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Journal of the Neurological Sciences 457 (2024) 122880

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Clinical short communication

Stroke, HIV and the Immune Reconstitution Inflammatory Syndrome in the absence of opportunistic infections

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ARTICLE INFO

Keywords:
Stroke
HIV
Antiretroviral therapy
Immune reconstitution inflammatory syndrome
IRIS
South Africa

ABSTRACT

Introduction: Stroke in people living with HIV (PLWH) has been described to occur soon after the initiation of antiretroviral therapy (ART) possibly related to the Immune Reconstitution Inflammatory Syndrome (IRIS). We sought to investigate whether there was a temporal association between stroke and recent ART initiation in the absence of opportunistic infections (OIs), and to identify risk factors for this.

Methods: This cross-sectional study recruited PLWH with new-onset stroke at a hospital in Johannesburg, South Africa, from 2014 to 2017, excluding all patients with OIs. Patients were assessed for ART duration, CD4 count, HIV viral load, inflammatory markers and cardiovascular risk factors.

Results: 77 PLWH were recruited, of which 35 were on ART at the time of stroke. Of the patients with confirmed ART duration ($n = 28$), 9 (32.1%) had a stroke within the first 6 months of starting ART (crude incidence rate of 0.73 cases per patient year). In the period beyond 6 months, 19 strokes occurred (crude incidence rate of 0.21 cases per patient year), translating to a 3.5 times greater risk in the first 6 months ($p = 0.0002$). There were no clearly identified risk factors when comparing those who had strokes in the first 6 months to those after 6 months and ART-naïve patients.

Conclusion: Almost a third of strokes in PLWH may be related to IRIS, with a crude incidence rate 3.5 times higher in the first 6 months following ART-initiation compared to beyond 6 months. This appears to be independent of OIs. Risk factors are unclear.

1. Introduction

The rollout of antiretroviral therapy (ART) has been key in reducing HIV-associated mortality, morbidity and opportunistic infections (OIs). However, many people living with HIV (PLWH) in South Africa and other resource-limited settings still initiate ART at late stages with established advanced immunodeficiency. (1) Approximately 10–20% of PLWH, particularly those with low baseline CD4 counts and/or high HIV viral loads, may experience an immune reconstitution inflammatory syndrome (IRIS) following ART initiation. (2) This is a dysregulated, hyper-inflammatory response that is usually directed at opportunistic infections, almost always occurs within 6 months of ART initiation, and may cause considerable morbidity and mortality. (2)

Neurological complications of immune reconstitution represent the most debilitating form of IRIS, conferring a high mortality and significant morbidity in the form of permanent neurological deficit in up to 50% of cases. (3) *Mycobacterium tuberculosis*, cryptococcus neoformans and JC virus account for the majority of cases of central nervous system (CNS)-IRIS. (3)

It has been suggested that CNS-IRIS may occur in the absence of OIs. Proposed mechanisms for this relatively novel concept include a dysregulated and destructive excessive immune response to occult OIs or HIV-associated proteins. Residual virus in the CNS and persistent release

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https://doi.org/10.1016/j.jns.2024.122880
Received 30 November 2023; Received in revised form 5 January 2024; Accepted 6 January 2024
Available online 8 January 2024
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Non-standard Abbreviations and Acronyms

ART	Antiretroviral therapy
cIMT	Carotid intima-media thickness
IRIS	Immune reconstitution inflammatory syndrome
NIHSS	National Institute of Health Stroke Scale
OI	Opportunistic infection
PLWH	People living with HIV
PWV	Pulse wave velocity
TRF	Traditional cardiovascular risk factor

of HIV-associated proteins from infected cells may occur even in the face of viral suppression. (3) The possibility of an autoimmune aggression towards self-antigens has also been proposed, but lacks sufficient evidence. (4)

HIV has been shown to be a significant and independent risk factor for stroke. (5,6) Over 50% of previously described PLWH with stroke in SSA are ART-naïve. (5) In Sub-Saharan Africa (SSA), infection is implicated in 23–55% of stroke in PLWH. (5) There have been case reports describing stroke as an IRIS phenomenon, all of which were associated with an OI; namely cryptococcal meningitis, (7) varicella zoster (8) and cytomegalovirus. (9) All of these pathogens are known to cause strokes, and thus the reports of them causing stroke in the setting of an IRIS are not surprising. Recently a group from Malawi described 64 PLWH with stroke, of whom 25% had their event within 6 months of initiating ART. Most of these patients had no evidence of OIs. (10) Subsequent cohorts have produced conflicting results, casting some doubt over whether stroke can be a manifestation of IRIS in the absence of specific opportunistic infections. (11–13)

Atherosclerosis in PLWH may be partially related to HIV-related inflammation and endothelial dysfunction. It is possible that this process may be acutely accelerated in the presence of an aberrant immune response, as is seen in IRIS. Whether or not this translates to an increased stroke risk is unknown. The utility of surrogate markers of subclinical atherosclerosis, including carotid intima-media thickness (cIMT) and aortic pulse wave velocity (PWV) have never been tested in this setting.

We sought to investigate whether there was a temporal association between stroke and recent ART initiation among PLWH in the absence of OIs, and whether risk factors for stroke and markers of atherosclerosis differed between those with “early” stroke (within 6 months of ART initiation) compared to “late” stroke and those PLWH who were not on ART.

2. Methods

This cross-sectional study took place at the Charlotte Maxeke Johannesburg Academic Hospital, a 1000-bed quaternary-level hospital in Johannesburg, South Africa, from August 2014 to November 2017.

We recruited consecutive patients aged 18 years and older who presented within 48 h of a new onset stroke. Stroke was defined as per the World Health Organization case definition. Exclusion criteria were the presence of OIs, including on cerebrospinal fluid (CSF) examination (elevated protein, a low serum:CSF glucose ratio, pleocytosis or positive viral PCR), the presence of intracranial mass lesions on radiographic imaging, or other stroke mimics. Full informed consent was obtained as per the Declaration of Helsinki. Ethics approval was granted by the University of the Witwatersrand Human Research Ethics Committee (Certificate number M140429, renewed as M190688).

All patients were assessed and examined by the same specialist neurologist (ES). Traditional cardiovascular risk factors (TRFs) were defined as described in Appendix A (Supplementary material). Stroke aetiology was assigned following the interpretation of the following investigations by ES and the treating physicians: electrocardiogram, transthoracic echocardiography, carotid artery doppler studies, CT brain and CT angiography of the brain, neck and aortic arch, as well as the laboratory investigations detailed in Appendix B (Supplementary material). Vasculopathy was diagnosed in patients with intra- or extracranial angiographic abnormalities with no alternate explanation. The type of vasculopathy was labelled as atherosclerotic vasculopathy (AV) in the presence of large vessel occlusion with the additional ultrasound visualisation of atherosclerotic plaque causing a $>$ 50% occlusion of the internal or common carotid artery ipsilateral to the stroke. In the absence of this plaque, non-atherosclerotic vasculopathy (NAV) was diagnosed. HIV-associated vasculitis was diagnosed in the setting of the classic angiographic features of vasculitis without an identified causative opportunistic infection, while small vessel disease (SVD) was defined as the presence of a traditional clinical lacunar syndrome with an infarct $<$20 mm in size. (14)

HIV testing (ELISA) was performed in all consenting patients. A suppressed VL was defined as a VL of $<$50 copies/ml. A lumbar puncture was performed in all PLWH provided no contra-indication was present. Cerebrospinal fluid (CSF) was examined as per the protocol in Appendix B (Supplementary material). Stroke severity was graded according to the National Institutes of Health Stroke Scale (NIHSS). (15) The patient's duration of ART was recorded as “Unconfirmed” if there was no available written or electronic proof of the initiation date from a healthcare provider. Carotid intima-media thickness (cIMT) and aortic pulse wave velocity (PWV) were measured as markers of subclinical atherosclerosis. The methods are detailed in Appendix B (Supplementary material).

2.1. Statistical methods

Data was analysed using Statistica Ver 14.0.0.15, TIBCO Software Inc. Continuous variables were evaluated for normality using Shapiro-Wilk and Kolmogorov-Smirnov tests. Chi square, ANOVA and Kruskal-Wallis statistical tests were then performed for parametric and non-parametric variables where appropriate. Continuous data were reported as mean $\pm$ SD for parametric, or median and interquartile range for non-parametric data. Proportions were compared using the z-test. P values $<$0.05 were considered significant.

3. Results

107 PLWH were screened for participation in the study, of which 30 were excluded as illustrated in Fig. 1. The mean age of the 77 included participants was 44.9 $\pm$ 12.0 years, and 50.7% were male.

35/77 (45.4%) of the PLWH were on ART at the time of their stroke. 32 of these were on a fixed dose combination comprising emtricitabine, tenofovir and efavirenz, while 3 patients were on a protease-inhibitor containing regimen. The median duration of ART was 36 months (IQR 5.5–66 months). The 42 ART-naïve patients were either newly diagnosed with HIV on this presentation ($n = 30$), were in the process of ART initiation ($n = 4$), or had previously refused ART ($n = 8$).

When compared to ART-naïve patients, there was no increased prevalence of TRFs in the ART-exposed group (Table S1 – Appendix C Supplementary material). Hypertension was actually more prevalent in the ART-naïve group (59.5% vs 34.3%, $p = 0.03$, Table S1). There was no difference in mean CD4, stroke severity or markers of subclinical atherosclerosis (cIMT and PWV) between the 2 groups (Table S1 – Appendix C Supplementary material).

The duration of ART was known and verified in 28 of the patients on ART, of which 9 (32.1%) had been on ART for $\leq$6 months at the time of their stroke. (Fig. 1, Fig. 2 and Fig. S1 – Appendix C supplementary material).

The crude incidence rate for the first 6 months post-ART initiation was 0.73 strokes per one person year (Table 1), compared to 0.21 per one person year for the period beyond 6 months post-ART initiation (Table 1). This difference was statistically significant (z-test, $p <$ 0.0005), (Appendix D - Supplementary material) and translated to a 3.5

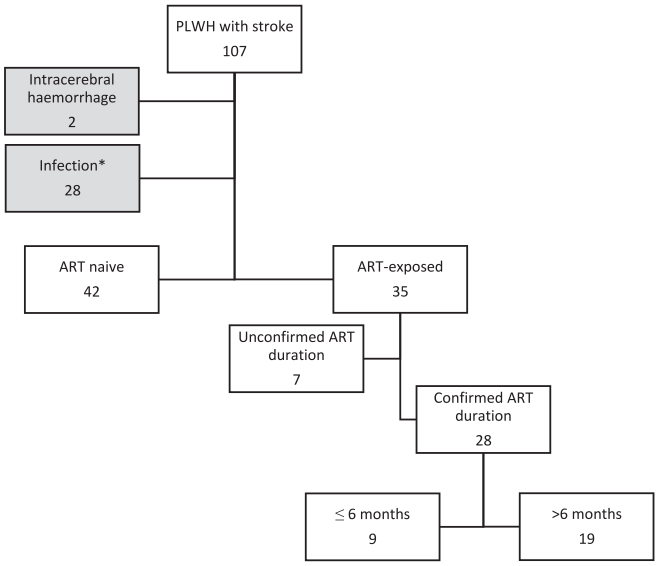

Fig. 1. Flowchart of PLWH presenting with acute stroke.
*Including meningitis ($n = 20$) and varicella zoster virus vasculopathy ($n = 8$).
Groups excluded from the study are shaded in grey.
ART, antiretroviral therapy; PLWH, people living with HIV. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

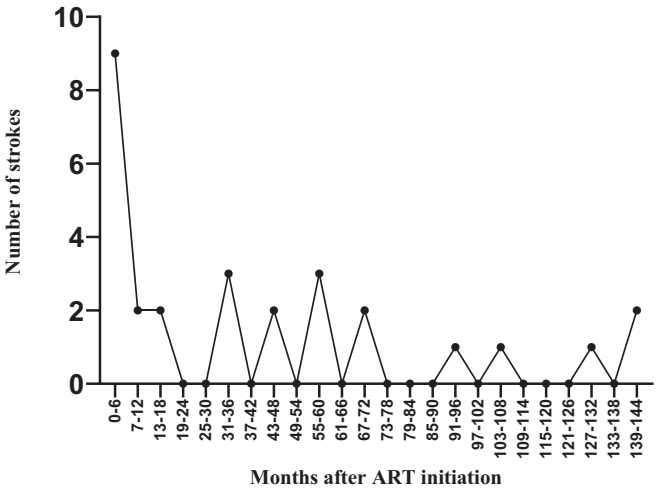

Fig. 2. Number of strokes according to duration of ART.

times greater crude incidence rate for ART duration ≤6 months when compared to ART duration >6 months (Table 1).

The group of patients with a stroke while on ART for ≤6 months (the "early" group) was compared to those on ART for >6 months (the "late" group), and showed no difference in demographics, TRFs, CD4, VL, stroke severity or markers of subclinical atherosclerosis. (Table 2). The blood markers detailed in Table S2 (Appendix C Supplementary material) also showed no significant difference between the two groups. These included white cell count, haemoglobin, creatinine, CRP, ESR, angiotensin-converting enzyme and uric acid. (Table S2).

Comparison of the early group to the ART-naïve revealed a lower prevalence of hypertension in the early group, with no other significant differences in the other variables in Table 1, nor in blood markers (Table S2) We did not however have data on nadir CD4 counts.

Stroke aetiology was similar across the groups. (Table 2). 2 out of the 9 patients (22.2%) in the early group were diagnosed with non-atherosclerotic vasculopathy. One of these was intracranial (middle cerebral artery, with CD4 354 cells/uL, VL 452 copies/ml), and the other extracranial (internal carotid artery, with CD4 1168 cells/uL, VL suppressed). Both patients with cardioembolic stroke in the early group had dilated cardiomyopathy secondary to HIV. 1 patient had small vessel disease secondary to chronic uncontrolled hypertension and 1 had a stroke secondary to recreational drug usage (listed as "Other" in Table 2). Of those with atherosclerotic vasculopathy ($n = 4$), 2 were on ART >6 months, and 2 were ART-naïve. None of these patients were exposed to protease inhibitors. Small sample sizes in the ART groups precluded further meaningful analyses comparing stroke aetiologies across the groups.

4. Discussion

We demonstrated that almost one-third of strokes in PLWH on ART in our cohort occurred in the first 6 months of initiating ART. The crude incidence rate for stroke in this period was 3.5 times higher when compared to the period >6 months after ART initiation. This was despite the exclusion of all overt infections. We found no clear difference in demographics, TRFs, HIV-related factors, blood markers or surrogate markers of atherosclerosis between those who had a stroke within 6 months after starting ART and those whose strokes occurred later, outside the possible window for an IRIS reaction.

It is postulated that IRIS may result in stroke by either unmasking a latent infection, or possibly due to an immune response to HIV particles or even self-antigens. (3) A landmark case-control study from Malawi reported that the highest risk of stroke in PLWH was within 6 months of ART initiation (adjusted OR 15.6, 95% CI 4.21–46.6, $p < 0.001$). (6) Out of 64 PLWH with stroke, 16 (25%) fell into this category. These patients had a median CD4 of 92 cells/mm^3, with lower VLs than other categories. Nadir CD4 counts were not reported. In contrast, we did not detect any difference in CD4 counts between those in the early group and the late group or ART-naïve patients. This may be due to our exclusion of infections, which generally occur at lower CD4 counts. Our high prevalence of possible IRIS-related stroke despite the exclusion of infection supports a role for a non-infectious inflammatory mechanism. This corroborates with the Malawian findings of HIV-associated vasculopathy being the commonest aetiology of stroke in the IRIS group (9 of 16), with only 3 of the patients' aetiology being attributed to opportunistic infections. (10) We did not detect a higher prevalence of vasculopathy (or any other specific aetiology) in our early group, although our small sample size limited comparisons.

Other small HIV stroke studies in SSA have reported promising yet varying results on the role of IRIS, none of which specifically excluded OIs. A Zambian study reported almost a third of strokes in PLWH (17/48, 29%) occurred soon after ART initiation, however they incorporated a longer time frame (1 year post ART initiation) and had large amounts of missing data on immunological and virological parameters. (13). A study from Cape Town, South Africa reported that 39.3% (22/56) of ART-exposed PLWH with stroke may be related to IRIS, most of which

Table 1
Comparing crude incidence rates for stroke in the periods ≤6 months and > 6 months post ART-initiation.

Time period	Stroke cases	Total person-time at risk (months)*	Cases per patient year (Crude incidence rate)	Risk ratio
≤ 6 months	9	147.25	0.73	**3.5**
> 6 months	19	1090	0.21	

* Sum of the total number of months from ART initiation to stroke (see Appendix D - Supplementary methods for details).

Table 2
Comparing traditional cardiovascular risk factors, HIV-related factors and stroke aetiology of those on ART for ≤6 months ("Early" group) to those on ART for >6 months ("Late" group), and to the ART-naïve PLWH.

	ART-naïve ($n = 42$)	≤6 months ART ("Early") ($n = 9$)	>6 months ART ("Late") ($n = 19$)	*p*-value
Age (years)	45.2 ± 12.5	45.7 ± 11.3	48.5 ± 10.5	0.60
Male (%)	52.4	77.8	47.4	0.30
Hypertension (%)	59.5*	11.1*	47.4	0.03*
Diabetes mellitus (%)	9.5	0.0	5.3	0.56
Dyslipidaemia (%)	23.8	36.8	22.2	0.54
Smoking (%)	31.0	22.2	26.3	0.84
Obesity (%)	23.1 ($n = 26$)†	25.0 (n = 8)†	40.0 ($n = 15$)†	0.50
Median number of TRFs (IQR)	1 (1–2)	0 (0–1)	2 (1–2)	0.16
Median ART duration (months) (IQR)	–	4 (2–5)	60 (36–96)	0.0004
CD4 (cells/uL)	323 ± 164 ($n = 38$)†	394 ± 325	424 ± 198	0.16
Median VL (copies/ml) (IQR)	45,015 (19200–192,800) ($n = 30$)†	0 (0–49)	0 (0–0)	<0.0001
% with VL suppression	–	77.8	84.2	0.68
NIHSS	12.3 ± 5.9	11.2 ± 4.3	12.9 ± 5.6	0.77
cIMT (mm)	0.71 ± 0.14 ($n = 31$)†	0.72 ± 0.23 (n = 8)†	0.72 ± 0.20 ($n = 14$)†	0.99
PWV (m/s)	8.26 ± 2.61 ($n = 22$)†	7.76 ± 2.69 ($n = 7$)†	8.35 ± 3.05 ($n = 13$)†	0.89
Stroke Aetiology				
Cardioembolic	9 (21.4%)	2 (22.2%)	4 (21.1%)	
Atherosclerotic Vasculopathy	2 (4.8%)	0 (0.0%)	2 (10.5%)	
Non-atherosclerotic vasculopathy	6 (14.3%)	2 (22.2%)	2 (10.5%)	
HIV-associated vasculitis	3 (7.1%)	0 (0.0%)	2 (10.5%)	0.75
Small vessel disease	8 (19.0%)	1 (11.1%)	5 (26.3%)	
Undetermined	13 (31.0%)	3 (33.3%)	4 (21.1%)	
Miscellaneous	1 (2.4%)	1 (11.1%)	0 (0.0%)	

ART, antiretroviral therapy; cIMT, carotid intima media thickness; IRIS, Immune Reconstitution Inflammatory Syndrome; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; PWV, pulse wave velocity; TRFs, traditional risk factors; VL, viral load.
* p-value = 0.01 "Early" group vs ART-naïve.
† Indicates the number of patients for whom data was available (in the event of missing data).

occurred within 6 months of restarting ART after an unspecified period of defaulting treatment (11). The stroke aetiologies and presence of OI's were not reported in relation to IRIS. It should also be noted that not all recent SSA stroke studies have detected any role for IRIS, including one from Pretoria, South Africa, which reported that none of their 32 PLWH with stroke fulfilled the criteria for IRIS. (12) The fact that the findings on this potentially preventable phenomenon have not been consistently observed emphasises its complexity and has opened a space that certainly merits further investigation.

Ours is the first study to describe a high prevalence of possible IRIS-related strokes having reasonably excluded infections, and the first to explore the role of atherosclerosis in this setting. We hypothesized that atherosclerosis, as an inflammation-mediated pathology, may be accelerated in patients with an aberrant immune response as is seen in IRIS. However we found no evidence of this, with no increased prevalence of atherosclerotic vasculopathy, nor any difference in markers of subclinical atherosclerosis (cIMT and PWV) in our early group when compared to both the late group and ART-naïve patients. This points towards IRIS-induced accelerated atherosclerosis being an unlikely stroke mechanism in these patients, though our study was not adequately powered to provide a definitive conclusion.

Other possibilities to explain an association between ART initiation and early stroke may include the effects of occult OIs which may have remained undetected despite our stringent efforts to exclude them. We noticed this with varicella zoster virus (VZV), which was implicated in causing stroke in the absence of any cerebrospinal fluid pleocytosis or biochemical abnormality except a positive CSF VZV PCR in 8 of the 28 patients that were excluded from this cohort. It is possible that other infections went undetected despite our efforts. The direct metabolic side effects of ART itself are unlikely to be contributing to stroke risk in our cohort as very few patients were on protease inhibitors (which are most commonly implicated). Furthermore, one would expect the risk of this to continue with time, and not be concentrated in the first few months after ART initiation, as was demonstrated here.

4.1. Limitations

We were unable to identify any risk predictors for early stroke following ART initiation. Our non-availability of data on nadir CD4 counts was a missed opportunity to identify if those with more profound pre-ART immunosuppression were most at risk. Our small sample size (compounded by information bias due to missing data on exact ART duration) limited the power of many comparisons, including our inability to adjust the reported crude incidence rates for potential confounders. Selection bias may also have played a role as patients were recruited from a quaternary-level hospital, where more atypical stroke patients are more likely to be referred.

5. Conclusion

Almost a third of strokes in PLWH may potentially be related to IRIS, with a crude incidence rate 3.5 times higher in the first 6 months following ART-initiation compared to beyond 6 months. This appears to be independent of OIs, nor with any evidence of atherosclerosis. The risk factors and underlying mechanisms are unclear and warrant further investigation in order to identify which patients are at greatest risk for this catastrophic outcome following ART initiation.

Grant support

ES was supported by the Discovery Foundation Academic Fellowship Award. The funder played no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

CRediT authorship contribution statement

Eitzaz Sadiq: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. **Sarah Katzew:** Writing – original draft, Writing – review & editing. **Jeremy Nel:** Formal analysis, Validation, Visualization, Writing – original draft,

Writing – review & editing. **Grace Tade:** Data curation, Investigation, Methodology, Project administration, Writing – review & editing. **Angela Woodiwiss:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Writing – review & editing. **Gavin Norton:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Girish Modi:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

None

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2024.122880.

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