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Differences in Predictors for Ischaemic and Haemorrhagic Strokes in HIV+ Individuals

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for the D:A:D Study group

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BACKGROUND

- HIV+ individuals are known to have a higher risk of stroke compared to HIV- individuals[1,2]. They also have a higher burden of traditional cardiovascular disease (CVD) risk factors and exposure to antiretroviral therapy (ART) may pose additional risk[3,4,5,6].
- In the general population, several shared risk factors for ischaemic and haemorrhagic strokes have been identified (hypertension, renal impairment, age, diabetes, prior stroke[7]), and hypertension and low estimated glomerular rate (eGFR) may be more strongly linked to haemorrhagic strokes than ischaemic strokes[8,9].
- As it is unknown whether there are differences in risk factors for ischaemic and haemorrhagic strokes in HIV+ individuals, the aim of our study was to investigate this in the large, heterogeneous D:A:D cohort.

METHODS

- D:A:D Study participants were followed from the time of the first blood pressure (BP) measurement at/after 1/1/1999 or individual study entry and until the first of a validated stroke, 6 months after last follow up or 1/2/2014.
- Elevated BP during follow-up was defined as one time-updated measurement of systolic BP ≥140 mm Hg and/or diastolic BP≥90 mm Hg, and incidence rates (IRs) for strokes were calculated for both stroke subtypes and stratified by presence/absence of elevated BP.
- Separate uni- and multivariable Poisson regression models were used to identify associations between possible risk factors and each subtype of stroke. Risk factors considered were:
  - ***Demographic/CVD-related:*** *Gender, ethnicity (time-fixed), age (/5 years older), calendar year, dyslipidemia (total cholesterol>6.2, HDL<0.9, TC:HDL ratio>6.5), previous CVD event (myocardial infarction/stroke), family history of CVD, body mass index (BMI), diabetes, smoking status (all time-updated)*
  - ***HIV-related:*** *Mode of HIV-acquisition (time-fixed), previous AIDS diagnosis, HIV-RNA viral load, CD4 count, cumulative exposure (/5 years) to ART (protease inhibitors (PIs), non nucleoside transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs)), HBV and HCV -infection (all time-updated)*
- In sensitivity analyses, we additionally included Cockcroft Gault estimated eGFR as one time-updated covariate after restricting follow-up to the start of systematic collection of eGFR on 1/2/2004.
- Risk factors differing in multivariable Poisson models were selected and formally tested for whether their predictive ability differed on each stroke subtype, using the method described by Wei et al.[10]; these analyses used Cox proportional hazards models, restricted to fixed baseline covariates only.

RESULTS

- General characteristics of study participants at time of inclusion (baseline) and at time of stroke are displayed in **Table 1.**

Table 1 — General characteristics of 43,564 persons included

Demographic/CVD-related		At D:A:D Study entry N	At D:A:D Study entry %	At stroke event N	At stroke event %
Gender	Male	32,064	73.6	481	81.5
Age (years)	Median (IQR)	39 (33-46)		55 (46-64)	
Ethnicity	White	22,418	51.5	310	52.5
Smoking status	Current smoker	18,250	41.9	262	44.4
	Ex-smoker	7,648	17.6	140	23.7
	Never/Unknown	176,66	40.5	188	31.9
Previous CVD	Yes	662	1.5	108	18.3
Family history of CVD	Yes	3,100	7.1	67	11.4
Elevated BP	Yes	10,281	23.6	293	49.7
Diabetes	Yes	1,340	3.1	95	16.1
Dyslipidemia	Yes	17,378	39.9	347	59.5
BMI (kg/m²)	Median (IQR)	23 (21-25)		23 (21-26)	
eGFR (ml/min/1.72m²)	Median (IQR)	104 (89-121)		84 (67-99)	
HIV-related					
Previous AIDS	Yes	10,019	23.0	237	40.2
Ever received ART	Yes	27,582	63.3	565	95.8
Mode of HIV-acquisition	MSM*	19,183	44.0	266	45.1
	IDU	6,580	15.1	82	13.9
	Heterosexual	15,126	34.7	192	32.5
	Other/Unknown	2,675	6.1	50	80.5
CD4 (cells/mm³)	Median (IQR)	423 (270-610)		446 (250-650)	
HIV RNA (log_{10} copies/ml)	Median (IQR)	2.5 (1.7-4.2)		1.7 (1.7-2.5)	
HCV+¹	Positive	7,886	17.6	113	19.2
HBV+²	Positive-active	1,962	4.5	15	2.5

*MSM: Men who have sex with men. 1.Seropositive/HCV-RNA pos. 2. HB surface antigen, HBe antigen or HBV DNA+ pos.

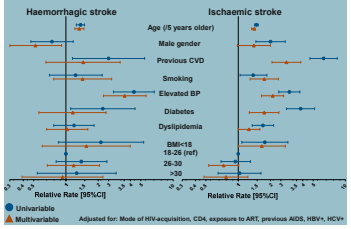
Table 2 — Crude incidence rates of stroke, stratified by a) Type of stroke b) Elevated blood pressure (BP)

a) Type of stroke*	N stroke events	PYRS	Rate /1,000 PYRS	95% CI
All	590	339,979	**1.74**	1.60, 1.88
Haemorrhagic stroke	83	341,962	**0.24**	0.19, 0.30
Ischaemic stroke	296	340,995	**0.87**	0.77, 0.97
Unknown	211	341,357	**0.62**	0.54, 0.70

Type of stroke*	b) Without elevated BP N Event	N PYRS	Rate/1,000 PYRS	95% CI	With elevated BP N Event	N PYRS	Rate/1,000 PYRS	95% CI
All stroke	297	255,133	**1.16**	1.03, 1.30	293	84,850	**3.45**	3.06, 3.85
Haemorrhagic stroke	34	256,307	**0.13**	0.09, 0.18	49	85,660	**0.57**	0.41, 0.73
Ischaemic stroke	148	255,698	**0.58**	0.49, 0.67	148	85,297	**1.74**	1.46, 2.02
Unknown	115	255,939	**0.45**	0.37, 0.53	96	85,424	**1.12**	0.90, 1.35

*Stroke event censored after first haemorrhagic/ischaemic stroke event

Figure 1 — Association between demographic/CVD-related factors and stroke



- Of the 43,564 included persons, there were 590 strokes over 339,979 person years (PYRS) (IR of 1.74 (95%CI [1.60, 1.88]); 83 (14%) were haemorrhagic, 296 (50%) were ischaemic and the remaining 211 (35.8%) strokes were of unknown etiology. Crude IRs for stroke were higher in those with elevated BP than in those without (**Table 2**).
- In separate univariable models, factors most strongly associated with increased risk for both stroke subtypes were age (/5 years older), elevated BP, a low CD4 count (< 200 cells/mm^3) and previous CVD (**Figure 1, 2**).
- The risk factor profile for the two stroke subtypes appeared to differ in separate multivariable models; ischaemic strokes appeared to be more strongly associated with traditional CVD risk factors (male gender, dyslipidemia, previous CVD, diabetes, smoking) than were haemorrhagic strokes. Conversely, elevated BP were associated with both stroke subtypes, but the association appeared to be stronger for haemorrhagic strokes (**Figure 1**).
- Of the HIV-related variables, only low CD4 count was associated with the risk of both stroke subtypes; previous AIDS and HIV acquisition via injection drug use (IDU) appeared to be more strongly associated with ischaemic strokes than were haemorrhagic strokes (**Figure 2**).
- In sensitivity analyses, eGFR <60 ml/min appeared to show a stronger association with the risk of haemorrhagic than ischaemic strokes (adjusted relative rate 3.01 [1.28, 7.04] vs. 1.08 [0.68, 1.72]).
- In the formal comparative analysis, the direction of effects for selected risk factors were mostly similar to findings from separate Poisson models. None of the factors differed significantly in their predictive ability for either stroke subtype, except for male gender; stronger predictive ability for ischaemic stroke (p<0.001)), and IDU; stronger predictive ability for haemorrhagic stroke (p=0.04) (**Figure 3**).

CONCLUSIONS

- Age, elevated BP and low CD4 count were the strongest predictors for both stroke subtypes.
- As has been reported in the general population, haemorrhagic strokes seemed to be more strongly associated with elevated BP than ischaemic strokes, and with low eGFR in sensitivity analyses. Conversely, ischaemic strokes appeared to be more strongly associated with traditional CVD risk factors.
- Only male gender and IDU were found to have statistically significant predictive abilities for ischaemic and haemorrhagic strokes, respectively.
- Even if other risk factors also appeared to differ, we were unable to demonstrate any statistical difference in predictive ability for these risk factors, although this may be due to a limited number of haemorrhagic strokes. Other limitations include lack of systematic collection of data on atrial fibrillation and alcohol use.
- Our findings are similar to those reported in the general population and emphasize the importance of preventive measures and screening, using stratified predictors to provide more precise risk estimation for the different stroke subtypes in HIV+ individuals.

Figure 2 — Association between HIV-related factors and stroke

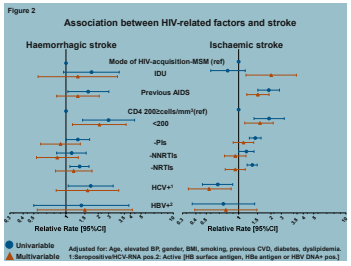
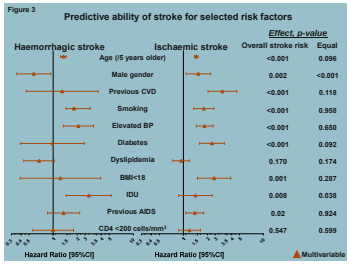


Figure 3 — Predictive ability of stroke for selected risk factors



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