patients had recognized potential stroke etiologies. Two had high-risk cardiac causes of embolism (aortic valvular disease and aortic and mitral valvular disease complicating infective endocarditis). CNS cryptococcal infection with CSF cryptococcal antigen positivity was present in one patient. Opportunistic infections were present in four patients, but were not believed likely to be related to their cerebrovascular disease. These illnesses included CNS toxoplasmosis (1) diagnosed by the typical appearance of ring-enhancing parenchymal lesions on MRI responsive to sulfa and concomitant pulmonary tuberculosis without evidence of CNS infection (3). Two patients had a positive VDRL in the blood (dilutions 1 : 2), but had negative serum FTA-ABS and negative CSF VDRL. Of note, one HIV-seropositive, 32-year-old man had a low titer anticardiolipin antibody. In the control group, competing causes of stroke were noted in two patients with hypertension and small vessel disease infarction a possibility, and smoking and alcohol excess as a risk factor in another.

Conventional risk factors for a stroke in the HIV group, including hypertension, diabetes mellitus, hyperlipidemia, cardiac disease, smoking and alcohol excess, were infrequent. This was not surprising in light of the young mean age of the population. In addition to the two patients with the cardioembolic disease, there were six smokers, only two of them smoked more than 10 cigarettes per day and two whom admitted to occasional alcohol binges. In four patients, risk factor analysis was incomplete or unknown due to their presentation with dysphasia, coma or no family corroborative history.

Final diagnosis of a stroke
When grouped according to the TOAST classification, 20 of the 22 HIV group were categorised as a stroke of unknown cause (Table 3). In the remaining two patients cardioembolic causation was most likely. In the control group the distribution of stroke subtypes occurred mostly in the other (7/22), unknown (8/22) and cardioembolic groups (5/22) and one each in the small vessel disease and large vessel disease groups, a highly statistically significant result by Fisher's exact t-test ($P=<0.0001$).

Discussion

Our case-control study reveals that HIV seropositive patients with a stroke have a statistical likelihood of a large vessel occlusive disease without any other identifiable cause of a stroke despite a comprehensive and contemporary investigative protocol. The absence of drug abuse, paucity of opportunistic

Table 2 Angiographic findings – occulsion *vs* other vasculopathies

	Occlusion	*Other vasculopathies*				
	LVO	*LVS*	*Diss*	*Other*	*Normal*	P-*value*
HIV group (n=10)	8	0	0	2	0	
Control (n=21)	7	5	2	0	6	0.01*

*, Fisher's exact test; (1) LVO, large vessel occlusion of the middle, anterior, posterior cerebral, internal carotid, vertebral, basilar arteries; (2) LVS, stenosis or irregularity of the above vessels; (3) Diss, dissection of the above vessels; (4) Other, aneurysms, superior sagittal sinus thrombosis.

Table 3 Pathoetiological subtypes – TOAST classification. Comparison of the unknown subtypes *vs* the remaining subtypes of stroke categories

	Unknown	*Remaining categories*				
	Unknown	*Other*	*Card*	*SVD*	*LVD*	P-*value*
HIV group	20	0	2	0	0	
Control group	8	7	5	1	1	0.0001*

*, Fisher's exact test; Card, cardioembolic; SVD, small vessel disease; LVD, large vessel disease.

infection, and young age of the subjects underscores the likely causal relationship between HIV and strokes. The pathophysiologic mechanism appears to be thromboembolic with the possibility that this may be related to a hypercoagulable state. Our study was not able to address the issue of prothrombotic mechanisms, but several reports have already alluded to the frequency of anticardiolipin positivity and protein S deficiency in patients with a HIV-related stroke (Sorice *et al*, 1994; Stahl *et al*, 1993). In all the HIV-infected patients in this series, stroke heralded the diagnosis of infection. Only two patients had AIDS-defining illnesses at presentation; one had cerebral toxoplasmosis and another disseminated cryptococcosis. This database did not permit us to determine the frequency with which stroke was the heralding manifestation of AIDS. Anecdotally, stroke has been observed as the presenting manifestation of HIV infection (Gam *et al*, 1994; Palomeras and Roquer, 1996; Casada Naranjo *et al*, 1992). In the clinical series addressing the neurological complications of HIV, the stroke has been reported as the presenting manifestation of AIDS in 0.5–3.7% (Pinto, 1996; McArthur, 1987; Koppel *et al*, 1985; Snider *et al*, 1983). One HIV-infected patient had a stroke complicating protein S deficiency as their heralding event (Roquer *et al*, 1996). Many mechanisms for a stroke, both ischemic (more common) and hemorrhagic have been postulated (Table 4). Although vasculitis, whether due to secondary infection and meningitis or a primary HIV vasculitis is often mentioned (Pinto, 1996; Engstrom *et al*, 1989; Berger *et al*, 1990; Baily and Mandal, 1995; Price *et al*, 1992; McGuire and So, 1994; Levy *et al*, 1985), the clinical and autopsy support for this is surprisingly limited (Yankner *et al*, 1986; Scaravilli *et al*, 1989; Calabrese, 1991) and is often shown to be due to confounding causes, such as, opportunistic infection (Sarazin, 1995) or drugs (Gradon and Wityk, 1995). It does not appear to be the mechanism in the majority of cases reported thus far, although more recent transcranial Doppler studies imply a vasculopathy of some kind whether it be due to vasospasm, vasculitis, or another process (Brilla *et al*, 1999; Zunker *et al*, 1996). We found no evidence for a CNS vasculitis in our population. A hematological prothrombotic perturbation appears more likely. The reports of superior sagittal sinus thrombosis (Pedraza *et al*, 1997), including our own example, are further evidence for a prothrombotic abnormality.

Table 4 Potential mechanisms of stroke in HIV disease (adapted and expanded from Berger *et al*, 1990)

A. Ischemic
- (1) Prothrombotic
  - Anticardiolipin antigody, lupus anticoagulant
  - Hyperviscosity syndrome
  - Cerebrel venous thrombosis with dehydration and cachexia
- (2) Cardioembolic
  - Nonbacterial thrombotic endocarditis
  - Bacterial endocarditis
  - Paradoxical embolization through patent foramen ovale
- (3) Vasculitic
  - Primary vasculitis
  - Secondary to opportunistic infection (Herpes zoster, Treponema pallidum, M. Tuberculosis, fungal infection)
- (4) Vasospasm
- (5) Vasculopathy – aneurysm formation with distal embolization
- (6) Drug abuse

B. Intracerebral hemorrhage
- (1) Thrombocytopenia (autoimmune)
- (2) Primary CNS lymphoma
- (3) Metastatic Kaposi's sarcoma
- (4) Drug abuse
- (5) Hypertension
- (6) Cerebral toxoplasmosis
- (7) Cerebral tuberculoma
- (8) DIC
- (9) Vascular malformations
- (10) Mycotic aneurysms
- (11) CMV
- (12) Aspergillus

The relatively high rate of the presumed HIV-related stroke requires consideration. Autopsy reports cite the frequency of cerebral infarction in HIV seropositive patients between 8–34% (Mizusawa *et al*, 1988; Berger *et al*, 1990). The clinical frequency has been much lower, ranging between 0.5–7% (Engstrom *et al*, 1989; McArthur, 1987; Koppel *et al*, 1985; Snider *et al*, 1983; Levy *et al*, 1985). In the only prior case controlled study to date, however, the incidence of stroke was no different in patients dying from AIDS than among an age- and sex-matched control group (Berger *et al*, 1990). Ours is a different HIV seropositive-stroke patient population to the ones reported to date in that the incidence of drug abuse is negligible (apart

from marijuana none as per history) and HIV in black Africans is chiefly acquired by heterosexual activity (Swanvelder *et al*, 1998). Another important distinguishing feature from our population is that the majority of studies to date reported on the presence of cerebrovascular disease in persons with advanced immunosuppression.

The frequency of 15% (22/151) is remarkably similar to the 18% found in one retrospective study (Gillams *et al*, 1997). In most of our patients (20/22; 92%), there was no other explanation for their stroke. The mechanism of a HIV-related stroke may be complex and multifactorial. A variety of opportunistic infections may contribute to its causation. Both bland infarction and cerebral hemorrhage may be observed (Pinto, 1996; Roquer *et al*, 1998). We, as others (Gillams *et al*, 1997; Sarazin *et al*, 1995; Gradon and Wityk, 1995), have placed reliance on MR, rather than catheter angiography to detect vessel irregularity characteristic of vasculitis. While catheter angiography remains more sensitive for the vascular narrowing and beading that attend cerebral vasculitis, MR angiography has successfully demonstrated these abnormalities (Barboriak *et al*, 1998). The vast majority of abnormal MR angiograms in HIV seropositive patients merely revealed large vessel occlusions. These enigmatic large vessels occlusions mechanistically appear to be thrombotic or thromboembolic events. Pathologically this may represent tantalizing evidence of vascular bed specific hemostasis, the phenotypic expression of a systemic loss of anticoagulant function due to endothelial cell derived procoagulant and anticoagulant perturbations (Rosenberg and Aird, 1999).

Potential criticisms of our study include the retrospective nature of the series, bias from the fact that patients were hospital based and non population-based, and an only 45% angiography (10/22) rate in those with HIV seropositivity. However, the likelihood of other biases, such as, Berkson's admission rate bias seems unlikely, as all patients' primary presentation was a cerebrovascular condition.

In conclusion, based on our case control series in which HIV-seropositive patients were free of drug abuse, had few opportunistic infections, and were relatively free of other confounding stroke etiologies, an association between HIV and cryptogenic stroke was observed. The exact pathophysiological mechanisms await further elucidation, but the large vessel thrombosis observed may have been the consequence of a prothrombotic tendency.

Materials and methods

Data collection

The DSDB was established in July 1992 as a prospective, observational, hospital-based study with a collection of acute care and follow-up clinical and laboratory data on patients with a stroke. The study was designed to facilitate research on the characteristics, clinical course, and outcome of patients with an acute stroke. There was particular emphasis on the etiology of a stroke and cognitive impairment in the acute and subacute phase. The same neurologist (M Hoffmann) examined each patient at the time of an acute stroke. All patients underwent entry and subsequent computerized tomographic (CT) scanning of the brain, cranial magnetic resonance imaging (MRI) or both. Information was collected on each patient concerning the details of medical, neurological and social history, general and neurological examinations, cognitive examination, laboratory studies, final diagnosis or diagnoses, and complications.

Setting and patient selection

The population of KwaZulu Natal (KZN), the catchment area is approximately 8 million. The Department of Neurology of the University of Natal is the only academic neurology department in this region. Approximately 85% of young stroke patients (15–49 years) in this region are referred to the academic hospital based stroke clinic. These patients are largely indigent patients without medical insurance. Fifteen per cent of all stroke patients were seen in a private stroke unit. The stroke neurologist at the University of Natal (M Hoffmann) staffed both these stroke units. Although some patients may not have been referred to either center, the patient population seen is thought to be representative of the population at large. The time frame for recruitment was the 72-month period from July 1992 to July 1998. The DSDB represented a unique tool to establish the particular stroke mechanisms and etiological subtypes that may be prevalent in the KZN province of South Africa.

Stroke protocols

Since patients often have several risk factors and more than one possible cause of a stroke (e.g., atrial fibrillation and carotid artery stenosis), terminating the evaluation at the first positive test is not the optimal approach. A tailored protocol was devised and incorporated, the hierarchy outlined in Table 5. In tier one, all patients underwent a battery of standard investigations that included blood tests, neuroimaging, cardiac tests, and bedside testing of a higher cortical function. The second tier of studies was performed when considered appropriate. The third tier of studies was seldom performed.

The latter two tiers were used as appropriate–tailored to each individual patient's constellation of clinical features. Hence, a three tier investigative protocol was used, incorporating a basic minimum work-up (tier 1), tests often used (tier 2), and tests seldom used (tier 3). Because of the clinical presentations of strokes in the young with a high

Table 5 Investigations for stroke

(1) **Mandatory investigations in all patients**
Basic stroke relevant blood tests
Complete blood count
Platelets
Serum electrolytes
Urea
Creatinine
Lipid profile including lipoprotein (a)
Erythrocyte sedimentation rate (ESR)
Serum glucose
International Normalized Ratio (INR)
Partial thromboplastin time (PTT)
ELISA for HIV with confirmation by Western blot
Neuroimaging
Computerized tomography (CT) or
Magnetic resonance imaging (MRI) brain scan or
Single photon emission computed tomography (SPECT)
Cardiac testrs
Chest radiograph
Electrocardiogram (ECG)
Higher cortical function deficit (HCFD) bedside screening test

(2) **Additional work up when appropriate (the 2nd tier) included:**
Sonographic studies
Transcranial Doppler (TCD) of the intracranial large arteries
Duplex Doppler (DD) sonography of the cervicocephalic vessels (common, internal and external carotids, proximal vertebral (origin or V1) and extracranial (V2) vertebral arteries
Transcranial Doppler studies of the distal internal carotid arteries
Transcranial Doppler of the distal vertebral arteries (V3 and V4) intracranial segments
Transcranial Doppler with 10 ml aerated saline injection in antecubital vein for the detection of right to left shunt (patent foramen ovale, pulmonary shunts)
Angiography noninvasive and invasive
MR angiography
Spiral computerized tomography angiography
Catheter cerebral, extracranial and aortic arch angiography
Additional cardiac
Transthoracic (TTE) echocardiography
Transesophageal (TEE) echocardiography
Holter monitoring
Exercise stress testing
Prothrombotic tests
Antithrombin III
Protein C
Protein S
Anticardiolipin antibodies
Plasmin system defects
Autoimmune tests
Antinuclear factor
Rheumatoid factor
Formal neuropsychological testing
Cerebrospinal fluid analysis (CSF)

(3) **A category of seldom required tests (the third tier) for the following:**
Fasting plasma homocysteine levels for homocystinurina (heterozygotes)
Coagulation defects – factor VIII, IX, V, afibrinogenaemia
Hemaglobinopathies (Sickle Cell disease, hemoglobin SC)
Lactate levels – mitochrondrial cytopathies (MELAS)
Brain biopsy

endemicity of an infectious disease, all patients and controls in this study had the following tier 2 tests:

(i) serological assays: HIV testing by enzyme linked immunosorbent assay (ELISA) confirmed by Western blot analysis; Venereal Disease Research Laboratory; antinuclear antibody; cysticercosis ELISA, cryptococcal antigen; toxoplasma antibody assays; Bilharzial complement fixation test; Mantoux test.
(ii) hematological studies: protein S, protein C, antithrombin III, anticardiolipin antibody
(iii) sonographic studies: duplex Doppler of the cervical carotid vertebral arteries
(iv) cardiac studies: echocardiography (transthoracic and when appropriate, transesophageal)
(v) cerebrospinal fluid analysis: in all patients, unless contraindicated by mass lesions, large strokes or intracranial shift

Diagnostic classification
The databank was designed according to the four levels of illness in the World Health Organization model of impairment, disability and handicap (WHO ICIDH). Several scales were employed in this registry to accommodate these measurements in an objective and quantifiable manner. In addition, it facilitated accurate comparison within the registry and with other data banks and stroke trials. These included four classification systems each measuring different but important aspects of disease:

(1) A neurological deficit scale: Canadian Neurological Scale, (CNS) (Cote *et al*, 1989)
(2) A clinical stroke scale: Oxfordshire Community Stroke Project Scale, (OCSP) (Bamford *et al*, 1991)
(3) A handicap scale: Rankin, (R) (Rankin, 1957)
(4) An etiopathogenetic scale: Trial of Org 10172 in acute stroke (TOAST) (Adams *et al*, 1993)

Cognitive testing
A higher cortical function deficit (HCFD) screening examination was applied to all alert patients in the DSDB in the first 2 weeks of presentation, usually within the first 24 h. This consisted of a semiquantitative bedside cognitive function tests that evaluated a higher cortical function according to nine different neurological behavioral syndromes and their subtypes (40 and 17 miscellaneous) described in detail elsewhere (Hoffmann, 1998a,b). In brief these included, with subtypes in brackets: aphasias (8), apraxias (7), amnesias (4), agnosias (4), neglect syndromes (4), alexias (3), frontal lobe syndromes (3), visuospatial dysfunction (1) and anosognosia (1). Because of the range of cognitive syndromes addressed, relatively precise delineation of an entity such as HIV dementia was possible. In those with subclinical or mild cognitive dis-

turbance, neuropsychological testing with standardized batteries and normative data was applied.

The indications for neuropsychological testing included subtle deficits, stroke on brain imaging with normal bedside cognitive testing, and instances in which screening examination suggested but did not decisively delineate a recognized neurobehavioral syndrome. The sensitivity (80.2%; CI: 72–88%) and specificity (100%) of the HCFD screening tests were evaluated against formal neuropsychological testing and reported elsewhere (Hoffmann, 1998b). Neuropsychological testing was regarded as an elaboration of the bedside cognitive assessment in this study.

Final diagnosis
A final diagnosis for an ischemic stroke (excluding transient ischemic attacks) was made with the benefit of all available clinical and investigative data by the same cerebrovascular neurologist. For a diagnosis to be made within the framework of the extended TOAST classification, the diagnosis needed to be one of exclusion in which all clinically indicated tests according to the hierarchical protocol were negative save for the factor in question. Comorbidity was also documented. It is acknowledged that some would be definite diagnoses, some probable, and some possible by this method.

Data analysis considerations
The HIV stroke group was compared to a historical control group matched for race, gender and age that were seronegative for HIV. The data were analyzed using Chi-square analysis for contingency tables. Fisher's Exact Test was used as an alternative to Chi-square for situations in which the expected cell count in at least one cell was below 5. The *t*-test was used to compare means for interval or ratio data such as the comparison of age between the groups was accomplished using a two-sample *t*-test.

Abbreviations

R, right; L, left, N, normal; BF, black female; BM, black male; R/L HP, right and left hemiparesis; OCSP, Oxfordshire Community Stroke Project Scale; TAC, total anterior circulation; PAC, partial anterior circulation; LAC, lacunar; POC, posterior circulation; R/L MCA, right or left middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; ICA, internal carotid artery; CCA, common carotid artery; Vert, vertebral artery; MRV, magnetic resonance angiogram; SSS, superior saggital sinus; TTE/TEE, transthoracic and transesophageal echocardiogram; DD, duplex Doppler; Occl, occluded; Thromb, thrombus; Crypto, cryptococcal; Ag, antigen; MMVD, mixed mitral valve disease; MAVD, mixed aortic valve disease; AVM, arteriovenous malformation

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