CRITICAL LIMB ISCHEMIA IN 27 YEARS OLD HIV PATIENT:
A CASE REPORT

Ade Yonata\(^1,2\), Hayatun Nufus\(^1\), Teguh Harjono Karjadi\(^3\)
\(^1\)Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia
\(^2\)Faculty of Medicine, Universitas Lampung
\(^3\)Division of Allergy Immunology, Department of Internal Medicine, Faculty of Medicine,
Universitas Indonesia

Abstract
The prevalence of peripheral arterial disease (PAD) is high in the HIV-infected population and is much higher than expected in the general population. A 27 years old male patient came to Cipto Mangunkusumo General Hospital (RSCM) with chief complaint of pain on right leg which worsened since 2 days prior admission. Patient was diagnosed HIV positive 8 months prior admission and had already on ARV treatment Duviral (AZT/3TC) and Alluvia (lopinavir/ritonavir) since then. CT angiography showed stenosis of femoral communis artery with total stenosis of right posterior tibialis artery. Patient was diagnosed with critical limb ischemia and got amputation. Some theories of PAD mechanism in HIV patient have been proposed. Highly active antiretroviral therapy (HAART) has decreased the mortality and illnesses related to HIV infection. However, a variety of atherogenic metabolic abnormalities, including dyslipidemia, lipodystrophy, and also thickened intima-media thickness have been observed after the introduction of HAART, especially using Protease Inhibitors. Human Immunodeficiency Virus itself is also thought to have role in injury to the arterial wall such as via chemokine CCL2/MCP-1, a critical mediator of atherosclerosis. All HIV-infected patients candidate to antiretroviral therapy and patients already under treatment should undergo an assessment that includes the evaluation of the cardiovascular risk. [JuKe Unila 2014; 4(8):218-224]

Keyword: AIDS, HAART, HIV, peripheral arterial disease

Introduction
The prevalence of symptomatic and asymptomatic peripheral arterial disease (PAD) is high in the HIV-infected population and is much higher than expected in the general population.\(^1,2\) A study suggests the presence of an epidemic of PAD around 20 years earlier in the HIV-infected than in the general population.\(^1\) Ninety-two consecutive HIV-infected patients were evaluated and PAD was found in 20.7% of the patients.\(^1\)

Critical limb ischemia (CLI) can be life threatening and can require emergency intervention to minimize morbidity and mortality.\(^3\) Among the 1 to 2 percent of patients with critical limb ischemia, the guidelines estimated the following outcomes at one year: alive with two limbs 50 percent, amputation 25 percent, cardiovascular mortality 25 percent.\(^3\)

Some theories of PAD mechanism in HIV patient have been proposed. Combination antiretroviral therapy has dramatically decreased the mortality and illnesses related to HIV infection. However, a variety of atherogenic metabolic abnormalities, including dyslipidemia, lipodystrophy, and insulin resistance have been observed soon after the introduction of combination antiretroviral therapy.\(^1,2\) Human Immunodeficiency Virus itself is also thought to have role in injury to the arterial wall.\(^1,2\)

This case presents and discusses diagnosis and treatment of critical limb ischemia in HIV patient as well as discusses the relationship between HIV
and his critical limb ischemia. This case presentation specifically aims to show and to find the possible mechanism of PAD in this HIV patient compared to the recent theory of PAD in HIV patient. This discussion hopefully will help clinician to predict incident of PAD in their HIV patients and then to prevent it.

Case
A 27 years old male patient came to Cipto Mangunkusumo General Hospital Hospital (RSCM) with chief complaint of pain on right leg which worsened since 2 days ago. Three weeks prior admission patient felt pain on his right leg continuously even at rest. Patient felt the pain starting from knee to the fingers. One week prior admission patient was hospitalized at Private Hospital because his right leg emerged petchiae and the foot became reddish and swelling. The right leg thumb also became black. Two days prior admission the pain on the right leg became worse. Patient was then sent to RSCM. There was history of mild pain on the legs before since one month prior admission, 2-3 times while walking on far distance.

Patient was diagnosed HIV positive 8 months prior admission and had already on ARV treatment, Duviral and Alluvia. Four months ago patient had ever got convulsion and then was performed CT Scan at Private Hospital and was diagnosed with Toxoplasmosis Encephalitis and got cotrimoxazol, pirimetamin, and clindamycin. Patient had also been diagnosed with tuberculosis at Private Hospital and still on the third month of tuberculosis treatment with history of allergic to rifampicin and increasing of transaminase enzyme. Patient was on tuberculosis treatment of Etambutol 2x500 mg/Ofloxacin 1x400 mg/INH 1x300 mg. No data of CD4 could be found.

There was neither history of heart problem nor liver disease. Patient was a smoker, smoking for about 1 pack of cigarettes per day but had already stopped smoking since 9 months ago. No history of hypertension and diabetes.

Physical examination showed petchiae on the right leg to the toe and the foot was reddish and swelling, while the right leg thumb was black. There was coolness to palpation and decreased of popliteal artery pulse and absent of posterior tibialis artery and dorsalis pedis artery pulses. ABI index of right leg showed no result because of difficult to examine. There was sensory loss in finger area and around foot but not in other areas.

Initial laboratory examination at Emergency Room revealed anemia (Hb 8.5) g/dL, Ht 25%, leucositosis

![Figure 1. Right leg of patient showed critical limb ischemia](image)
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(leucocyte 14,400/ul), hypoalbuminemia (3.0 gr/dL), prothrombin time 20.2 with control of 11.4 (1.7 x control), aPTT 49.0 with control of 33.1 (1.48 x control), fibrinogen 568 mg/mL, INR 1.74, D-Dimer 0.8 mg/L. Electrocardiography within normal limit, chest X-ray showed no infiltrate, CTR<50 %.

USG from Private Hospital showed a possibility of proximal of right femoral communis artery and proximal of left popliteal artery stenosis.

CT angiography result showed stenosis of femoral communis artery, superficial artery, poplitea artery through anterior tibialis artery, with total stenosis of right posterior tibialis artery. There is no vascularization of distal of leg until right foot. Stenosis anterior-posterior tibialis artery and branch of left peroneus, There is no vascularization of distal of leg until right foot.

Patient was given antibiotic of ceftazidime 3x1 gr and metronidazole 3x500 mg iv. For HIV condition, patient was continued to get ARV drugs of Aluvia 2x2 and Duviral, cotrimoxazole 1x960 mg, and pirimetamin 1x25 mg for his toxoplasmosis. For Tuberculosis patient was treated with Etambutol 2x500 mg/Ofloxacin 1x400 mg/INH 1x300 mg, because of allergic to rifampicin and elevation of transaminase. Laboratory examination in the ward showed CD4 12 sel/ul (5%). Profil lipid showed dislipidemia with triglyceride 182 mg/dL, total cholesterol 239 mg/dL, HDL cholesterol 39 mg/dL, LDL 164 mg/dL. Patient was given additional therapy of simvastatin.

Patients was then prepared for amputation above knee. For preparation of amputation patient was given FFP before operation with target of aPTT <1.5, heparin was stopped for amputation preparation. Post amputation patient was then moved to the ward in vascular surgery department. Treatment in the ward was same with the additional treatment from vascular surgery department as follow: heparine drip of 20,000 unit/day and then reduced to 10,000 unit/day and switch to warfarin 2x2 mg, pentoxifyline 600 mg/24 hours, tromboles 2x1, cilostazol 2x100 mg.

Discussion

PAD is a nearly pandemic condition that has the potential to cause loss of limb or even loss of life. Fontaine in 1954 classified the severity of vascular insufficiency into 4 stages (I, asymptomatic; II, intermittent claudication; III, rest pain; IV, ulcer/gangrene). At present, the TransAtlantic Inter-Society Consensus (TASC), a diagnostic and therapeutic guideline, combined the Fontaine classification with the Rutherford classification of the US as the criteria in 2000, re-defining degree I of class I as asymptomatic. Many people live daily with peripheral vascular disease; however, in settings such as critical limb ischemia, this can be life threatening and can require emergency intervention to minimize morbidity and mortality.

According to the 2007 Inter-Society Consensus for the Management of PAD (TASC II), acute limb ischemia is defined as a sudden decrease in limb perfusion that causes a potential threat to limb viability (manifested by ischemic rest pain, ischemic ulcers, and/or gangrene) in patients who present within two weeks of the acute event. Patients with similar manifestations
who present later than two weeks are considered to have chronic critical limb ischemia. At 1 year following presentation, 25% of patients have resolved CLI, 20% have ongoing CLI, 30% are alive with amputation, and 25% are dead.3

There have been many reports on HIV/AIDS-associated vasculopathy since its first description in 1987, but relatively few have dealt with peripheral arterial occlusive disease. PAD is more prevalent in the HIV-infected population than in the general population.1,2 A study by Periard et al., reported a six-fold increased risk for PAD in HIV-infected individuals as well as an earlier onset of the disease compared with HIV-negative patients.1

Periard et al., identified age, smoking, diabetes, and CD4 T-cell count <200 cells/μl as significant predictors of PAD.1 Depairon et al., found that 55% of HIV-infected patients had at least one carotid or femoral plaque compared with 38% of healthy controls.6 The risk of arterial thrombosis in HIV-positive patients younger than 45 years of age was found to be three times higher, and in patients older than 45 years two to six-fold higher, compared with the age-related annual incidences of arterial thrombosis in the Framingham study.2

Several possible mechanisms might be responsible for premature development of PAD in the HIV-infected population. First, HIV-infected patients tend to have lifestyle-related cardiovascular risk factors, including a high prevalence of smoking as identified in our study. Second, combination antiretroviral therapy–related dyslipidemia, lipodystrophy, and impaired glucose tolerance may be associated with the development of premature atherosclerosis, as previously shown.7,8

Highly active antiretroviral therapy (HAART) has prolonged many patient’s lives, but many cardiac sequelae of HIV are not affected by HAART and continue to develop even with treatment. In addition, HAART itself causes in a high proportion of patients a metabolic syndrome, characterized by lipodystrophy or lipoatrophy, dyslipidemia, and insulin resistance that may be associated with an increase in peripheral artery and coronary artery diseases. HIV infection and a low CD4 T-cell count have, however, been shown to be independent risk factors for atherosclerotic disease independent from HAART. Furthermore, in the SMART study, cessation or interruption of antiretroviral treatment was associated with an increased incidence of major cardiovascular events.11-13

HIV Protease Inhibitors (PIs) act by blocking the HIV aspartyl protease, a viral enzyme that cleaves the HIV gag and gag-pol polyprotein backbone at nine specific cleavage sites to produce shorter, functional proteins. Some protease inhibitors available now areamprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, tipranavir. In Indonesia some available protease inhibitors are nelfinavir, indinavir, ritonavir, lopinavir, and saquinavir.

PIs are associated with usually reversible dyslipidemia, and long-term exposure to PIs is probably necessary for atherosclerosis to develop, whereas a short duration of PI exposure may temporarily modify lipid levels without
substantial development of atherosclerosis. Moreover, not all patients develop dyslipidemia on exposure to PIs.²,¹⁰,¹¹

Maggi et al., found an increased proportion of carotid plaques or thickened intima-media thickness in HIV-infected patients treated with PIs, compared with the proportion among healthy control subjects. They also found a more rapid onset of new lesions and a more rapid thickening of previous lesions in patients treated with PIs than in patients treated with non-nucleoside reverse-transcriptase inhibitors.⁹ Sevastianova et al., found that prolonged PIs exposure was associated with increased peripheral arterial stiffness measured by pulse wave velocity.¹⁰

An approach to the treatment of dyslipidemia in patients treated with PIs is to switch to PIs-free combination regimens. Although large randomized trials are lacking, some favourable effects have been shown. Of interest are preliminary data indicating that patients never treated with HAART, which started a PIs-sparing regimen including some non-nucleoside reverse transcriptase inhibitors, such as nevirapine or efavirenz, showed a significant increase of HDL-cholesterol.²,¹⁰,¹¹

Pathogenetic research supports the direct role of HIV in the development of arteriosclerosis. Endothelial dysfunction is a key step in the development of atherosclerosis and is known to be an early predictor of cardiovascular events. Increased levels of soluble cellular adhesion molecules (VCAM-1 and ECAM), E-selectin as well as other markers of endothelial activation including von Willebrand factor, PAI-1, and tissue-derived plasminogen activator (tPa) suggest that the human immunodeficiency virus activates and disregulates endothelial cells. HIV immune-modulation may also play a role as low levels of CD4 T-cells have been shown to be independent risk factors for the development of atherosclerosis. The association between infection, inflammation, and atherosclerosis is well known. This suggests a causal relationship between the chronic inflammatory response caused by HIV as well as opportunistic infections such as cytomegalovirus and accelerated atherosclerosis.¹,²

Eugenin et al., demonstrated that human arterial smooth-muscle cells (SMC) can be infected in vitro and in vivo with HIV, resulting in a marked increase in SMC secretion of chemokine CCL2/MCP-1 which has been shown to be a critical mediator of atherosclerosis.¹¹ Their data suggest that direct infection of human arterial SMCs by HIV may be an additional factor to endothelial cell dysfunction in the development of atherosclerosis and the vasculopathy seen in HIV-infected individuals.¹¹

The 2005 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on PAD and the 2007 TASC II identified groups at risk for lower extremity PAD. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) identified risk factor for PAD: race, gender, smoking, diabetes mellitus, hypertension, dyslipidemia, hyperviscosity and hypercoagulable states, hyperhomocysteinemia, and chronic renal insufficiency. In this patient we found only smoking for
known risk factor. Laboratory examination later showed dyslipidemia condition in this patient without any clear record of previous dyslipidemia. Patient was still young with age of 27 and no hypertension or diabetes history. Patient did not have any record of atherosclerotic coronary problem and chronic renal insufficiency. Hyperhomocysteinemia was not examined in this patient.

Several study showed PAD is more prevalent in the HIV-infected population than in the general population. A study suggests the presence of an epidemic of PAD around 20 years earlier in the HIV-infected than in the general population. Several possible mechanisms might be responsible for premature development of PAD in the HIV-infected population. Besides lifestyle-related cardiovascular risk factors such as smoking, highly active antiretroviral therapy (HAART) has been proposed to increase the risk for PAD development.

PIs has been suggested to cause metabolic syndrome, characterized by lipodystrophy or lipatrophy, dyslipidemia, and insulin resistance that may be associated with an increase in peripheral artery and coronary artery diseases. This patient had been treated with Aluvia and Duviral for about 8 months. Aluvia is coformulation of lopinavir + ritonavir (lopinavir/ritonavir). Both lopinavir and ritonavir are actually protease inhibitors. Long term exposure to PIs is probably necessary for atherosclerosis to develop but we did not find any specific time mentioned in the references. This patient had consumed Alluvia for 8 hours so we could consider it as a long time exposure of PIs. From laboratory examination we found this patient had dyslipidemia condition which maybe related with protease inhibitor treatment, although we did not find lipodystrophy, impaired glucose tolerance, or other cardiovascular event. It is suggested to have regular examination and to control all atherosclerotic risk factors such as dyslipidemia, hypertension, and hyperglycemia, in HIV patient to reduce PAD and coronary event.

Duviral which contains AZT (zidovudine) dan 3TC (lamivudine) is a nucleoside reverse transcriptase inhibitor (NRTI). In our references NRTI had not been stated to have any influence of PAD development in HIV patient.

As also stated in the reference, Human Immunodeficiency Virus itself also thought to have role in injury to the arterial wall. In this patient we did not perform viral load, but we found a very low of CD4 count of 12 cell/uL and also other opportunistic infection such as toxoplasmosis encephalitis in this patient. Low CD4+ T cell counts may reflect the duration and severity of uncontrolled HIV infection and be a surrogate marker of potential endothelial toxicity of HIV. All of those might indicate large number of Human Immunodeficiency Virus, so the role of large number of HIV in this patient still can be considered.

**Conclusion**

The relationship between chronic limb ischemia and HIV has been discussed. Cardiovascular complications in the course of human immunodeficiency virus (HIV) infection are multifactorial and may be caused by the virus itself. Highly active
antiretroviral therapy (HAART) was suggested to cause in a high proportion of patients a metabolic syndrome, characterized by lipodystrophy or lipoatrophy, dyslipidemia, and insulin resistance that may be associated with an increase in peripheral artery and coronary artery diseases. Careful cardiovascular evaluation in the course of HIV disease can identify PAD complications early enough to treat. All HIV-infected patients candidate to antiretroviral therapy and patients already under treatment should undergo an assessment that includes the evaluation of the cardiovascular risk with the available guidelines.

Reference