Incidence of stroke in patients with HIV infection: A population-based study in Taiwan

Hui-Lin Lin\textsuperscript{1,2}, Chih-Hsin Muo\textsuperscript{3}, Cheng-Yu Lin\textsuperscript{3}, Hsuan-Ju Chen\textsuperscript{4}, Pei-Chun Chen\textsuperscript{3}\textsuperscript{*}

\textsuperscript{1} PHD Program for Aging, China Medical University, Taichung, Taiwan, \textsuperscript{2} Department of Physical Medicine and Rehabilitation, Lin Shin Hospital, Taichung, Taiwan, \textsuperscript{3} Department of Public Health, China Medical University, Taichung, Taiwan, \textsuperscript{4} Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan

* peichun@mail.cmu.edu.tw

Abstract

Background

Few studies have evaluated whether people infected with human immunodeficiency virus (HIV) are at an increased risk of stroke in an Asian population. We investigated the association between HIV infection and the risk of developing stroke by age, calendar year of HIV diagnosis, and follow-up duration in Taiwan.

Methods

Using the claims data of a universal health insurance program, we identified 5,961 patients with HIV and 23,844 matched non-HIV subjects without previous stroke from 1998 to 2005 and followed them up until the end of 2011 to measure the incidence of stroke. Cox proportional hazards models adjusted for potential confounders were used to estimate hazard ratios (HR) and 95% confidence intervals (CI), with the non-HIV group as reference.

Results

During a median follow-up of 8 years, the incidence rates for total, ischemic, and hemorrhagic stroke per 1000 person-years were 2.12, 1.22, and 0.60, respectively, in patients with HIV infection, and 1.98, 1.14, and 0.54, respectively, in the comparison group. HIV infection was associated with an elevated risk of developing total stroke (adjusted HR [95% CI], 1.57 [1.15–2.14]) and ischemic stroke (1.91 [1.25–2.91]) in patients aged less than 45 years, but no association was observed in other age groups (P for interaction with age, p = 0.048 and 0.024, respectively). Patients diagnosed with HIV infection in 1998–1999 had a greater HR for total stroke and ischemic stroke than those diagnosed in 2000–2002 and 2003–2005 (P for interaction, for total stroke p = 0.034, for ischemic stroke p = 0.056). The HRs did not differ by follow-up duration.
Conclusions

HIV infection among a young age group is associated with increased risk of developing overall and ischemic stroke. The findings highlight the importance of screening and correcting risk factors for young stroke prevention immediately and aggressively.

Introduction

Human immunodeficiency virus (HIV) infection largely affects sexually active young adults. With the development of the combination antiretroviral therapy (cART) regimen, used for people living with HIV/AIDS (PLWHA) since 1996, HIV replication was effectively inhibited, leading to a reduction of the risk of developing an AIDS-defining complication and prolonging the lifespan of patients with HIV [1]. However, the health of effectively treated patients with HIV is not fully restored and has led to a higher prevalence of the disease than in those without HIV infection [2].

Stroke is a significant cause of death and disability worldwide [3]. Acute or chronic infection is well recognized to be a contributing factor in strokes and can influence the outcome of strokes [4]. Several studies have reported the association between HIV infection and the risk of stroke [1, 5–17]. However, most of these studies have been confined to Western populations [1, 5–12, 15–17]. Little is known regarding the association between HIV infection and the risk of stroke in Asian people [6, 13, 14]. Multiple factors, including age, sex, family history, the effect of HIV itself, the effect of antiretroviral therapy, traditional cardiovascular risk factors etc., influence the risk of stroke in HIV-infected individuals. Genetics in different populations also play a role. Epidemiology data have been revealed to be different in Western and Asian countries due to the influence of population-specific phenotypic effects and gene susceptibility on the progression of HIV infection [18, 19]. Black people have shown more prominent cerebrovascular endothelial dysfunction leading to an elevated risk of stroke compared with other race/ethnic groups after adjusting for several traditional vascular risk factors in an ART-treated PLWHA group [20]. A recent multiethnic study revealed that the incidence rate of stroke was greater in non-Hispanic Black people than in other ethnic groups in persons living with HIV infection, but only 2% of the study subjects (n = 116) were Asian/Pacific Islanders [15]. Furthermore, studies of the US population have shown a greater risk of stroke in women and in younger people [8, 12, 15, 16], but limited data is available for other ethnic groups. A recent population-based cohort study in Taiwan reported that patients that are HIV-positive had an increased risk of stroke, as compared with individuals who are HIV-negative [14]. The incidence rate of stroke among individuals that are HIV-infected in that study [14] was lower than that in previous reports in Western countries [5, 7–9, 11, 12]. However, data by types of stroke and whether the HIV-related risk of stroke differs by age and sex was not reported in that study [14]. Furthermore, little is known regarding the risk of stroke in association with HIV infection by calendar years of diagnosis [21] and the duration of follow-up. Using a national database from Taiwan, we explored the risk of overall and different types of stroke in patients with HIV infection by age, sex, calendar year of diagnosis, and follow-up years.

Methods

Study design and data source

We conducted a retrospective cohort study using claims data of a universal health insurance program in Taiwan [22]. The National Health Insurance (NHI) program is a mandatory...
single-payer national health insurance program providing comprehensive healthcare coverage to more than 99% of the 23 million people in Taiwan [23]. The NHI claims data is provided to scientists for research purposes, and all personal identification information was encrypted for the protection of patient privacy [6]. This study was approved by the Institutional Review Board of China Medical University & Hospital (CRREC-106-074).

**Identification of patients living with HIV infection and the comparison group**

Fig 1 shows the flow chart for the subject selection process. We identified a cohort of patients diagnosed with HIV infection for the first time during the period of 1 January 1998 and 31 December 2005, according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 042 and V08 listed in the Registry for Catastrophic Illness Patient Database. Taiwan’s NHI defines 31 categories of catastrophic illness, including HIV infection. When patients are diagnosed and confirmed as having such definite catastrophic illnesses, they are qualified to apply for catastrophic illness certificates by their attending physician, and thus become exempt from copayments. To apply for the catastrophic illness certificates for HIV infection, patients’ infectious disease physicians must provide pertinent medical records and data for formal review, including clinical histories, the definite positive results of the HIV antibody and antigen combination assays in the laboratory tests, and the results of viral load and CD4 count examinations to validate the diagnoses. An expert committee composed of infectious disease physicians issues catastrophic illness certificates of HIV after a review of the applications. For each of the patients with HIV, the date on which he or she was registered for the catastrophic illness served as the index date. Individuals who had received stroke diagnoses before the index date were excluded from the data analysis.

Using a dataset containing NHI claims of one million subjects randomly selected from the insured population during 1996–2000 (the Longitudinal Health Insurance Database [24]), we randomly selected patients without an HIV diagnosis to form a comparison group. Subjects in the comparison group were frequency matched with those in the HIV infection group at a 4:1 ratio based on age (every 5 years), sex, and the calendar year of the HIV diagnosis and were randomly assigned index dates in the same year of the HIV diagnosis in the HIV infection group. Individuals previously diagnosed with stroke were excluded.

**Follow-up for stroke development**

Subjects in the HIV infection group and the comparison group were observed for the occurrence of stroke, defined as a hospital discharge diagnosis with stroke (ICD-9-CM codes 430–438). We classified patients with stroke into three categories: hemorrhagic stroke (ICD-9-CM codes 430–432), ischemic stroke (ICD-9-CM codes 433, 434, and 435.9), and undetermined type of stroke (ICD-9-CM codes 435–438 exclude 435.9). The follow-up period started on the index date and ended at the earliest of the following dates: stroke occurrence, withdrawal from the NHI program, or 31 December 2011.

**Baseline comorbidities**

Comorbidities including diabetes mellitus (ICD-9-CM codes 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM codes 272), chronic kidney disease (ICD-9-CM codes 580–587), cancer (ICD-9-CM codes 140–208), coronary heart disease (ICD-9-CM codes 410–414), and atrial fibrillation (ICD-9-CM codes 427.31), which are known risk factors of stroke, were considered as potential confounders (S1 Table). All comorbidities were identified
by the presence of diagnosis codes in at least two outpatient claims or one hospital inpatient claim within two years before the index date.

Statistical analysis
We compared the baseline characteristics of patients with HIV and the comparison group using t-tests for continuous variables and chi-squared tests for categorical variables. For each group, the incidence density rates of stroke were calculated by using the number of patients with incident stroke events divided by total follow-up person-years. We used Cox proportional hazards models, which yielded hazard ratios (HR) and 95% confidence intervals (CI), to assess the risk of developing total, ischemic, and hemorrhagic stroke in association with HIV infection. The models were adjusted for age, sex, and the comorbidities to control for potential confounding factors. The Cox models were performed in patient subgroups stratified by age, year of HIV diagnosis, and follow-up period to observe whether the risks differ between the stratifications. Interaction effects of age and year of diagnosis with HIV were examined by using likelihood ratio tests comparing Cox models excluding and including the interaction terms. The proportional hazards assumption, i.e., whether the risk differs by follow-up time, was also tested by including interaction terms between the HIV infection and a function of follow-up time in the models. We used the SAS 9.4 software package (SAS Institute, Cary, NC USA) to perform all data management and analyses.

Results
Characteristics of subjects in the HIV-infected group and the comparison group
There were 6,078 patients with HIV infection identified from 1998 to 2005 (Fig 1). We excluded subjects with missing or invalid data on the date of withdrawal from the NHI.
HIV infection and stroke by age and sex

Table 2 shows the incidence rates and HRs for stroke overall and in subgroups stratified by age and sex. During the follow-up period, the incidence rates for total, ischemic, and hemorrhagic stroke per 1000 person-years were 2.12, 1.22, and 0.60, respectively, in the patients with HIV infection. The corresponding rates in the comparison group were 1.98, 1.14, and 0.54. In the multivariable-adjusted models, overall we did not observe a statistically significant association between HIV infection and the risk of developing total stroke (adjusted HR [95% CI], 1.21 [0.98–1.51]), ischemic stroke (1.23 [0.93–1.64]), and hemorrhagic stroke (1.18 [0.78–1.78]).

The adjusted HR for total stroke was greater among women than in men (adjusted HR [95% CI], 2.25 [1.15–4.41] and 1.15 [0.91–1.44], respectively), but the sex difference was not statistically significant (for the interaction with sex p = 0.085).

The age-stratified analyses showed that HIV infection was associated with an increased risk of total stroke and ischemic stroke in subjects <45 years of age (adjusted HR [95% CI], 1.57 [1.15–2.14] and 1.91 [1.25–2.91], respectively), but not in other age stratifications (for interaction with total stroke p = 0.048, for interaction with ischemic stroke p = 0.024). Similarly, the HRs differed significantly by age among men. Increased risk was found in men <45 years of age but not in older subjects (for interaction with total stroke p = 0.056, for interaction with ischemic stroke p = 0.034). Elevated HRs in young patients were also noted among women, but the interaction effect with age was not statistically significant. However, we did not observe associations between HIV infection and the risk of developing hemorrhagic stroke.

HIV infection and the risk of stroke by year of diagnosis

Table 3 shows the association between HIV infection and the risk of developing stroke in analyses stratified by year of diagnosis of HIV infection. The adjusted HR for total stroke was greater in patients diagnosed with HIV infection in 1998–1999 (HR = 1.51, 95% CI = 1.08–2.10) than those in 2000–2002 (HR = 0.75, 95% CI = 0.48–1.18) and 2003–2005 (HR = 1.44, 95% CI = 0.98–2.11) (p for interaction, p = 0.034) (Table 3). Similar results were observed for ischemic stroke but not for hemorrhagic stroke. Patients diagnosed with HIV infection in 1998–1999 had an increased risk of ischemic stroke (HR = 1.73, 95% CI = 1.13–2.65), but no significant association was observed in those diagnosed in 2000–2002 (HR = 0.68, 95% CI = 0.39–1.28) and 2003–2005 (HR = 1.33, 95% CI = 0.80–2.20) (p for interaction, p = 0.056) (Table 3).
HIV infection and the risk of stroke by follow-up period

Fig 2 shows the analyses of the association between HIV infection and the risk of developing stroke stratified by 1-year intervals of follow-up duration. The adjusted HRs were slightly increased in the first year and in years 5–6 after HIV diagnosis than in other time periods, but the difference in risk was not statistically significant (p = 0.94). The HRs for ischemic stroke and hemorrhagic stroke also did not differ over follow-up time (p = 0.38 and p = 0.90, respectively).

The models were adjusted for age, sex, and comorbidities including diabetes, hypertension, hyperlipidemia, chronic kidney disease, cancer, coronary heart disease, and atrial fibrillation.

Table 1. Characteristics of patients with HIV infection and subjects in the comparison group.

| Variable                                      | Patients with HIV (n = 5961) | Comparison group (n = 23844) | p-value |
|-----------------------------------------------|------------------------------|------------------------------|---------|
| Sex* (n (%))                                  |                              |                              |         |
| Male subjects                                 | 5495                         | 21980                        | 92.2    |
| Female subjects                               | 466                          | 1864                         | 7.8     |
| Age at HIV diagnosis, years (n (%))a          |                              |                              |         |
| 0–25                                          | 1101                         | 4404                         | 18.5    |
| 25–35                                         | 2534                         | 10136                        | 42.5    |
| 35–45                                         | 1468                         | 5872                         | 24.6    |
| 45–55                                         | 491                          | 1964                         | 8.2     |
| 55–65                                         | 248                          | 992                          | 4.2     |
| ≥65                                           | 119                          | 476                          | 2.0     |
| Median (mean ± SD)b                           |                              |                              |         |
| All                                           | 32.3 (34.3 ± 11.1)           | 32.4 (34.3 ± 11.3)           |         |
| Male subjects                                 | 32.2 (34.2 ± 10.9)           | 32.3 (34.2 ± 11.1)           |         |
| Female subjects                               | 33.9 (36.4 ± 12.7)           | 33.9 (36.3 ± 12.9)           |         |
| Comorbidities*c                               |                              |                              |         |
| Diabetes                                      | 183                          | 514                          | 3.1     |
| Hypertension                                  | 245                          | 1060                         | 4.1     |
| Hyperlipidemia                                | 137                          | 626                          | 2.3     |
| Chronic kidney disease                        | 97                           | 170                          | 1.6     |
| Cancer                                        | 60                           | 101                          | 1.0     |
| Coronary heart disease                        | 99                           | 339                          | 1.7     |
| Atrial fibrillation                           | 9                            | 20                           | 0.2     |
| Duration of the follow-up, years (median, (interquartile range))c |                              |                              |         |
| Male subjects                                 | 8.1 (4.1)                    | 8.4 (5.5)                    | <0.0001 |
| Female subjects                               | 7.6 (4.9)                    | 8.4 (5.6)                    | <0.0001 |
| All                                           | 8.1 (4.2)                    | 8.4 (5.6)                    | <0.0001 |
| Age at diagnosis of stroke, years (median, (mean ± SD))c |                              |                              |         |
| Male subjects                                 | 48.6 (50.3 ± 15.7)           | 56.8 (57.2 ± 14.5)           | <0.0001 |
| Female subjects                               | 51.1 (54.3 ± 12.4)           | 61.0 (59.2 ± 11.3)           | 0.22    |
| All                                           | 49.1 (50.8 ± 15.3)           | 58.1 (57.3 ± 14.3)           | <0.0001 |

Abbreviations: HIV, human immunodeficiency virus; N.A., not applicable; SD, standard deviation.
*a Chi-squared test.
*b T-test.
*c Wilcoxon Rank sum test.

https://doi.org/10.1371/journal.pone.0217147.t001
Patients with undetermined stroke were excluded in the analysis by stroke subtypes (n = 79). HR indicates hazard ratio; CI, confidence interval.

**Discussion**

The investigation of HIV infection as an independent risk factor of stroke incidence in different countries is worth noting. Our findings provide information for Asian subjects that individuals with HIV infection among a younger age cohort had increased risk of overall and ischemic stroke, and HIV infection-related risk of stroke was higher among subjects diagnosed in the early cART era.
Epidemiological studies in different areas and with different ethnic groups revealed variations in the incidence of stroke among people with HIV infection. In general, studies from Asia yielded lower incidence. Chow et al. reported that the incidence rate of ischemic stroke per 1000 person-years was 5.27 in the HIV cohort and 3.75 in patients without HIV [8], and the incidence of hemorrhage stroke per 1000 person-years was 2.29 in the HIV-infected group compared with 1.23 in non-HIV group [12] in a local US health care system. One recent study in Taiwan showed the incidence rates of total stroke, ischemic stroke, and hemorrhagic stroke were 2.53 vs. 1.4; 1.87 vs. 1.01; 0.66 vs. 0.39 per 1000 person-years in the HIV-infected group compared with the non-HIV cohort [14]. Another recent study found 2.2 cardiovascular events per 1000 person-years in the TREAT Asia HIV Observational Database [25]. Our observations revealed that the incidence rate of overall stroke per 1000 person-years was 2.12 among patients with HIV infection and 1.98 among the comparison group, which is lower than the studies reported in Western countries [5, 7–9, 11, 12], but similar to those in Asia [14, 25]. The reasons for the lower incidence rate of stroke in HIV-infected individuals in Asia remain unclear. Explanations may include the differences in study methods such as data sources, survey methods, time periods, the inclusion criteria for subject selection, and different population genetics.

The strength of the associations in our analyses, which showed an adjusted HR of 1.21 (95% CI 0.98–1.51) for total stroke and 1.23 (95% CI 0.93–1.64) for ischemic stroke, was weaker than that observed in a Danish study [5] and a recent study in Taiwan [14] (HR [95% CI] for total stroke, 1.60 [1.30–1.95] and 1.83 [1.58–2.13], respectively), but similar to findings in a US study (HR [95% CI], 1.21 [1.01–1.46] for ischemic stroke) [8]. The statistical non-significance may reflect insufficient statistical power to detect the moderate association because of the relatively lower incidence of stroke and the smaller number of outcome events in our analysis than in the US study [8]. Furthermore, our study suggests variability of the association across patient subgroups of age and calendar year of diagnosis of HIV infection, which warrants further investigation.

Few studies have reported the association between HIV infection and risk of stroke by age and sex. Our observation was in line with the finding of Chow et al. [8], which showed a

### Table 3. Risk of stroke in patients with HIV infection according to calendar year of diagnosis.

| Year of diagnosis of HIV infection | Total Stroke* | Ischemic stroke | Hemorrhage stroke |
|-----------------------------------|---------------|----------------|------------------|
| HIV group                        | Comparison group | HR (95% CI)* | HIV group | Comparison group | HR (95% CI)* | HIV group | Comparison group | HR (95% CI)* |
| No. Event | No. Rate | No. Event | No. Rate | No. Event | Rate | No. Event | Rate | No. Event | Rate |
| 1998–1999   | 1302  45  3.21  5208 160  2.44 | 28  2.00  89 1.36 | 11  0.78  47 0.72 | 1.51 (1.08–2.10) | 1.73 (1.13–2.65) | 1.18 (0.61–2.27) |
| 2000–2002   | 1786  22  1.40  7144 155  2.21 | 11  0.70  87 1.24 | 8  0.51  42 0.60 | 0.75 (0.48–1.18) | 0.68 (0.39–1.28) | 0.95 (0.45–2.04) |
| 2003–2005   | 2873  36  1.91 11492 110  1.39 | 20  1.06  69 0.87 | 10  0.53  27 0.34 | 1.44 (0.98–2.11) | 1.33 (0.80–2.20) | 1.52 (0.72–3.18) |

Abbreviations: No., Number; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio.

*Patients with undetermined stroke were excluded in the analysis by stroke subtypes (n = 79).

Incidence rate per 1000 person-years.

Adjusted for age, sex, and comorbidities including diabetes, hypertension, hyperlipidemia, chronic kidney disease, cancer, coronary heart disease and atrial fibrillation.

P values of test for interaction effect between HIV infection and year of diagnosis: 0.034 for total stroke, 0.056 for ischemic stroke and 0.643 for hemorrhage stroke.

https://doi.org/10.1371/journal.pone.0217147.t003
### HIV infection and stroke

#### Table: Risk of stroke in association with HIV infection according to time of follow-up

| Years of follow-up | HIV     |  | Comparison |  |  | HR (95% CI) |
|--------------------|---------|---|------------|---|---|-------------|
|                    | No. at risk | Event no. | Ratea | No. at risk | Event no. | Ratea | |
| All stroke         |          |          |       |          |          |       |         |
| 0-1                | 5961     | 18       | 3.17  | 23844     | 38       | 1.60  | 2.02 (1.14-3.56) |
| 1-2                | 5556     | 6        | 1.09  | 23530     | 33       | 1.41  | 0.88 (0.37-2.10) |
| 2-3                | 5436     | 8        | 1.49  | 23278     | 32       | 1.38  | 1.17 (0.53-2.56) |
| 3-4                | 5322     | 7        | 1.33  | 23071     | 45       | 1.96  | 0.74 (0.33-1.65) |
| 4-5                | 5226     | 8        | 1.55  | 22892     | 39       | 1.71  | 1.07 (0.50-2.29) |
| 5-6                | 5125     | 13       | 2.56  | 22707     | 31       | 1.37  | 2.05 (1.07-3.94) |
| 6-7                | 4994     | 8        | 1.82  | 22410     | 45       | 2.45  | 0.84 (0.39-1.80) |
| 7-8                | 3910     | 8        | 2.31  | 17649     | 26       | 1.75  | 1.48 (0.67-3.29) |
| 8-9                | 3062     | 3        | 1.11  | 14038     | 37       | 3.01  | 0.42 (0.13-1.37) |
| 9-10               | 2395     | 7        | 3.37  | 11196     | 29       | 2.96  | 1.23 (0.53-2.82) |
| 10-11              | 1812     | 5        | 3.22  | 8613      | 25       | 3.22  | 1.14 (0.43-3.04) |
| 11-12              | 1319     | 3        | 2.74  | 6405      | 17       | 2.90  | 1.04 (0.30-3.55) |
| 12-13              | 915      | 5        | 6.86  | 4587      | 17       | 3.91  | 1.75 (0.64-4.82) |
| 13-14              | 575      | 4        | 9.27  | 2936      | 11       | 3.95  | 2.20 (0.69-6.98) |
| Ischemic stroke    |          |          |       |          |          |       |         |
| 0-1                | 5961     | 7        | 1.23  | 23844     | 24       | 1.01  | 1.22 (0.52-2.85) |
| 1-2                | 5556     | 4        | 0.73  | 23530     | 18       | 0.77  | 1.11 (0.37-3.28) |
| 2-3                | 5436     | 4        | 0.74  | 23278     | 17       | 0.73  | 1.06 (0.34-3.32) |
| 3-4                | 5322     | 4        | 0.76  | 23071     | 27       | 1.18  | 0.73 (0.25-2.10) |
| 4-5                | 5226     | 4        | 0.77  | 22892     | 20       | 0.88  | 1.10 (0.37-3.26) |
| 5-6                | 5125     | 9        | 1.77  | 22707     | 21       | 0.93  | 2.14 (0.98-4.70) |
| 6-7                | 4994     | 5        | 1.13  | 22410     | 23       | 1.25  | 1.00 (0.37-2.69) |
| 7-8                | 3910     | 5        | 1.44  | 17649     | 14       | 0.94  | 1.70 (0.61-4.74) |
| 8-9                | 3062     | 0        | 0.00  | 14038     | 18       | 1.47  | NA      |
| 9-10               | 2395     | 4        | 1.93  | 11196     | 16       | 1.63  | 1.26 (0.41-3.87) |
| 10-11              | 1812     | 4        | 2.58  | 8613      | 19       | 2.44  | 1.19 (0.39-3.61) |
| 11-12              | 1319     | 3        | 2.74  | 6405      | 7        | 1.20  | 2.49 (0.64-9.77) |
| 12-13              | 915      | 3        | 4.11  | 4587      | 13       | 2.99  | 1.22 (0.34-4.42) |
| 13-14              | 575      | 3        | 6.96  | 2936      | 8        | 2.87  | 2.22 (0.57-8.57) |
| Hemorrhage stroke  |          |          |       |          |          |       |         |
| 0-1                | 5961     | 6        | 1.06  | 23844     | 8        | 0.34  | 3.44 (1.18-10.0) |
| 1-2                | 5556     | 1        | 0.18  | 23530     | 10       | 0.43  | 0.45 (0.06-3.52) |
| 2-3                | 5436     | 2        | 0.37  | 23278     | 6        | 0.26  | 1.58 (0.32-7.85) |
| 3-4                | 5322     | 2        | 0.38  | 23071     | 12       | 0.52  | 0.74 (0.16-3.29) |
| 4-5                | 5226     | 3        | 0.58  | 22892     | 16       | 0.70  | 0.92 (0.27-3.18) |
| 5-6                | 5125     | 3        | 0.59  | 22707     | 7        | 0.31  | 1.81 (0.45-7.22) |
| 6-7                | 4994     | 0        | 0.00  | 22410     | 13       | 0.71  | NA      |
| 7-8                | 3910     | 3        | 0.86  | 17649     | 6        | 0.40  | 2.54 (0.63-10.3) |
| 8-9                | 3062     | 3        | 1.11  | 14038     | 13       | 1.06  | 1.11 (0.32-3.92) |
| 9-10               | 2395     | 2        | 0.96  | 11196     | 11       | 1.12  | 0.94 (0.21-4.26) |
| 10-11              | 1812     | 1        | 0.64  | 8613      | 3        | 0.39  | 1.61 (0.17-15.5) |
| 11-12              | 1319     | 0        | 0.00  | 6405      | 6        | 1.02  | NA      |
| 12-13              | 915      | 2        | 2.74  | 4587      | 3        | 0.69  | 4.25 (0.71-25.6) |
| 13-14              | 575      | 1        | 2.32  | 2936      | 2        | 0.72  | 2.77 (0.25-30.7) |

79 Undetermined stroke is not listed in Fig 2.

*aRate, per 1000 person-years.

bAdjusted for age, gender, diabetes, hypertension, hyperlipidemia, chronic kidney disease, cancer, coronary heart disease and atrial fibrillation.

Fig 2. Risk of stroke in association with HIV infection according to time of follow-up.

https://doi.org/10.1371/journal.pone.0217147.g002
greater HIV infection-related risk of ischemic stroke in young people and women. However, their study did not report the results of testing for interaction [8] with age and sex. We found that the difference in the risk of total stroke and ischemic stroke associated with HIV infection was statistically significant by age but not by sex. Previous studies have also indicated that the risk of hemorrhagic stroke associated with HIV infection increased particularly in younger patients and with more advanced disease [11, 12, 14, 26]. However, it may not be appropriate to make conclusions about the risk of hemorrhagic stroke in our analysis because the number of events was very small in the age and sex stratifications.

The potential mechanisms of ischemic stroke and hemorrhagic stroke in patients with HIV infection are multifactorial. HIV-related causes of ischemic stroke include aneurismal formation, vasculitis, accelerated atherosclerosis, HIV-associated cerebral blood vessel disease, opportunistic infection or neoplasia, cardioembolism, coagulopathy, and HIV-associated hyperviscosity [1, 27]. Possible HIV-related causes of hemorrhagic stroke include HIV-associated aneurysmal vasculopathy [28], vasculitis [29], immune thrombocytopenia [30], AIDS associated tumors, or infection [31, 32].

Our observations showed that the mean age diagnosed with stroke was 7-years younger in the HIV infection cohort than in the comparison group. This result is consistent with previous studies, which reported that patients with HIV developed stroke younger than those without HIV infection in individuals without traditional risk factors [33], even with good immune function [34], both in ischemic stroke [8, 33] and in hemorrhagic stroke [12, 26]. In Africa, patients with HIV that developed stroke were younger with a median age of 33.4 years in South Africa [33] and 39.8 years in Malawi [35]. Stroke incidence is usually low in young individuals and rises exponentially with age [36], because the vascular risk factors of stroke do not occur frequently in young individuals [37]. The remarkably high risk of stroke association with HIV infection in young people, and the younger age at diagnosis of stroke in the HIV infection group than in the comparison group implies that HIV infection plays an important role in young stroke.

Our finding in the analysis stratified by calendar year of diagnosis is consistent with the study by Alvaro-Meca et al., which revealed a decline in the stroke risk among HIV-infected individuals in more recent years after the introduction of HAART (highly active antiretroviral therapy) [21]. There may be a number of reasons for this decline. First, the adverse side effects of older antiretroviral regimens or more effective treatments in the recent era has led to seeing a higher stroke risk in the early HAART epoch than in more recent periods. Second, limited tools for making a stroke diagnosis in the earlier period might have resulted in an overestimated misdiagnosis [38, 39]. For example, HIV encephalopathy [40] or an HIV-related CNS opportunistic infection can mimic stroke [41].

In a stratified analysis by follow-up duration, we observed greater HRs for stroke in the first year after the diagnosis of HIV infection, but the interaction effect with follow-up time was not statistically significant. However, the number of stroke events in the HIV infection group in the stratifications of follow-up time was small. Further studies with larger sample sizes may help clarify this issue. From a prevention point of view, the importance of earlier risk factor correction and stroke prevention should still be emphasized once the definite diagnoses of HIV infection are established.

Our study has some limitations. First, patient characteristics including smoking history and status, BMI, and laboratory data, are not available in the claims data. Therefore, we were unable to assess the extent to which the confounding effects by these factors, if they exist, could explain the observed association between HIV infection and the incidence of stroke. However, such a confounding effect is unlikely to fully account for all the observed associations, particularly for the subgroups of young patients and those diagnosed in earlier years, in
which the associations were relatively strong. Further studies that collect these variables could help clarify this issue. Second, our necessary reliance on administrative claims data recorded by physicians and hospitals to establish diagnoses of HIV infection and stroke are less accurate than those designed in prospective settings. To minimize bias and strengthen the reliability, only patients with Catastrophic Illness Certificates of HIV infection were included. Issuing the certificates requires approval by an expert committee after review of the medical records. Stroke events were defined as hospitalized patients whose first major diagnoses were stroke. Third, information on the treatments of HIV infection is not available in this study. Thus, we were unable to evaluate the association between the treatments and the stroke risk in patients with HIV infection in this post-cART era. Fourth, our study based on observational claims data analysis cannot establish the mechanism of developing stroke in association with HIV infection. Finally, the non-significant results may be due to insufficient statistical power to detect the moderate association or the small number of events in the analyses of hemorrhagic stroke.

Conclusions

This nationwide population-based study in Taiwan reveals that young individuals with HIV infection have an elevated risk of subsequent stroke. Ischemic stroke risk was higher in the early stage of antiretroviral therapy and declined in the more recent era. An etiology survey and risk factor control for stroke prevention should be provided to young HIV-infected individuals aggressively and as early as possible.

Supporting information

S1 Table. The disease and ICD-9-CM code.

(DOCX)

Acknowledgments

This work was supported by grants from the Ministry of Health and Welfare, Taiwan (MOHW107-TDU-B-212-123004), China Medical University Hospital, China Medical University (CMU 106-S-01), Academia Sinica Stroke Biosignature Project (BM10701010021), MOST Clinical Trial Consortium for Stroke (MOST 106-2321-B-039-005-), Tseng-Lien Lin Foundation, Taichung, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan.

Author Contributions

Conceptualization: Hui-Lin Lin.
Data curation: Hui-Lin Lin.
Formal analysis: Chih-Hsin Muo, Cheng-Yu Lin.
Funding acquisition: Pei-Chun Chen.
Methodology: Hui-Lin Lin.
Resources: Hsuan-Ju Chen.
Supervision: Pei-Chun Chen.
Writing – original draft: Hui-Lin Lin.
Writing – review & editing: Pei-Chun Chen.
References

1. Benjamin LA, Bryer A, Emsley HCA, Khoo S, Solomon T, Connor MD. HIV infection and stroke: current perspectives and future directions. The Lancet Neurology. 2012; 11(10):878–90. https://doi.org/10.1016/S1474-4422(12)70205-3 PMID: 22995692

2. Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med. 2013; 173(8):614–22. Epub 2013/03/06. https://doi.org/10.1001/jamainternmed.2013.3728 PMID: 23459863.

3. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet (London, England). 2012; 380(9859):2197–223. Epub 2012/12/19. https://doi.org/10.1016/s0140-6736(12)61689-4

4. Emsley HCA, Hopkins SJ. Acute ischaemic stroke and infection: recent and emerging concepts. The Lancet Neurology. 2008; 7(4):341–53. https://doi.org/10.1016/S1474-4422(08)70061-9 PMID: 18339349

5. Rasmussen LD, Engsig FN, Christensen H, Kronborg G, Kronborg G, Pedersen C, et al. Risk of cerebrovascular events in persons with and without HIV: a Danish nationwide population-based cohort study. AIDS (London, England). 2011; 25(13):1637–46. Epub 2011/06/08. https://doi.org/10.1097/QAD.0b013e3283493fb0 PMID: 21646903.

6. Yen YF, Jen I, Chen M, Chuang PH, Liu YL, Sharp GB, et al. Association of Cytomegalovirus End-Organ Disease with Stroke in People Living with HIV/AIDS: A Nationwide Population-Based Cohort Study. PloS one. 2016; 11(3):e0151684. Epub 2016/03/18. https://doi.org/10.1371/journal.pone.0151684 PMID: 26986005.

7. Vinikoor MJ, Napravnik S, Floris-Moore M, Wilson S, Huang DY, Eron JJ. Incidence and clinical features of cerebrovascular disease among HIV-infected adults in the Southeastern United States. AIDS research and human retroviruses. 2013; 29(7):1068–74. Epub 2013/04/10. https://doi.org/10.1089/AID.2012.0334 PMID: 23565888.

8. Chow FC, Regan S, Seske S, Meigs JB, Grinspoon SK, Triant VA. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. Journal of acquired immune deficiency syndromes (1999). 2012; 60(4):351–8. Epub 2012/05/15. https://doi.org/10.1097/QAI.0b013e31820a0cfc PMID: 22580566.

9. Sico JJ, Chang CC, So-Armah K, Justice AC, Hylek E, Skanderson M, et al. HIV status and the risk of ischemic stroke among men. Neurology. 2015; 84(19):1933–40. Epub 2015/04/12. https://doi.org/10.1212/WNL.00000000000000958 PMID: 25862803.

10. Marcus JL, Leyden WA, Chao CR, Chow FC, Horberg MA, Hurley LB, et al. HIV infection and incidence of ischemic stroke. AIDS (London, England). 2014; 28(13):1911–9. Epub 2014/06/18. https://doi.org/10.1097/QAD.0000000000000352 PMID: 24937309.

11. Durand M, Sheehy O, Baril JG, LeLorier J, Tremblay CL. Risk of spontaneous intracranial hemorrhage in HIV-infected individuals: a population-based cohort study. J Stroke Cerebrovasc Dis. 2013; 22(7):e34–41. Epub 2012/05/05. https://doi.org/10.1016/j.jstrokecerebrovasdis.2012.03.014 PMID: 22554568.

12. Chow FC, He W, Bacchetti P, Regan S, Seske SK, Meigs JB, et al. Elevated rates of intracerebral hemorrhage in individuals from a US clinical care HIV cohort. Neurology. 2014; 83(19):1705–11. Epub 2014/10/05. https://doi.org/10.1212/WNL.0000000000000996 PMID: 25280902.

13. Bijker R, Choi JY, Ditangco R, Kiertiburanakul S, Lee MP, Swamogsatham S, et al. Cardiovascular Disease and Cardiovascular Disease Risk in HIV-Positive Populations in the Asian Region. The open AIDS journal. 2017; 11:52–66. Epub 2018/01/06. https://doi.org/10.2174/1874613601711010052 PMID: 29302277.

14. Yen YF, Chen M, Jen I, Lan YC, Chuang PH, Liu YL, et al. Association of HIV and Opportunistic Infections With Incident Stroke: A Nationwide Population-Based Cohort Study in Taiwan. Journal of acquired immune deficiency syndromes (1999). 2017; 74(2):117–25. Epub 2016/10/28. https://doi.org/10.1097/QAI.00000000000001216 PMID: 27787346.

15. Chow FC, Wilson MR, Wu K, Ellis RJ, Bosch RJ, Linas BP. Stroke incidence is highest in women and non-Hispanic Blacks living with HIV in the ALLRT cohort. AIDS (London, England). 2018. Epub 2018/03/17. https://doi.org/10.1097/qad.0000000000001799

16. Chow FC, Regan S, Zanni MV, Looby SE, Bushnell CD, Meigs JB, et al. Elevated ischemic stroke risk among women living with HIV infection. AIDS (London, England). 2018; 32(1):59–67. Epub 2017/09/20. https://doi.org/10.1097/qad.0000000000001650 PMID: 28926405.

17. Ovbiagele B, Nath A. Increasing incidence of ischemic stroke in patients with HIV infection. Neurology. 2011; 76(5):444–50. Epub 2011/01/21. https://doi.org/10.1212/WNL.0b013e31820a0cf0c PMID: 21248273.
18. Enrique Gonzalez RD, Bamshad Mike, Mummidri Srinivas, Geervaghese Reni, Catano Gabriel, Anderson Stephanie A., Walter Elizabeth A., Stephan Kevin T., Hammer Michael F., Mangano Andrea, Sen Luisa, Clark Robert A., Ahuja Seema S., Dolan Matthew J., and Ahuja Sunil K. Global survey of genetic variation in CCR5, RANTES, and MIP-1a: Impact on the epidemiology of the HIV-1 pandemic. PNAS 2001; April 24, 2001 u vol. 98 u no. 9 u 5199.

19. Geretti AM. HIV-1 subtypes: epidemiology and significance for HIV management. Curr Opin Infect Dis. 2006; 19(1):1–7. Epub 2005/12/24. PMID: 16374210.

20. Chow FC, Boscardin WJ, Mills C, Ko N, Carroll C, Price RW, et al. Cerebral vasoreactivity is impaired in treated, virally suppressed HIV-infected individuals. AIDS (London, England), 2016; 30(1):45–55. Epub 2015/09/16. https://doi.org/10.1097/qad.0000000000000875 PMID: 26372478.

21. Alvaro-Meca A, Berenguer J, Diaz A, Micheloud D, Aidamiz-Echevarria T, Fanciulli C, et al. Stroke in HIV-infected individuals with and without HCV coinfection in Spain in the combination antiretroviral therapy era. PloS one. 2017; 12(6):e0179493. Epub 2017/06/16. https://doi.org/10.1371/journal.pone.0179493 PMID: 28627855.

22. Chen Y-C, et al. * 86.2: 365–380. Taiwan’s National Health Insurance Research Database: administrative health care database as study object in bibliometrics.” Scientometrics. 2011.

23. Cheng TM. Taiwan’s new national health insurance program: genesis and experience so far. Health Aff (Millwood). 2003; 22(3):61–76. Epub 2003/05/22. https://doi.org/10.1377/hlthaff.22.3.61 PMID: 12757273.

24. National Health Insurance Research Database. Longitudinal Health Insurance Database for one million people insured. https://nhird.nhri.org.tw/en/Data_Subsets.html.

25. Bijker R, Jiamsakul A, Uy E, Kumarasamy N, Ditango R, Chaiwarith R, et al. Cardiovascular disease-related mortality and factors associated with cardiovascular events in the TREAT Asia HIV Observational Database (TAHOD). HIV medicine. 2019; 20(3):183–91. Epub 2019/01/09. https://doi.org/10.1111/hiv.12867 PMID: 30620108.

26. Behrouz R, Topel CH, Seifi A, Birnbaum LA, Brey RL, Misra V, et al. Risk of intracerebral hemorrhage in HIV/AIDS: a systematic review and meta-analysis. Journal of neurovirology. 2016; 22(5):634–40. Epub 2016/04/05. https://doi.org/10.1007/s13365-016-0439-2 PMID: 27044037.

27. Singer EJ, Valdes-Sueiras M, Commis DL, Yong W, Carlsson M. HIV stroke risk: evidence and implications. Ther Adv Chronic Dis. 2013; 4(2):61–70. Epub 2013/04/05. https://doi.org/10.1177/20462312471840 PMID: 23556125.

28. Ake JA, Erickson JC, Lowry KJ. Cerebral aneurysmal arteriopathy associated with HIV infection in an adult. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2006; 43(5):e46–50. Epub 2006/08/04. https://doi.org/10.1086/506566 PMID: 16886142.

29. Chetty R. Vasculitides associated with HIV infection. J Clin Pathol. 2001; 54(4):275–8. Epub 2001/04/18. https://doi.org/10.1136/jcp.54.4.275 PMID: 11304843.

30. Park YD, Belman AL, Kim TS, Kure K, Llena JF, Lantos G, et al. Stroke in pediatric acquired immunodeficiency syndrome. Ann Neurol. 1990; 28(3):303–11. Epub 1990/09/01. https://doi.org/10.1002/ana.410280302 PMID: 22411113.

31. Roquer J, Palomeras E, Knobel H, Pou A. Intracerebral haemorrhage in AIDS. Cerebrovasc Dis. 1998; 8(4):222–7. Epub 1998/07/31. https://doi.org/10.1159/000015855 PMID: 9684062.

32. Berlit P, Popescu O, Weng Y, Malessa R. Disseminated cerebral hemorrhages as unusual manifestation of toxoplasmic encephalitis in AIDS. J Neurol Sci. 1996; 143(1):187–9. Epub 1996/11/01. PMID: 8981323.

33. Tipping B, de Villiers L, Wainwright H, Candy S, Bryer A. Stroke in patients with human immunodeficiency virus infection. Journal of neurology, neurosurgery, and psychiatry. 2007; 78(12):1320–4. Epub 2007/05/02. https://doi.org/10.1136/jnnp.2007.116103 PMID: 17470469.

34. Arentzen M, Jubt F, Evers S, Hesselmann V, Fiori W, Reichelt D, et al. Cerebrovascular events in HIV-infected patients: an analysis of a cohort of 3203 HIV+ patients during the times of cART. Int J Neurosci. 2015; 125(8):601–11. Epub 2014/08/27. https://doi.org/10.3109/00207454.2014.956870 PMID: 25158008.

35. Helkkinheimo T, Chimbayo D, Kunwenda JJ, Kampondeni S, Allain TJ. Stroke outcomes in Malawi, a country with high prevalence of HIV: a prospective follow-up study. PloS one. 2012; 7(3):e33765. Epub 2012/04/06. https://doi.org/10.1371/journal.pone.0033765 PMID: 22479439.

36. Correia M, Magalhaes R, Silva MR, Matos I, Silva MC. Stroke types in rural and urban northern portug: incidence and 7-year survival in a community-based study. Cerebrovascular diseases extra. 2013; 3(1):137–49. Epub 2013/12/19. https://doi.org/10.1055/s-0035-1581 PMID: 24348498.

37. Putaala J, Metso AJ, Metso TM, Konkola N, Kraeuner Y, Haapaniemi E, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. Stroke.
38. Libman RB, Wirkowski E, Alvir J, Rao TH. Conditions that mimic stroke in the emergency department. Implications for acute stroke trials. Archives of neurology. 1995; 52(11):1119–22. Epub 1995/11/01. PMID: 7487564.

39. Hatzitolios A, Savopoulos C, Ntaios G, Papadidakalou F, Dimitrakoudi E, Kosmidou M, et al. Stroke and conditions that mimic it: a protocol secures a safe early recognition. Hippokratia. 2008; 12(2):98–102. Epub 2008/10/17. PMID: 18923652.

40. Forster A, Griebe M, Wolf ME, Szabo K, Hennerici MG, Kern R. How to identify stroke mimics in patients eligible for intravenous thrombolysis? Journal of neurology. 2012; 259(7):1347–53. Epub 2012/01/11. https://doi.org/10.1007/s00415-011-6354-9 PMID: 22231865.

41. Philip-Ephraim EE, Charidimou A, Williams E, Kajogbola G. Stroke-Like Presentation of Cerebral Toxoplasmosis: Two HIV-Infected Cases. Cerebrovascular diseases extra. 2015; 5(1):28–30. Epub 2015/05/12. https://doi.org/10.1159/000375180 PMID: 25960735.