

THROMBOSIS DISORDER IN ELDERLY PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION: A LITERATURE REVIEW

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DOI: <https://doi.org/10.33508/jwmj.v6i4.6018>

ABSTRACT

Thrombosis disorder in elderly patients with HIV infection is a chronic disorder that is interesting to discuss because of its multifaceted impact. Elderly patients with HIV infection face a dual risk from aging and HIV effects, which can exacerbate coagulation disorders. Thrombosis can lead to severe complications, especially in cardiovascular issues, significantly increasing morbidity and mortality. The pathophysiology of thrombosis disorder in HIV patients involves vascular, immune, and liver synthesis function problems, resulting in increased thrombogenesis. Clinical manifestations include deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarct. Management is complex due to difficulties in diagnosis and increased therapeutic burden. Therapies involve using rosuvastatin and low-dose aspirin in managing inflammation and thrombosis. This article outlines the prevalence, pathophysiology, clinical manifestations, and management of thrombosis disorder in elderly patients with HIV infection.

Keywords: HIV, thrombosis, elderly, inflammation, aging

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INTRODUCTION

Thrombosis disorder prevalence in elderly patients with HIV (*Human Immunodeficiency Virus*) has not been widely documented in large-scale epidemiological studies, but early findings suggest a significant association between the two conditions, and the increasing elderly population makes it increasingly relevant and important to discuss further. For instance, a study by Rasmussen, *et al.* (2014) showed that HIV infection is related to the incidence of spontaneous bleeding and blood clotting disorder also known as thrombosis.¹ In the elderly population, the prevalence of thrombotic disorders increases with age due to physiological changes in the blood coagulation system, followed by increased comorbidities such as cardiovascular and cerebrovascular diseases.² A study by Heit, *et al.* (2016) showed that venous thromboembolism conditions increase with age.³

Currently, patients with HIV infection are living longer due to increasingly effective Antiretroviral therapy (ART), so that the elderly population with HIV infection is increasing. According to a report from the Ministry of Health, patients with HIV infection in 2022 in Indonesia who are over or equal to 50 years old are 9.3% with the majority being men. This number has increased from 2013 with the number of

elderly reported with AIDS (Acquired Immunodeficiency Syndrome) which is 6.5%.⁴ As this population ages, the prevalence of thrombotic disorders in older adults with HIV infection is expected to increase.

The impact of thrombotic disorders in elderly patients with HIV infection is multifaceted. Elderly HIV patients face dual risks from the effects of aging and HIV infection, both of which can worsen thrombotic disorders. Thrombosis disorders can cause severe complications, especially cardiovascular problems, which will significantly increase morbidity and mortality.⁵ Thrombosis disorders themselves can also accelerate the aging process in HIV patients, placing patients in a more rapid decline in physiological body function and increasing the risk of death. According to a comprehensive report by the Indonesian Ministry of Health, the AIDS mortality rate in Indonesia is around 0.87% in the period January - December 2022. This figure even increased from the 2020 period which was 0.59%.⁴

Management of thrombotic disorders in elderly with HIV infection is complex due to the high difficulty in diagnosis and the increased burden of therapy. Establishing a diagnosis of thrombotic disorders is difficult because of overlapping symptoms with other age-related

conditions, and side effects of ART and standard coagulation physiology tests that are not always accurate due to the complex pathophysiology of thrombotic disorders associated with HIV infection.⁵ The burden of HIV therapy in the elderly increases due to the additional need to balance thrombosis therapy with the risk of bleeding and its potential interaction with ART. In addition, the stigma associated with HIV among the elderly also makes them reluctant to disclose the infection to family and friends, which affects treatment efforts and patient quality of life.⁴

Therefore, this literature review aims to explain thrombosis disorders in elderly HIV-infected patients, with a focus on the pathophysiology, clinical manifestations, supporting examinations, and specific therapies for thrombosis disorders and HIV in the elderly.

HIV INFECTION IN THE ELDERLY

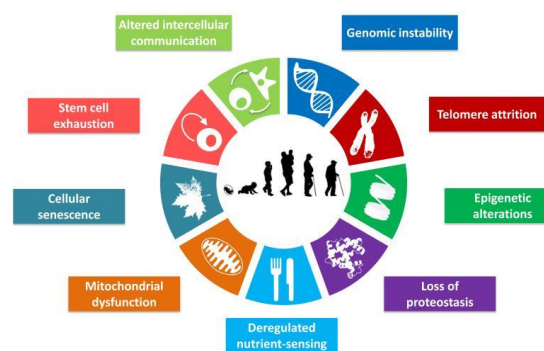
The demographics of the HIV patient population, especially the elderly, have continued to change in recent years. Statistically, patients aged 50 or older are considered to be the elderly group. As many as 10% of HIV sufferers in the world are now over 50 years old. Meanwhile, in the United States, 50% of people with HIV and AIDS are over 50 years old and it is even estimated that this number will increase to 70% by 2030. This change may be due to

the effectiveness of ART treatment and accurate early diagnosis, which increases the survival rate of people with HIV and AIDS.⁶

AGING AND THROMBOSIS DISORDER IN HIV INFECTION

The aging process in elderly people infected with HIV is based on several mechanisms, namely changes in intercellular communication, genome damage, telomere shortening, epigenetic changes, abnormal proteostasis, changes in nutrient sensing, mitochondrial dysfunction, and cellular aging (Figure 1.). All of these processes lead patients to fall into a state of aging, which is defined as a condition of loss of physiological body function and increasing the risk of death.²

Figure 1. *Hallmarks of Aging.*²



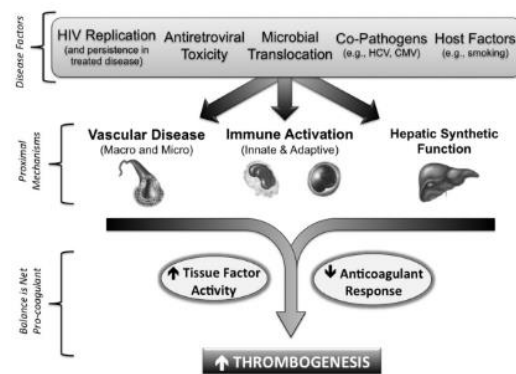
One of the mechanisms of aging is the change in intercellular communication characterized by patients being in a chronic inflammatory condition so that there is a decrease in immune regulation. In the elderly without HIV infection, there is a process called "Inflammaging", a

phenomenon in which there is an increase in the level of pro-inflammatory cytokines in the body with age. This phenomenon is involved in the pathogenesis of aging disease conditions such as obesity, type 2 Diabetes Mellitus (DM), and atherosclerosis, and affects the function of various tissues and organs, including stem cells. Damage to stem cells has an impact on decreased tissue regeneration and repair, increased pro-inflammatory cytokines that cause aging, and genetic damage to the stem cells themselves.²

In HIV patients, this aging condition is accelerated or aggravated by inflammation and/or thrombosis effects. Thrombosis disorders in HIV infection occur due to several processes, namely vascular, immune, and liver synthesis function problems. The vascular process is based on the occurrence of thrombosis in the micro and macrovascular; the immune process is based on the loss of T cell regulatory function; and the last is a disorder in the synthesis and regulation of coagulation factors by the liver. These three processes then induce thrombogenesis due to increased tissue factor activity and decreased anticoagulant response.⁷ The course of this process is influenced or induced by factors, one of which is the amount of virus replication. High levels of the virus in the body trigger an inflammatory response (in the form of a

non-specific immune response such as due to infection) and a hypercoagulable state. Other factors are ART toxicity, microbial translocation in organs, opportunistic infections, and patient behavioral factors.⁸ This process is explained in Figure 2.

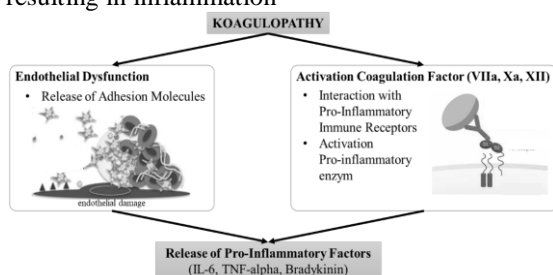
Figure 2. Pathogenesis of coagulation disorders in HIV patients



Thrombosis disorders cause patients to fall into chronic inflammation through several mechanisms (Figure 3). Increased thrombogenesis can cause dysfunction of the surrounding endothelium. Damaged endothelium can activate the inflammatory response by releasing adhesion molecules and pro-inflammatory factors (such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha)), then inducing an inflammatory reaction. In addition to causing thrombus formation that can damage the endothelium, activation of the coagulation system also produces clotting products that have pro-inflammatory properties. For example, factor VIIa and factor Xa, can interact with receptors on immune cells such as Toll-like Receptors

(TLRs), Protease-Activated Receptors (PARs), which then stimulate the immune system to produce inflammatory mediators.⁹ Another influencing factor is factor XII which can activate the serine protease enzyme, kallikrein, which can then trigger the release of inflammatory mediator peptides, namely bradykinin.¹⁰

Figure 3. Pathogenesis of thrombosis disorders resulting in inflammation



Chronic inflammatory conditions affect various biological processes associated with aging such as impaired organ function (heart, bones, and skin), decreased immune system function, increasing susceptibility to infection and disease, and disruption of aging hormones (such as Gonadotrophin Releasing Hormone).² This is also in line with the findings of coagulation biomarkers, namely D-Dimer, which are associated with the occurrence of venous thromboembolism and cardiovascular disease in HIV infection.⁵ The aging process that occurs in the elderly with HIV infection has an impact on the organs of the body as shown in Table 1.

Table 1. Impact of the Aging Process on Organs

Organ	Conditions Related to Aging
Heart	Cardiovascular diseases such as heart attacks and strokes
Bone	Osteoporosis and the risk of fractures
Kidney	Chronic kidney disease
Nervous System	HIV-associated neurocognitive disorder (HAND)
Liver	Liver damage, cirrhosis, and hepatoma
Skin	Skin aging due to epidermal stem cell dysfunction
Metabolism	Metabolic syndrome (insulin resistance, hypertension, dyslipidaemia)

Antiretroviral therapy (ART) significantly reduces viral replication, immune activation, and coagulation biomarkers in elderly HIV-infected patients. However, despite the reduction, these biomarker levels often do not return to normal, even after several years of therapy. ART reduces immune activation and coagulation biomarkers through several mechanisms, namely reducing viral load, inhibiting inflammation, and improving endothelial dysfunction.¹¹

ART can reduce the amount of virus in the blood, thereby reducing chronic stimulation of the immune system. ART works by targeting various stages of the HIV life cycle, preventing the virus from replicating and spreading to other cells. Examples of ART such as protease inhibitors prevent the virus from cutting the long polyprotein chains produced during replication into functional proteins, thus

inhibiting the maturation of the virus particle and the virus becomes non-infectious.¹² Nucleoside reverse transcriptase inhibitors inhibit the reverse transcriptase enzyme used by HIV to convert viral RNA into proviral DNA that can be integrated into the host cell genome.¹³ Thus, ART reduces the viral load thereby reducing the ongoing activation of immune cells that can trigger inflammation and coagulation.

ART reduces the production of pro-inflammatory cytokines triggered by HIV viral replication. These cytokines, such as IL-6 and TNF- α , can promote coagulation by activating endothelial cells and monocytes to express tissue factor (TF), which is a major initiator of the extrinsic coagulation pathway.^{14,15}

ART reduces endothelial cell damage that often occurs with HIV infection. Endothelial dysfunction contributes to the pro-coagulant state by increasing the expression of adhesion molecules such as ICAM and VCAM, and markers of endothelial damage such as von Willebrand factor (vWf).¹⁶

HIV causes damage to the intestinal lining, allowing microbial products such as lipopolysaccharide (LPS) to enter the bloodstream, which in turn induces inflammation and coagulation. ART can help restore the integrity of the intestinal mucosa, reduce microbial translocation,

and thereby reduce inflammation and the risk of coagulation.¹⁷

CLINICAL MANIFESTATION OF THROMBOSIS DISORDER IN ELDERLY PATIENTS WITH HIV INFECTION

Elderly people with HIV infection are known to have a more significant decline in clinical conditions compared to elderly people without HIV infection, such as an earlier decline in muscle mass, reduced body weight, decreased physical strength, energy and activity.¹⁸ The use of ART is also said to change fat distribution in HIV patients, causing metabolic abnormalities that manifest in physical changes in patients.¹⁹ Other clinical manifestations may be related to the patient's worsening comorbid conditions such as dementia.¹⁸

Thrombosis disorders in the elderly with HIV infection have several disease manifestations such as DVT (deep vein thrombosis) and pulmonary embolism with clinical manifestations in the form of pain and swelling in the legs, chest pain, coughing up blood, shortness of breath and signs of respiratory failure.²⁰; ischemic stroke with clinical manifestations of sudden weakness or numbness on one side of the body, confusion, difficulty speaking, or visual disturbances; and myocardial infarction with manifestations of chest pain, shortness of breath, cold sweats, to

syncope. Overall, there is not much difference in the clinical manifestations of thrombosis disorders in the elderly with HIV infection compared to others, with the note that the clinical manifestations of the disease in the elderly are not always clear or full-blown.²¹

In the HIV patient population, clinical symptoms may vary depending on age group. HIV patients under the age of 50 years often present with a variety of HIV marker conditions, including dermatological, neurological, and gastroenterological disorders. Sexually transmitted infections, such as latent syphilis and herpes simplex virus infection, are also common in this group. On the other hand, in elderly HIV-infected patients the dominant clinical symptoms include a high prevalence of AIDS-defining diseases, such as *Pneumocystis jirovecii* pneumonia (PCP) and tuberculosis infection. Although the proportion of HIV marker conditions at diagnosis does not differ significantly between age groups, older adults tend to experience more age-related complications, including neurocognitive disorders such as HIV-associated neurocognitive disorders (HAND), cerebro-cardio-vascular problems, and bone problems such as osteoporosis. In addition, older adults with HIV infection often have significant oral health problems, requiring a holistic care approach that takes into account their

medical complexity and improves their overall quality of life.²²

APPROACH TO MANAGEMENT OF THROMBOSIS DISORDERS IN ELDERLY PATIENTS WITH HIV INFECTION

Current studies are investigating several strategies to reduce inflammation and/or thrombotic disorders in the elderly population infected with HIV. Fuderburg, et al (2014) conducted a study using rosuvastatin 10-20 mg/day because it has the potential to reduce markers of monocyte activation, which are associated with inflammation and cardiovascular disease risk in HIV-infected individuals. This study showed that the use of rosuvastatin in HIV infection can reduce markers of monocyte activation (soluble Tumor Necrosis Factor Receptor II (sTNFR-II)) and improve endothelial function, which has the potential to reduce the risk of cardiovascular disease and inflammation.²³

Research from O'Brien, et al (2013) used aspirin as an antiplatelet and anti-inflammatory in HIV infection. The aspirin used was a low dose, starting with a dose of 360 mg followed by a continuation dose of 80 mg/day. This study showed that the use of low-dose aspirin in HIV infection that had received ART with virological suppression caused a decrease in platelet activity, a decrease in the level of T cell and

monocyte activation, and an increase in leukocyte response to certain TLR agonist stimulation.²⁴

The management of specific coagulation disorders in the elderly HIV population is no different from other populations, where the management is adjusted to the actual clinical and supporting conditions of each patient or individual. For example, giving anticoagulants to patients with a tendency to thrombosis or giving coagulation factor transfusions to patients with a tendency to bleeding.²⁴

Other Therapies

Treatment of comorbid diseases is important considering that comorbid diseases in the elderly are a major factor in causing death compared to HIV infection itself. Therefore, management of comorbid diseases must be prioritized, especially cardiovascular, liver, kidney, bone, and nervous system diseases.²⁵

Challenges

The challenges of managing HIV infection in the elderly are related to the low level of education about HIV infection in the elderly. This increases the possibility of HIV transmission, decreased adherence to ART, and retention in care. Several studies have shown that the first year of ART treatment is associated with a higher risk of non-adherence and drug discontinuation. Another challenge is the CD4+ T

lymphocyte response to ART combinations which tends to decrease in the elderly.²⁵

CONCLUSION

Thrombosis disorders in elderly with HIV infection are chronic disorders that can lead to serious complications such as venous thromboembolism and cerebro-cardio-vascular disease. Clinical manifestations can vary from DVT to ischemic stroke, with basic management of complex coagulation disorders related to ART interactions and the risk of further bleeding or thrombosis. Appropriate management approaches include treatment of comorbid conditions and anti-inflammatory and anticoagulant strategies tailored to each patient's condition.

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