Etiology and Risk Factors of Stroke in HIV-Infected Patients in Siriraj Hospital: A Case-Control Study

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Background: *Stroke and HIV infection are major health problems in Thailand. There is limited data regarding the etiology and risk factors of stroke in HIV-infected Thai patients.*
Objective: *To study the risk factors, types, and mechanisms of stroke in HIV-infected patients.*
Material and Method: *The authors reviewed records of consecutive HIV-infected patients with acute first stroke in a large urban medical center from August 1, 2009 through December 31, 2010. Age-matched controls of HIV-infected patients without stroke were consecutively recruited at a 2:1 ratio. Data collection included demographics, stroke subtypes, risk factors of stroke, and HIV disease parameters. Multiple logistic regression analysis ($p < 0.05$) identified factors associated with stroke in HIV-infected patients.*
Results: *There were 37 subjects and 74 controls. In HIV-positive stroke patients, 81.1% were males and mean age was 50.5 years. There were 33 and 4 cases of ischemic and hemorrhagic strokes respectively. HIV infection was previously diagnosed in 70%, mean CD4 count was 287 cells/uL and 33% had CD4 counts < 200 cells/uL. Prior antiretroviral medications were used in 49%. TOAST classification of stroke was as follows: large artery atherosclerosis 2 (6.1%), small vessel occlusion 9 (27.3%), cardioembolism 2 (6.1%), other determined etiology 9 (27.3%) (vertebral artery dissection 1, anti-thrombin III deficiency 1, thrombotic thrombocytopenic purpura 1, tuberculous meningitis 4, cryptococcal meningitis 1, intravenous heroin 1) and undetermined 11 (33.2%) (incomplete evaluation 10, negative evaluation 1). Multivariate analysis demonstrated the following to be significant risk factors of stroke: smoking $p = 0.001$, adjusted OR 6.9 (95%CI 2.3, 21.1) and tuberculous meningitis $p = 0.034$, adjusted OR 11.9 (95% CI 1.2, 117.2).*
Conclusion: *Stroke etiology in HIV-infected patients is more heterogeneous than in non-immunocompromised hosts. Smoking and concurrent tuberculous meningitis were significantly associated with stroke in HIV-infected Thai patients. Further prospective cohort studies should be performed in a larger population of more severely immunocompromised patients in Thailand.*

Keyword: *Stroke, HIV, AIDS, Thai*

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The burden of stroke in Thailand is considerable, with 150,000 new cases every year[1]. Stroke is the second largest cause of death in Thailand after human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)[2,3]. AIDS significantly increased the risk of stroke, with cerebral infarctions occurring more often than intracranial hemorrhage[4]. Clinical diagnosis of stroke in HIV positive patients occurred at rates of 0.5-5%[5,6]. A recent study using criteria from the Trial of Org 10172 in Acute Stroke Treatment (TOAST)[7] to classify subtypes of ischemic stroke in HIV-infected patients revealed large artery atherosclerosis in 12%, cardiac embolism in 18%, small vessel occlusion in 18%, other determined etiology in 23% and undetermined in 29%[8].

Potential etiologies of ischemic stroke in HIV-infected patients are as follows[9]: cardioembolic stroke (which may be caused by infectious or marantic endocarditis), HIV myocarditis and dilated cardiomyopathy[10-12]. Also frequently reported are

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opportunistic infections which cause cerebral vasculitis or vasculopathy including tuberculosis, cytomegalovirus encephalitis, varicella-zoster virus infection, syphilis, cryptococcosis, candidiasis and other mycoses[6,10,13-16]. Lymphoma, an opportunistic tumor, has also been implicated[16]. Other causes include prothrombotic states, especially protein S deficiency[17,18] and intravenous drug use, such as cocaine and heroin[19,20]. Recent studies suggest an HIV-related vasculopathy as the mechanism of ischemic stroke in patients without embolic sources or central nervous system (CNS) infections and who do not have other vascular risk factors[8,21,22]. This vasculopathy is evidenced by impairment of cerebrovascular hemodynamic function and vasoreactivity[23,24]. Protease inhibitors, a class of antiretroviral medication, may cause hyperlipidemia, insulin resistance and endothelial dysfunction[25,26], contributing to accelerated atherosclerosis. Although the most frequent vascular event is myocardial infarction, stroke is not uncommon[27] and its incidence could increase as HIV-infected patients using protease inhibitors get older.

Potential causes of intracerebral hemorrhage in HIV-positive patients include CNS opportunistic diseases, such as lymphoma, toxoplasmosis, tuberculosis and metastatic Kaposi's sarcoma[5,28,29]. Thrombocytopenia is another common cause in this population[30].

In Thailand no data is available regarding stroke etiology in HIV-infected patients. The present study aims to determine risk factors, types and mechanisms of stroke in HIV-infected Thai patients.

Material and Method

This was a case-control study from August 1, 2009 through December 31, 2010. Study subjects included consecutive cases of stroke outpatients or inpatients in Siriraj Hospital's information database acquired by searching ICD-10 codes for stroke, cerebral infarction and intracerebral hemorrhage. Inclusion criteria for study participants included age $\geq$ 18 years, presence of HIV infection, and first diagnosis of stroke, which is defined according to the World Health Organization as rapidly developing signs of focal or global disturbances of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin[30]. Computerized tomogram (CT) or magnetic resonance imaging (MRI) of the brain was performed in all patients. Two-to-one age-matched controls of HIV-infected patients without stroke were consecutively recruited from the hospital database using ICD-10 codes for HIV disease and AIDS. Patients who had intracranial space-occupying lesions other than stroke detected by neuroimaging studies were excluded. The present study was approved by the Siriraj Institutional Review Board.

Data collection included demographics and stroke subtypes according to TOAST classification. In addition, factors predisposing to stroke were also documented, *i.e.*, hyperlipidemia, hypertension, diabetes mellitus, atrial fibrillation, previous percutanous coronary intervention, smoking, hypercoagulable states, intravenous drug use, concurrent tuberculous meningitis and cryptococcal meningitis. HIV disease parameters such as CD4 cell counts, new or known HIV diagnosis and use of antiretroviral medication were also collected.

Statistical analysis

Patient characteristics were analyzed using mean $\pm$ SD and median (min, max) for continuous variables according to their distributions. Categorical variables were analyzed in the terms of their relative frequencies. Chi-square and Mann-Whitney U tests were applied to compare categorical and continuous variables respectively. Statistical analysis was performed using commercially available SPSS software (version 15.0). All tests were 2-tailed and multivariable analysis were performed by multiple logistic regression analysis (forward stepwise). Probability values less than 0.05 were considered statistically significant.

Results

Demographics

There were 37 HIV-infected stroke patients in the present study group, and 74 HIV-infected patients without stroke in the control group (Table 1). Females accounted for 18.9% and 37.8% of patients in the present study and control groups, respectively ($p = 0.043$). Mean age of the present study group was 50.5 years (range 26-81) while the mean age of the control group was 50.4 years (range 19-84).

Stroke subtypes

Ischemic stroke

Among 33 patients with ischemic stroke, two had large artery atherosclerosis (6.1%), including one with extracranial internal carotid stenosis and one with intracranial stenosis. Nine cases had small vessel occlusion (27.3%). In two cases, the mechanism was defined as cardioembolism (6.1%), both having atrial

fibrillation. Transthoracic echocardiography and carotid doppler ultrasound were normal. Nine cases were classified as other determined etiologies (27.3%), including one case of vertebral artery dissection, two cases with prothrombotic states (6.1%) (one case each of anti-thrombin III deficiency and of thrombotic thrombocytopenic purpura) and six cases of suspected vasculitis (18.1%) (four cases of concurrent tuberculous meningitis (12.1%), one case of cryptococcal meningitis and one case of intravenous heroin use). There were 11 cases (33.2%) of undetermined etiology, including ten cases of incomplete evaluation (30.3%) and one case with negative evaluation.

Hemorrhagic stroke

There were four patients of hemorrhagic stroke. In the first case, there was bleeding at the right external capsule and insular cortex, likely related to intravenous amphetamine use. The second patient had a ruptured cavernoma at the right pons. The third case had hemorrhage at the left periventricular area caused by severe thrombocytopenia. The last patient had cerebellar hemorrhage secondary to hypertension. These patients were included in the outcome analysis, but not taken into account for the statistical analysis of stroke mechanisms.

Stroke risk factors

Hyperlipidemia, hypertension, diabetes mellitus, atrial fibrillation, previous percutanous coronary intervention, smoking, hypercoagulable states, intravenous drug use, concurrent tuberculous meningitis and cryptococcal meningitis were documented in 21.6, 18.9, 5.4, 5.4, 0, 37.8, 2.7, 10.8, 10.8, and 2.7% in HIV-infected stroke patients, whereas 33.8, 14.9, 4.1, 0, 1.4, 8.1, 0, 4.1, 1.4 and 1.4% were present in HIV-infected patients without stroke, respectively. Of these, two factors were found to be statistically significant after multivariate regression analysis (Table 2): smoking p = 0.001, adjusted OR 6.9 (95%CI 2.3, 21.1) and tuberculous meningitis p = 0.034, adjusted OR 11.9 (95%CI 1.2, 117.2).

HIV disease parameters

Eleven patients from our study group (29.7%) were newly diagnosed with HIV-infection after their index stroke event, whereas all patients in the control group were known HIV-infected (p < 0.001). CD4 counts were available for 33 (89.2%) subjects; all controls had available data. Mean CD4 counts were 287 and 313 cells/uL in the present study and control groups, respectively (p = 0.944). Eleven subjects (33.3%) had CD4 counts < 200 cells/uL, while 33 controls (44.6%) were in the same category (p = 0.274). Antiretroviral medication was previously used in 48.6% of subjects and 77.0% of controls (p = 0.003). There was no significant difference in use of protease inhibitors between the two groups. About two-thirds of patients developed strokes within 2 years from diagnosis of HIV infection.

Survival time analysis

Kaplan-Meier curves (Fig. 1 and 2) revealed a marked reduction in time to stroke for study subjects

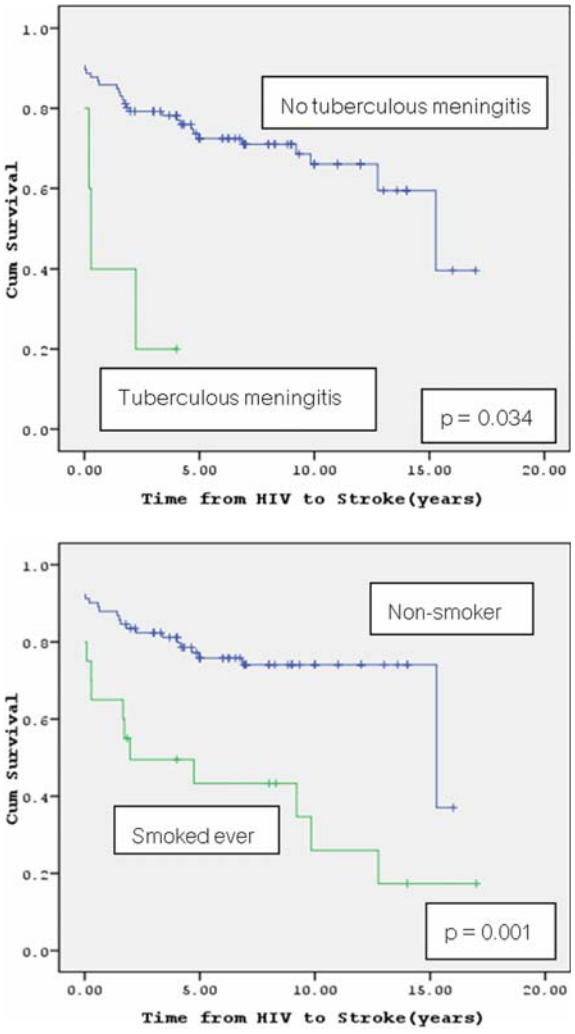

Fig. 1, 2 Kaplan-Meier curves showing reduced time to stroke for HIV-infected patients with concurrent tuberculous meningitis and those with history of smoking

with concurrent tuberculous meningitis. Subjects who had smoked also had reduced time to stroke compared with non-smokers.

Discussion

The present study demonstrated that stroke etiology in HIV-positive patients was more heterogeneous than HIV-negative patients. In addition, smoking and tuberculous meningitis were significantly associated with stroke in HIV-infected patients in the final model of multivariate analysis.

Compared with a previous study on HIV-infected stroke patients[7], our patients' mean age was higher (50.5 versus 42 years), mean CD4 count at the time of stroke was higher (287 versus 113 cells/μL), the proportion of subjects with CD4 counts < 200 cells/uL was lower (33 versus 84%), fewer patients had already been diagnosed with HIV infection (70.3 versus 92%), and fewer patients had been taking antiretroviral medication (48.6 versus 58%).

In view of stroke mechanisms, the authors had fewer cases of large artery atherosclerosis (6.1 versus 12%) and a larger proportion of those with small vessel occlusion (27.3 versus 18%). The explanation why the present study had more cases of small vessel disease could be because the presented patients were older, had better immune status and greater atherosclerotic risks.

Cardiac embolism in the presented patients was less (6.1 versus 18%). All were caused by atrial fibrillation, while in the previous study[7], cardioembolic strokes were due to cardiomyopathy, reduced left ventricular ejection fraction and intracardiac thrombi. This could be explained by the fact that cardiac diseases such as the afore-mentioned occur in the later stages of HIV infection.

The authors had a similar proportion of those with other determined etiology (27.3 versus 23%), with vasculitis (18.1 versus 13%) and hypercoagulability (6.1 versus 9%) being important causes of stroke. Most cases of cerebral vasculitis in the present study were caused by tuberculous infection, which is the leading opportunistic infection among AIDS patients in Thailand.

Stroke of undetermined etiology accounted for as much as one third of the present cases and nearly all were due to incomplete evaluation. This has been similarly observed by others[17,21]. Among the reasons for incomplete workup in the presented patients were included financial problems, being lost to follow-up, and death before the appointed date for further evaluation, which was often a long wait due to the large queue of patients in our government hospital.

Considering the use of antiretroviral medications in the present study, the authors found that a greater proportion of subjects were antiretroviral naive when compared with controls (51.4% versus 23%). However, there was no significant difference in immune status, as reflected by CD4 counts. Both groups used protease inhibitors in comparable proportions (27.8 versus 26.3%, p = 1.000) and there was no significant difference of hyperlipidemia (21.6 versus 33.8%, p = 0.186).

Concerning risk factors for stroke, the present study found that hypertension, diabetes mellitus and hyperlipidemia did not significantly increase the risk of stroke, similar to a previous study[22]. However, smoking contributed significantly to stroke in the present study, but it was not demonstrated in the same previous study.

The present study has several limitations. There is a chance of missing some HIV-positive stroke patients because the authors used diagnostic codes for screening subjects. Stroke patients with atypical presentations could have been left out of our study. In addition, the present subjects may not represent all HIV-infected stroke patients in Thailand because the authors conducted the present study in a single tertiary care hospital in Bangkok. Organisms causing stroke as a result of infectious vasculitis may vary according to region. Finally, data regarding functional status on discharge was not available in medical records. Thus, the authors could not determine the prognosis of stroke, as reflected by disability level, in the present HIV-infected stroke patients.

Despite limitations, the present study involved a systematic collection of information on HIV-infected stroke patients in a developing country. The strength of the present study is that the authors compared HIV-positive patients with and without stroke and were able to identify risk factors which predispose to cerebrovascular events in this immunocompromised population.

Clinical implications include aggressive modification of atherosclerotic risk factors, optimal treatment and prophylaxis, if indicated, of opportunistic infections of the central nervous system and use of more comprehensive diagnostic evaluations to determine the etiology of stroke. Future prospective cohort multicenter studies are needed to further determine the clinical presentations, risk factors, etiologies and prognosis of stroke in HIV-infected patients with more severe immunosuppression.

Table 1. Patient characteristics

	HIV		p-value
	Stroke (n = 37)	No stroke (n = 74)	
Demographics			
Female sex (%)	7/37 (18.9)	28/74 (37.8)	0.043
Age (years) Mean ± SD	50.5 ± 11.1	50.4 ± 13.4	0.686
Median (min, max)	50 (26, 81)	49 (19, 84)	-
Stroke subtype (n = 37)			
Ischemic (%)	33 (89.2)	NA	-
Hemorrhagic (%)	4 (10.8)	NA	-
TOAST classification (n = 33)			
Large artery atherosclerosis (%)	2/33 (6.1)	NA	-
Small vessel occlusion (lacune) (%)	9/33 (27.3)	NA	-
Cardioembolic (%)	2/33 (6.1)	NA	-
Other determined etiology (%)	9/33 (27.3)	NA	-
Undetermined etiology (%)	11/33 (33.2)	NA	-
Time from Dx HIV to stroke			
≤ 2 years (%)	25/37 (67.6)	NA	-
>2 to 5 years (%)	7/37 (18.9)	NA	-
>5 years (%)	5/37 (13.5)	NA	-
Stroke risk factors			
Hyperlipidemia (%)	8/37 (21.6)	25/74 (33.8)	0.186
Hypertension (%)	7/37 (18.9)	11/74 (14.9)	0.585
Diabetes mellitus (%)	2/37 (5.4)	3/74 (4.1)	1.000
Atrial fibrillation (%)	2/37 (5.4)	0/74 (0)	0.109
Percutaneous coronary intervention (%)	0/37 (0)	1/74 (1.4)	1.000
Smoked, ever (%)	14/37 (37.8)	6/74 (8.1)	<0.001
Hypercoagulable state (%)	1/37 (2.7)	0/74 (0)	0.333
Intravenous drug use (%)	4/37 (10.8)	3/74 (4.1)	0.219
Concurrent tuberculous meningitis (%)	4/37 (10.8)	1/74 (1.4)	0.042
Concurrent cryptococcal meningitis (%)	1/37 (2.7)	1/74 (1.4)	1.000
HIV disease parameters			
Mean CD4 count ± SD (cells/uL)	287 ± 18.8	31 ± 3255.8	0.944
CD4 < 200 cells/uL (%)	11/33 (33.3)	33/74 (44.6)	0.274
Previous diagnosis of HIV infection (%)	26/37 (70.3)	74/74 (100)	<0.001
Previous antiretroviral medication (%)	18/37 (48.6)	57/74 (77.0)	0.003
NRTI (%)	17/18 (94.4)	57/57 (100)	0.240
NNRTI (%)	14/18 (77.8)	41/57 (71.9)	0.765
PI (%)	5/18 (27.8)	15/57 (26.3)	1.000

NRTI = nucleoside reverse transcriptase inhibitors, NNRTI = non-nucleoside reverse transcriptase inhibitors, PI = protease inhibitors

Table 2. Factors associated with stroke in HIV-infected patients

Factors	HIV with stroke	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value
Female sex	7/37 (18.9%)	0.4 (0.1, 0.9)	NA	-
Prior antiretroviral use	18/75 (24%)	0.3 (0.1, 0.6)	NA	-
Tuberculous meningitis	4/5 (20%)	8.8 (0.9, 82.2)	11.9 (1.2, 117.2)	0.034
Smoked, ever	14/20 (70%)	6.9 (2.4, 20.0)	6.9 (2.3, 21.2)	0.001
CD4 count <200 cells/uL	11/44 (25%)	0.6 (0.3-1.5)	NA	-

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Potential conflicts of interest

None.

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สาเหตุและปัจจัยเสี่ยงต่อการเกิดโรคหลอดเลือดสมองของผู้ป่วยเอชไอวีในโรงพยาบาลศิริราช: การศึกษาแบบ case-control

ไบรอัน ลี, ถนอมศักดิ์ อเนกธนานนท์, นิพนธ์ พวงวรินทร์, ยงชัย นิละนนท์

ภูมิหลัง: *โรคหลอดเลือดสมองและการติดเชื้อเอชไอวีเป็นปัญหาสำคัญในประเทศไทย ปัจจุบันยังมีข้อมูลที่จำกัดเกี่ยวกับสาเหตุและปัจจัยเสี่ยงต่อการเกิดโรคหลอดเลือดสมองในผู้ป่วยเอชไอวีชาวไทย*

วัตถุประสงค์: *เพื่อศึกษาปัจจัยเสี่ยง ประเภท และกลไกการเกิดโรคหลอดเลือดสมองในผู้ป่วยเอชไอวี*

วัสดุและวิธีการ: *ทบทวนข้อมูลผู้ป่วยเอชไอวีที่เกิดโรคหลอดเลือดสมองเป็นครั้งแรกในโรงพยาบาลศิริราชระหว่างวันที่ 1 สิงหาคม พ.ศ. 2552 - 31 ธันวาคม พ.ศ. 2553 โดยจับคู่กับผู้ป่วยเอชไอวีในช่วงอายุเดียวกันที่ไม่เกิดโรคหลอดเลือดสมอง ในอัตราส่วน 2:1 เก็บข้อมูลสถิติเชิงประชากร ประเภทของโรคหลอดเลือดสมอง และข้อมูลที่เกี่ยวข้องกับการติดเชื้อเอชไอวี วิเคราะห์แบบ multiple logistic regression โดยถือค่า $p < 0.05$ มีนัยสำคัญทางสถิติ*

ผลการศึกษา: *มีผู้ป่วยเอชไอวีที่เกิดโรคหลอดเลือดสมอง 37 ราย เปรียบเทียบกับกลุ่ม control 74 ราย กลุ่มผู้ป่วยที่เกิดโรคหลอดเลือดสมองประกอบด้วยเพศชายร้อยละ 81.1 อายุเฉลี่ย 50.5 ปี พบโรคหลอดเลือด สมองประเภทหลอดเลือดสมองตีบ 33 ราย ประเภทหลอดเลือดสมองแตก 4 ราย ผู้ป่วยร้อยละ 70 เคยตรวจเลือด พบเชื้อเอชไอวี โดยค่าเฉลี่ยของเม็ดเลือดขาว CD4 คือ 287 เซลล์/ไมโครลิตร และจำนวนผู้ป่วยร้อยละ 33 มีค่า CD4 น้อยกว่า 200 เซลล์/ไมโครลิตร ผู้ป่วยร้อยละ 49 เคยได้รับการรักษาด้วยยาต้านไวรัสเอชไอวี กลไกการเกิดโรค หลอดเลือดสมองตาม TOAST classification ประกอบด้วยหลอดเลือดแดงใหญ่แข็ง 2 ราย (ร้อยละ 6.1) หลอดเลือด ฝอยตีบ 9 ราย (ร้อยละ 27.3) ลิ่มเลือดจากหัวใจ 2 ราย (ร้อยละ 6.1) สาเหตุอื่นๆ 9 ราย (ร้อยละ 27.3) (ประกอบด้วย การเซาะแยกตัวของผนังหลอดเลือดแดง vertebral (vertebral artery dissection) 1 ราย การขาดโปรตีน anti-thrombin III 1 ราย โรค thrombotic thrombocytopenic purpura 1 ราย โรคเยื่อหุ้มสมองอักเสบจากวัณโรค 4 ราย โรคเยื่อหุ้มสมองอักเสบจากเชื้อรา คริบโตค็อกคัส 1 ราย การฉีดเฮโรอีน เข้าหลอดเลือดดำ 1 ราย) และไม่ทราบสาเหตุ 11 ราย (ร้อยละ 33.2) (ประกอบด้วย ผู้ป่วยที่ได้รับการประเมินไม่ครบถ้วน 10 ราย และผู้ป่วยที่ตรวจครบถ้วนแล้วแต่ไม่พบสาเหตุ 1 ราย) ปัจจัยเสี่ยงโดย multivariate analysisได้แก่ การสูบบุหรี่ $p = 0.001$, adjusted OR 6.9 (95% CI 2.3, 21.1) และโรคเยื่อหุ้มสมองอักเสบจากวัณโรค $p = 0.034$, adjusted OR 11.9 (95% CI 1.2, 117.2).*

สรุป: *สาเหตุของการเกิดโรคหลอดเลือดสมองในผู้ป่วยเอชไอวีมีความหลากหลายมากเมื่อเปรียบเทียบกับผู้ป่วยที่ไม่มีภูมิคุ้มกันบกพร่อง การสูบบุหรี่และโรคเยื่อหุ้มสมองอักเสบจากวัณโรคมีความเกี่ยวข้องกับการเกิดโรคหลอดเลือดสมองในผู้ป่วยเอชไอวีชาวไทย ควรมีการศึกษาเพิ่มเติมแบบติดตามไปข้างหน้า ในจำนวนประชากรไทยที่มีจำนวนมากขึ้น และมีภูมิคุ้มกันที่ต่ำกว่านี้*