HIV infection and stroke

ผศ.นพ.ธนา ขอเจริญพร
สาขาวิชาโรคติดเชื้อ ภาควิชาอายุรศาสตร์
คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

Thana Khawcharoenporn, M.D., M.Sc.
Division of Infectious Diseases,
Department of Internal Medicine,
Faculty of Medicine, Thammasat University,
Pathumthani, Thailand

Corresponding Author:
Thana Khawcharoenporn, M.D., M.Sc.
Division of Infectious Diseases,
Department of Internal Medicine,
Faculty of Medicine, Thammasat University,
Pathumthani, Thailand.
E-mail: thanak30@yahoo.com

Abstract

The combined antiretroviral therapy (cART) and comprehensive care have prolonged lifespan of persons living with human immunodeficiency virus (HIV). Several diseases associated with aging including cardiovascular diseases, chronic kidney diseases, chronic liver diseases and malignancies have emerged as important comorbidities in this population. Stroke is one of the aging cerebrovascular diseases that may occur coincidentally with or occur as a result of HIV infection. Direct mechanisms of HIV-related stroke include chronic inflammation-associated atherosclerosis, hypercoagulability and vasculopathy while indirect mechanisms are HIV-related opportunistic infections, cART-related adverse reactions and cardioembolism. Presentations of stroke in persons with and without HIV infection are generally similar; however, data for stroke management in HIV-infected population are currently limited. Stroke management and prevention should include identification and treatment of the specific etiology of stroke and relevant risk factors along with cART. Here, the epidemiology, pathogenesis, risk factors, clinical presentations, and management of HIV-associated stroke are reviewed.
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Keywords: human immunodeficiency virus; stroke; epidemiology; mechanism; management

Introduction

The introduction of combined antiretroviral therapy (cART) since 1990s has changed the course of human immunodeficiency virus (HIV) infection from a deadly disease to a chronic disease. The annual acquired immune deficiency syndrome (AIDS)-related death rate (per 100 deaths) has declined significantly from 10.8 in 1996 to 0.9 in 2011 as well as the annual death rate of non-AIDS-related causes (2.1 in 1996 to 0.9 in 2011) in a US study.[1] The longer life expectancy among HIV-infected individuals leads to concurrent diseases that usually occur in aging population, including diabetes mellitus, hypertension, dyslipidemia, chronic kidney diseases and malignancies while accelerated atherosclerosis due to HIV-related chronic inflammation poses risks for cardiovascular and cerebrovascular diseases.[2] Stroke is one of the cerebrovascular diseases and has been a major public health problem worldwide. The incidence of stroke in middle-to-low income countries has doubly increased for the past 10 years and is probably related to several vascular risk factors, aging population and infectious diseases.[3,4] In HIV endemic settings, the occurrence of stroke and HIV infection is most-likely coincidental. Nonetheless, infection with HIV can potentially directly and indirectly affect stroke risk in different mechanisms.

Knowledge of the effect of HIV on the cause, clinical presentation and management of stroke is essential for healthcare workers caring a patient with HIV who has had a stroke. On the other hand, stroke should also be considered as a presenting feature of HIV infection in patients with unknown HIV status. In this article, epidemiology, pathogenesis, risk factors, clinical presentations, and management of HIV-associated stroke are reviewed.

Epidemiology

The incidence of HIV-associated stoke has not been clearly defined because several factors in a patient can affect stroke risk and it is difficult to tease out how much each factor contributes to the development of stroke. In reported clinical series, about 1-5% of HIV-infected patients had stroke, however, the rate increased to 4-34% when using additional autopsy evidence of cerebral ischemic lesions for diagnosis of stroke.[3] The numbers of patients with concurrent stroke and HIV infection have been increased by 43% over the period of 9 years in the US.[5]

In the pre-cART era, a retrospective hospital-based case-control study reported a double risk of stroke associated with HIV infection, especially for cerebral infarction.[3] A US population-based study demonstrated an adjusted relative risk of 13.7 for ischemic stroke and 25.5 for hemorrhagic stroke of AIDS.[6] However, the selection of patients with such advanced HIV infection and increased risk of stroke might have resulted in the high relative risks in this study.

In the post-cART era, there have been no studies prospectively assess the effect of HIV infection on stroke risk.[6] A retrospective study from Denmark reported an increased risk of cerebrovascular events among HIV-infected individuals with adjusted incidence rate ratio of 1.6[7] while another study from the US demonstrated that the number of HIV-infected patients admitted for stroke increased by 43%.[5] However, it was not possible to define how much of the increase in the number of stroke was due to an increase in the incidence of HIV infection, the effect of cART on stroke risk, an increased incidence of stroke in HIV-infected patients, improved survival of those with HIV, increased other atherosclerosis risks or better recognition of stroke symptoms.

There have also been studies reporting no association between HIV infection and stroke. An autopsy study from the US demonstrated no difference in rates of cerebrovascular disease between patients with and without AIDS.[8] A study from South Africa reported the similar prevalence of HIV (16%) between patients younger than 50 years who had stroke and general population of the same age.[9] In addition, another study from South Africa revealed a non-significant risk of ischemic stroke among HIV-infected patients.[10] However, all of these study findings may have limited generalizability given the selective criteria of the study populations.

Pathogenesis

HIV infection can directly and indirectly cause stroke via several mechanisms as summarized in *Table 1*. Effects of HIV on cardiovascular organs and coagulation are major direct causes of stroke while opportunistic infections, endocarditis and cardioembolism are the major indirect causes.

Pathogenesis of ischemic stroke

HIV-associated vasculopathy

Any abnormalities of the intracranial or extracranial cerebral blood vessels that are directly or indirectly caused by HIV, excluding those associated with opportunistic infections or malignancies could be defined as HIV-associated vasculopathy.[3] The abnormalities

Table 1 Possible causes of human immunodeficiency virus (HIV) infection-related stroke

Type of stroke	Direct effect of HIV	Indirect effect of HIV

Ischemic	• HIV-associated aneurysm formation
	• HIV-associated vasculitis
	• Accelerated atherosclerosis
	• HIV-associated cardiomyopathy with cardioembolism
	• HIV-associated hypercoagulability
		• Opportunistic infections causing stroke
		  • Tuberculous meningitis
		  • Varicella zoster virus-associated vasculitis
		  • Meningovascular syphilis
		  • Cryptococcal meningitis
		  • Cytomegalovirus-associated vasculitis
		• Immune reconstitution inflammatory syndrome of opportunistic infections causing stroke
		• HIV-associated lymphoma causing stroke
		• Bacterial endocarditis with cardioembolism
		• Marantic endocarditis with cardioembolism
		• Antiphospholipid syndrome
		• Antiretroviral drug-associated stroke

Hemorrhagic	• HIV-associated aneurysm formation • HIV-associated vasculitis • HIV-associated thrombocytopenia	• Mycotic aneurysm secondary to bacterial endocarditis

include aneurysmal dilatation, vascular stenosis and/or occlusion and vasculitis. The aneurysmal dilatation in HIV-infected patients can be extracranial, involving the carotid, aorta, iliac, and other large arteries or intracranial, involving branches of the circle of Willis. The aneurysmal vasculopathy may be associated with leukoclastic vasculitis without evidence of atherosclerosis

or infection in the bloodstream or the aneurysm wall.[11,12] Vasculitis is defined as the histologically-confirmed inflammatory cells in the blood vessel wall together with associated wall damage. Direct HIV infection has been postulated as the pathogenesis of vasculitis given the identification of HIV antigen and particles in the perivascular tissue in some patients[12,13], while immune

deposition and indirect damage caused by T–cell derived growth factors and cytokines have been other suggested mechanisms.[12] Acceleration of atherosclerosis is another important mechanism causing stroke. This process could be facilitated by several risk factors including direct effect of HIV, such as low grade chronic systemic inflammation and indirect effect of HIV, such as cART and associated metabolic complications and HIV–associated opportunistic infections.[14,15]

Pathogenesis of HIV-associated atherosclerosis begins with endothelial dysfunction. The virus can induce production of various types of proinflammatory cytokines responsible for endothelial damage and increased vascular permeability. This allows for leukocyte recruitment and invasion and subsequent vascular inflammation.[16] With continuing inflammatory cell activation, the vascular damage leads to propagation of atherogenesis resulting in atherosclerosis. Further, the process is accompanied by platelet adhesion and aggregation, blood clotting activation and fibrinolysis derangement. The final results are vascular diseases, stenosis and occlusive thrombotic events which cause stroke.[17,18] The higher level of inflammatory markers including high–sensitive C–reactive protein (hs-CRP), interleukin–6 (IL-6) and cystatin in HIV–infected patients than those in non–HIV–infected controls suggests chronic ongoing inflammation as one of the responsible mechanisms of HIV–associated stroke.[19-22] In addition, the derangement of endothelial cell molecules involving in coagulation, such as von Willebrand factor, thrombomodulin, plasminogen activator inhibitor-1 antigen, tissue factor, and d-dimer leads to prothrombotic state among patients with HIV.[21,22]

Cardiomyopathy

HIV can cause myocarditis with subsequent development of dilated cardiomyopathy. The enlarged cardiac chambers, especially the left atrium pose risk for turbulence flow and clotting formation which lead to the occurrence of embolic stroke.[23] Cardiomyopathy can be a result of other viral myocarditis, such as coxsackieviruses, Epstein barr virus and cytomegalovirus and other opportunistic pathogens including *Toxoplasma gondii, Cryptococcus neoformans, Histoplasma capsulatum, Mycobacteria tuberculosis* and *Mycobacterium Avium* Complex. In addition, zidovudine use has been reported to be associated with cardiomyopathy.

Hypercoagulable state

HIV infection may pose a risk for both arterial and venous thrombosis. The underlying mechanisms for hypercoagulable state involve inflammation–mediated up–regulating procoagulants and suppressing fibrinolysis, local activation of tissue factor, HIV–mediated injury and dysfunction of endothelial surfaces, alteration of composition of coagulation factors, such as protein C or protein S deficiency, platelet activation and co–existing antiphospholipid syndrome.[3,24]

Opportunistic infections

Several opportunistic infections have been reported to cause stroke among HIV–infected patients. The first presentation of these opportunistic infections may be a focal neurological deficit mimicking stroke. Therefore, active searching for these infections is necessary in patients who have had stroke, especially those with advance immune suppression. Cerebrovascular complications of tuberculous meningitis are not uncommon and may be serious. About 20% of patients with tuberculous meningitis develop a focal neurological deficit.[25] The most common vascular pathological findings include infiltrative, proliferative and necrotizing processes, either in isolated or combination form. Varicella zoster virus may cause cerebral vasculitis and stroke mostly in patients with advanced HIV disease. Given the same route of transmission, syphilis is one of the most common sexually–transmitted diseases co–infecting with HIV. Central nervous system infection due to syphilis can occur as the first presentation without preceding primary or secondary state of the infection in those with low CD4 count. Meningovascular complications causing stroke have been increasingly described in HIV–infected patients.[26] Central nervous system cryptococcosis is one of the common opportunistic

infections among HIV-infected individuals. However, cerebral infarction due to cryptococcosis is uncommon. Histopathological evidence indicates a dense perivascular infiltrate suggesting vasculitis as an underlying mechanism for cryptococcosis-related stroke.[27] Other uncommon opportuinistic infections that cause stroke include cytomegalovirus infection and candidiasis.[3] Among HIV-infected patients who develops stroke or worsening stroke signs and symptoms after initiation of cART, unmasking immune reconstitution inflammatory syndrome (IRIS) due to occult cerebrovascular opportunistic infections should be in differential diagnoses. The unmasking IRIS is the condition that the improved immune function after cART attacks opportunistic pathogens, which have never been attacked because of the poor immune function before cART and causes significant inflammation to the organ systems where the pathogens infect.

Cardioembolism and endocarditis

About 4-15% of ischemic strokes in HIV-infected individuals are caused by cardioembolism.[9,28,29] While HIV-associated dilated cardiomyopathy has been frequently reported as a cause of cardioembolism, this condition can be a result of cardiomyopathy occurring after opportunistic infections, zidovudine use and elicited drug abuse. Non-bacterial thrombotic endocarditis occurs in about 3-5% of AIDS patients and commonly affects the left-side valves. The causative pathogens causing infective endocarditis are similar to those in general population except for the higher prevalence of *Staphylococcus aureus* among injecting drug HIV-infected drug users and opportunistic pathogens, such as candida, cryptococcus and aspergillus which usually infect the ride-sided valves. Both non-infective and infective endocarditis pose a significant risk for development of ischemic stroke.

Antiretroviral therapy

Combined antiretroviral therapy can directly cause tissue injury to arteries while metabolic complications, such as dyslipidemia and insulin resistance indirectly cause endothelial dysfunction.[30] However, it is uncertain how significant these mechanisms contribute to stroke among HIV-infected individuals. Long-term cART exposure has been shown to be associated with endothelial toxicity, vascular dysfunction and increased atherosclerotic risk[31-33], while short-term of cART may be associated with reduced risk of ischemic stroke and transient ischemic attack (TIA).[32] Non-nucleoside reverse transcriptase inhibitors and protease inhibitors may cause inflammation and increase cardiovascular risk. However, the evidence to support cerebrovascular risk specific to these drug classes is limited. Issues on abacavir-associated increased cardiovascular risk are unresolved despite that a meta-analysis does not support this increased risk due to abacavir.[34] There is need for more research to specifically assess the risk of abacavir on cerebrovascular events.

Pathogenesis of hemorrhagic stroke

Direct causes of HIV-associated hemorrhagic stroke include bleeding aneurysmal and vasculitic vasculopathy and HIV-associated thrombocytopenia while mycotic aneurysm secondary to bacterial endocarditis could be the indirect cause of hemorrhagic stroke among HIV-infected individuals.[3,6]

Risk Factors

Traditional risk factors for stroke are similar between HIV-infected individuals and general population (*Table 2*).[35-43] The major treatable atherosclerotic risk factors for stroke are hypertension, diabetes mellitus, tobacco smoking and dyslipidemia while the important but non-modifiable risk factors for stroke include age, ethnicity, sex, family history, and genetics. The risk of stroke is particularly increased in individuals with two or more risk factors based on the calculation derived from the Framingham Study.[44] In addition to these traditional risks, specific risk factors for stroke among HIV-infected individuals include a previous history of AIDS, being on cART for a longer duration and tuberculous meningitis.[32,45]

Table 2 Risk factors associated with stroke for general and HIV-infected populations

Type of population	Modifiable risk factor	Non-modifiable risk factor
General and HIV-infected populations	• Hypertension • Diabetes mellitus • Tobacco smoking • Dyslipidemia • Heavy alcoholic drinking • Cocaine abuse • Cardiac diseases (atrial fibrillation, history of myocardial infarction, left ventricular dysfunction, valvular diseases) • Hypercoagulability state • Obesity • Low physical activity • Obstructive sleep apnea	• Older age (particularly age more than 80 years) • Black race • Male sex (except for ages 35-44 years and more than 85 years) • Family history of stroke
HIV-infected population	• Tuberculous meningitis	• A previous diagnosis of acquired immune deficiency syndrome • Longer duration of combined antiretroviral therapy

Clinical Presentations

Stroke has been reported to occur at younger age among HIV-infected individuals compared to general population which could be due to the age of the population at risk of HIV infection or the HIV-associated accelerated atherosclerosis and other mechanisms independent of traditional stroke risk factors.[3] Patients with HIV-associated stroke in lower-income countries were reported to have stroke at younger age than those in high-income countries (median age of 33.4 years vs. 48.4 years).[5,46] Possible explanation may be the better cART access in high-income countries and the effect of cART in delaying the time to stroke onset.

Clinical presentations of stroke are similar between patients with and without HIV infection. While a sudden onset of a focal neurological deficit is typical for both groups, atypical presentations including acute confusion, fever, and stepwise focal neurological presentation over hours to days may be more common in HIV-infected patients.[47-49] The atypical presentations could be due to various direct and indirect mechanisms caused by HIV or other co-existing central nervous system infections and diseases. Thus, it is important to exclude alternative causes and mimics of stroke prior to making a final diagnosis of HIV-associated stroke. Common stroke mimics in people with HIV include toxoplasmosis, primary central nervous system lymphoma, neurocysticercosis, tuberculoma, brain abscess and brain tumors.

Ischemic stroke has been reported to be the predominant pathological type among HIV-infected patients in both low- and high-income countries.[5,28] A hospital-based study from South Africa demonstrated that partial anterior circulation stroke was more frequent but posterior circulation stroke was less frequent in HIV-infected patients than those in the original Oxfordshire Community Stroke Project.[46,50]

Management

The components of stroke management in HIV-infected patients include acute stroke management, establishing the cause of stroke and treatment, management of HIV infection and secondary prevention of stroke.[51] After initial assessment and diagnosis of stroke, a patient's airway, breathing, and circulation should be stabilized. Intubation may be necessary to restore adequate ventilation and to protect the airway from aspiration. In general population, determining if the patient is a candidate for thrombolytic therapy is an important next step and should be based on the time of ischemic stroke symptom onset (less than 4.5 hours from symptom onset) and contraindications to thrombolytic treatment.[51] However, the role of intravenous thrombolysis is uncertain in HIV-related stroke given the absence of randomized controlled studies that assess both benefit and risk of the therapy. The pathogenesis of the stroke can be HIV-associated vasculopathy, vasculitis and other causes that may increase risk of bleeding. Until more data on the role of thrombolysis therapy in HIV-related stroke become available, the use of thrombolytic agents should be judged on an individual basis.

Establishing the cause of stroke should begin with history taking and physical examination. These should include assessment of traditional vascular risk factors and HIV-related risk factors *(Table 2)*. Computed tomography of the brain should be initially performed to establish type of stroke and exclude other stroke mimic conditions.[51] Investigations for a patient's immune status and opportunistic infections include CD4 cell count, syphilis serology and lumbar puncture (if no contraindication and no clear evidence of an alternative cause) for cerebrospinal fluid gram stain, culture, acid-fast bacilli, mycobacterial culture, polymerase chain reaction for mycobacteria and varicella zoster virus, syphilis serology, and cryptococcal antigen. Additional magnetic resonance imaging of the brain may be indicated in cases suspected of vasculitis or vascular abnormalities. Blood cultures should be performed if infective endocarditis is possible while coagulation screening is appropriate if hemorrhagic stroke is present or antiphospholipid syndrome is

suspected. Other additional tests that may be required for ischemic stroke patients included electrocardiogram, bubble-contrast echocardiogram and carotid Doppler to rule out thromboembolic stroke.[51]

Management of HIV infection is composed of screening and treatment of opportunistic infections and initiation of cART. All opportunistic infections should be treated prior to cART initiation. Delayed cART is necessary for co-existing tuberculosis and cryptococcosis because of the burden associated with IRIS.[52] Among HIV-infected individual without opportunistic infections, the guidelines of World Health Organization recommend initiating cART when an HIV-infected patient's CD4 count has decreased to equal or less than 500 cells/µl[53] while Thai national guidelines recommend starting cART at any CD4 count level.[54] However, the most important criteria for cART initiation is a patient's commitment and readiness to be on cART. Given the outweighed benefits of long-term cART on all-cause mortality reduction over the increased risk of stroke,[55,56] cART is still the mainstay treatment for HIV-infected individuals. However, management of other stroke risk factors is critical along with cART.

There have been no studies that assess secondary prevention for stroke among HIV-infected individuals. However, several strategies used in non-HIV-infected patients may be applied for use in HIV-infected patients. These strategies target treatable and modifiable vascular risk factors and currently include blood pressure reduction, statin therapy, screening for and treating diabetes mellitus, antithrombotic therapy, and lifestyle modification.[57] Antihypertensive therapy is recommended for patients with any type of ischemic stroke or TIA who have an established systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. For patients with TIA or ischemic stroke of atherosclerotic origin who are able to tolerate statins, high-intensity statin therapy, independent of the baseline low-density lipoprotein cholesterol is recommended to reduce the risk of stroke.[58] Patients with a history of non-cardioembolic ischemic stroke or TIA should be treated with an antiplatelet agent including aspirin (50

to 100 mg daily), clopidogrel (75 mg daily), or the combination of aspirin and extended-release dipyridamole (25 mg/200 mg twice a day). Long-term anticoagulation with warfarin, dabigatran, apixaban, or rivaroxaban should be considered as prevention for patients with chronic non-valvular atrial fibrillation who have had an ischemic stroke or TIA. However, careful consideration of the risk of bleeding to benefit ratio is necessary in those at relatively low risk. Important lifestyle modifications for secondary stroke prevention include weight control, salt restriction, smoking cessation, a diet rich in fruits, vegetables, and low-fat dairy products, regular aerobic physical activity, and limited alcohol consumption.[57]

Specific recommended interventions for patients with acute hemorrhagic stroke include discontinuation of all anticoagulant and antiplatelet drugs, and immediate reversal of anticoagulant effects with the appropriate agents, maintenance of normothermia and evaluation and treatment of fever source, initial use of normal saline as maintenance and replacement fluid, initial management of elevated intracranial pressure by elevating the head of the bed to 30 degrees and use of analgesia and sedation, monitoring and treatment of elevated intracranial pressure, blood pressure control to keep target mean arterial pressure of 110 mmHg or blood pressure of 160/90 mmHg using intermittent or continuous intravenous medications and surgical interventions in patients who have brainstem compression and/or hydrocephalus due to ventricular obstruction.[59] Specific medical and/or surgical treatment should be provided for HIV-infected patients with hemorrhagic stroke according to causes of bleeding including aneurysmal bleeding, HIV-associated vasculitis and HIV-associated thrombocytopenia.

Conclusions

Epidemiology data on burden, stroke types and subtypes, pathogenesis and risk factors of HIV-related stroke are currently limited in both high-income and low-income countries. Direct effects of HIV on endothelial function and accelerated atherosclerosis and opportunistic infections have been described as additional pathogenesis mechanisms of stroke in HIV-infected individuals. Careful history taking and physical examination, appropriate laboratory, and radiological investigations are essential for initial assessment of HIV-related stroke to establish the cause of stroke, coexisting opportunistic infections that may be associated with stroke and excluding stroke mimic conditions. Further studies are needed to assess optimal management for stroke in HIV-infected individuals, including long-term risk-benefit ratio of cART and strategies for primary and secondary stroke prevention.

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บทคัดย่อ

การรักษาด้วยยาต้านไวรัสหลายตัวที่มีประสิทธิภาพสูงและการดูแลรักษาแบบองค์รวมทำให้ผู้ติดเชื้อเอชไอวีใน
ปัจจุบันมีอายุยืนยาวขึ้น โรคหลายชนิดซึ่งพบมากในกลุ่มประชากรสูงอายุได้แก่ โรคที่เกี่ยวข้องกับระบบหัวใจและหลอดเลือด
โรคไตเรื้อรัง โรคตับเรื้อรัง และโรคมะเร็งจึงเริ่มพบมากขึ้นในกลุ่มผู้ติดเชื้อเอชไอวี

โรคหลอดเลือดในสมองอุดตันหรือแตกอย่างเฉียบพลันเป็นโรคหนึ่งที่พบมากขึ้นในประชากรสูงอายุและอาจเกิดขึ้น
ควบคู่กับหรือเป็นผลมากจากการติดเชื้อเอชไอวี กลไกของการเกิดโรคหลอดเลือดในสมองอุดตันหรือแตกอย่างเฉียบพลันที่
เกิดจากเชื้อเอชไอวีโดยตรงได้แก่ ภาวะหลอดเลือดแดงแข็งที่เกี่ยวข้องกับกระบวนการอักเสบเรื้อรัง ภาวะการแข็งตัวของ
เลือดง่ายกว่าปกติ และความผิดปกติของหลอดเลือด ในขณะที่กลไกที่เกิดจากเชื้อเอชไอวีทางอ้อมได้แก่ โรคติดเชื้อฉวย
โอกาสที่เกี่ยวข้องกับโรคติดเชื้อเอชไอวี ผลข้างเคียงของยาต้านไวรัส และลิ่มเลือดจากหัวใจจากสาเหตุต่างๆ อาการและ
อาการแสดงของโรคหลอดเลือดในสมองอุดตันหรือแตกอย่างเฉียบพลันนั้นเหมือนกับอาการและอาการแสดงในประชากร
ทั่วไป อย่างไรก็ตาม ข้อมูลที่เกี่ยวข้องกับการรักษาโรคนี้ในผู้ติดเชื้อเอชไอวียังมีจำกัด หลักการรักษาและป้องกันโรคหลอด
เลือดในสมองอุดตันหรือแตกอย่างเฉียบพลันที่สำคัญนั้นประกอบด้วยการระบุสาเหตุของการเกิดโรค และการให้รักษาตาม
สาเหตุ และลดปัจจัยเสี่ยงของการเกิดโรคควบคู่ไปกับการรักษาด้วยยาต้านไวรัสในผู้ที่ติดเชื้อเอชไอวี บทความนี้ได้ทบทวน
ถึงระบาดวิทยา พยาธิกำเนิด ปัจจัยเสี่ยงต่อการเกิดโรค อาการและอาการแสดง และการรักษาโรคหลอดเลือดในสมองอุดตัน
หรือแตกอย่างเฉียบพลันที่เกี่ยวข้องกับการติดเชื้อเอชไอวี

คำสำคัญ: เชื้อเอชไอวี; โรคหลอดเลือดในสมองอุดตันหรือแตกอย่างเฉียบพลัน; ระบาดวิทยา; กลไก; การรักษา