HIV Infection and Immunodeficiency as Risk Factors for Ischemic Stroke

Julia L. Marcus[1], Wendy A. Leyden[1], Chun R. Chao[2], Felicia C. Chow[3], Michael A. Horberg[4], Leo B. Hurley[1], Daniel B. Klein[5], Charles P. Quesenberry, Jr.[1], William J. Towner[6], Michael J. Silverberg[1]

Kaiser Permanente Research
2000 Broadway, 2nd Floor
Oakland, CA 94612
Julia.L.Marcus@kp.org
510-891-3716

[1]Kaiser Permanente Northern California, Oakland, CA; [2]Kaiser Permanente Southern California, Pasadena, CA; [3]University of California, San Francisco, CA; [4]Kaiser Permanente Mid-Atlantic States, Rockville, MD; [5]Kaiser Permanente Northern California, Hayward, CA; [6]Kaiser Permanente Southern California, Los Angeles, CA

Background

- As HIV+ individuals aged, ischemic stroke hospitalizations in this population increased 60% during 1997-2006, despite a 7% decrease in the general population [Ovbiagele et al., *Neurology*, 2011]
- Incidence may have stabilized or even decreased in recent years with improved risk factor management and ART
- However, it is unclear whether HIV+ individuals are at increased risk, independent of age, compared with HIV- individuals
- We aimed to 1) determine the association of HIV infection and immunodeficiency with ischemic stroke and 2) identify stroke risk factors among HIV+ individuals

Methods

- **Study population**
  - Kaiser Permanente (KP) California cohort during 1996-2011
  - HIV+ and HIV- adults matched 10:1 on age, sex, initial year of follow-up, and medical center
- **Data sources**
  - KP HIV registries, with HIV+ status confirmed by review of charts or medical center case lists
  - KP electronic medical record, including lab results, pharmacy prescription fills, and clinical diagnoses
- **Outcome**
  - Inpatient or outpatient ischemic stroke diagnosis (ICD-9: 433x1; 434, excluding 434.x0; 436) [Tirschwell et al., *Stroke*, 2002]
- **Statistical analysis**
  - Cohort followed until stroke, left KP, death, or end of 2011
  - Incidence rates and rate ratios (RR) by HIV status and stratified by recent CD4 cells/μL, recent HIV RNA copies/mL, and nadir CD4 cells/μL
  - Adjusted RRs to identify risk factors among HIV+ individuals, including duration of PI and NNRTI use
  - Poisson models adjusted for age, sex, year, socioeconomic status (SES, neighborhood index), race/ethnicity, hypertension, smoking, diabetes, alcohol/drug abuse, overweight/obesity, and lipid-lowering therapy

Results

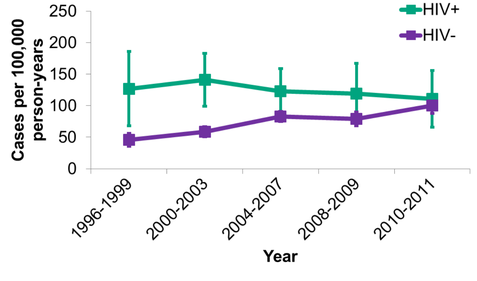
1. Cohort characteristics

	HIV+	HIV-
N	24,768	257,600
Age, mean (SD)	41 (10)	40 (10)
% Men	91	91
% White/Black/Hispanic	56/17/21	41/9/26
% Ever smoked	45	31
% Ever alcohol abuse	11	7
% Ever drug abuse	16	5
% Ever overweight/obese	48	53
% Prior diabetes	3	3
% Prior hypertension	8	9
% Prior lipid-lowering therapy	6	6
% Men who have sex with men	75	–
Years known to be HIV+, mean (SD)	4 (6)	–

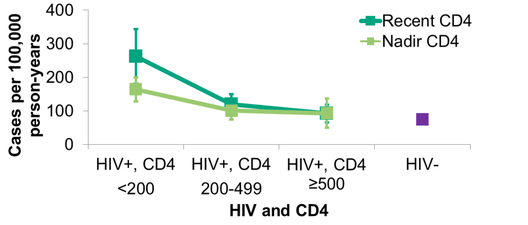
2. Ischemic stroke rates by HIV status

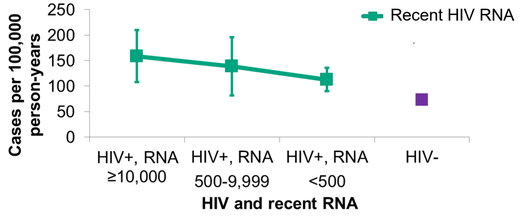
	HIV+	HIV-
Cases	151	1,128
Person-years	120,588	1,516,250
Rate per 100,000 person-years	125	74

3. Stroke rates by HIV status and year



4. Stroke rates by HIV status, CD4, and RNA





5. Rate ratios (95% CI) for HIV infection

HIV-positive (HIV- ref)				***P***
Unadjusted		1.7 (1.4-2.0)		<0.001
Adjusted[1]		1.4 (1.2-1.7)		<0.001
Recent CD4 (HIV- ref)				
	<200	200-499	≥500	*P* trend
Unadjusted	3.5 (2.6-4.8)	1.6 (1.2-2.1)	1.2 (0.9-1.7)	<0.001
Adjusted	3.2 (2.3-4.4)	1.3 (1.0-1.7)	1.0 (0.8-1.4)	<0.001
Recent HIV RNA (HIV- ref)				
	≥10,000	500-9.999	<500	*P* trend
Unadjusted	2.1 (1.5-3.0)	1.9 (1.2-2.8)	1.5 (1.2-1.9)	<0.001
Adjusted	2.5 (1.8-3.5)	1.9 (1.3-2.9)	1.1 (0.9-1.4)	<0.001
Nadir CD4 (HIV- ref)				
	<200	200-499	≥500	*P* trend
Unadjusted	2.2 (1.8-2.8)	1.4 (1.0-1.8)	1.3 (0.8-2.0)	<0.001
Adjusted	1.6 (1.3-2.1)	1.2 (0.9-1.5)	1.4 (0.8-2.2)	<0.001

[1] RRs adjusted for age, sex, year, SES, race/ethnicity, hypertension, smoking, diabetes, alcohol/drug abuse, overweight/obesity, and lipid-lowering therapy

6. Risk factors among HIV+ individuals[1]

	RR[2]	(95% CI)	*P*
Age, years			
40-49 vs. 18-39	1.8	(0.9-3.6)	0.12
50-64 vs. 18-39	5.2	(2.6-10.2)	<0.001
≥65 vs. 18-39	11.5	(5.4-24.4)	<0.001
Ever alcohol/drug abuse	2.0	(1.5-2.9)	<0.001
Prior hypertension	3.3	(2.2-4.7)	<0.001
Ever overweight/obese	0.5	(0.3-0.7)	<0.001
Recent CD4			
<200 vs. ≥500	2.5	(1.3-4.6)	0.004
200-499 vs. ≥500	1.3	(0.8-2.0)	0.32
Duration of HIV infection, years			
≥10 vs. <5	0.6	(0.4-1.0)	0.03
5-9 vs. <5	0.6	(0.4-0.9)	0.02

[1] No association with nadir CD4, recent HIV RNA, HIV-transmission risk factor, any prior ART use, year of stroke diagnosis, race/ethnicity, SES, smoking, diabetes, or lipid-lowering therapy

[2] RRs adjusted for age, sex, year, SES, race/ethnicity, hypertension, smoking, diabetes, alcohol/drug abuse, overweight/obesity, and lipid-lowering therapy

Summary and Conclusions

- HIV+ individuals have a 40% higher risk of ischemic stroke compared with HIV- individuals after adjustment for risk factors
- HIV+ individuals with recent CD4 ≥500 or recent HIV RNA <500 are not at significantly greater risk compared with HIV- individuals after adjustment for stroke risk factors, but lower recent CD4 and higher recent HIV RNA are associated with increased risk
- Recent CD4 and recent HIV RNA are stronger risk factors than nadir CD4
- The relative risk of ischemic stroke among HIV+ compared with HIV- individuals has decreased in recent years, with rates nearly converging in 2010-2011
- Treatment with ART to maintain immune function, combined with mitigation of stroke risk factors, could result in a similar risk of ischemic stroke among HIV+ compared with HIV- individuals

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