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Case Report

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# A Case of Deep Venous Thrombosis in an HIV-Infected Patient despite Therapeutic Anticoagulation

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**ABSTRACT**

Patients with human immunodeficiency virus (HIV) infection have an increased likelihood of venous thromboembolism (VTE) owing to factors such as acquired protein C and S deficiency, antiphospholipid antibody syndrome, and heightened levels of pro-inflammatory cytokines. This case report highlights an exceptionally uncommon occurrence of deep venous thrombosis in an HIV-infected patient receiving a therapeutic dose of enoxaparin. This underscores the need for cautious consideration of the risk of VTE in HIV-infected individuals, even with preventive or therapeutic anticoagulant treatment. Further research is recommended to investigate HIV as a potential risk factor of prophylactic anticoagulation.

**Keywords:** Deep venous thrombosis; Anti-coagulants; Human immunodeficiency virus (HIV); Enoxaparin

## INTRODUCTION

Human immunodeficiency virus (HIV) infection remains the highest health burden worldwide, affecting approximately 39 million people according to the World Health Organization by 2022 [1]. Arterial and venous thromboembolism (VTE) is up to 10-fold more prevalent in the HIV population than in the general population [2]. Deep venous thrombosis (DVT) and pulmonary embolism are common forms of VTE. Chronic HIV infection is associated with the development of acquired protein C and S deficiency, antiphospholipid antibody syndrome, endothelial dysfunction, and increased pro-inflammatory cytokine levels in the circulation[3-5]. Patients on antiretroviral therapy (ART) tend to have a longer life expectancy than their counterparts not on ART and are therefore at an increased risk of complications[6]. Therefore, prophylactic anticoagulation (AC) is considered more frequently for HIV-infected patients than for the general population [7]. A variety of therapeutic and preventive AC choices are available for individuals with HIV infection, including traditional anticoagulants such as warfarin and heparin (both unfractionated and low-molecular-weight) and direct oral anticoagulants [8].

Here, we present the unique case of an HIV-infected patient who developed DVT despite receiving a therapeutic AC dose. This case report aims to encourage healthcare providers to exercise increased caution in recognizing HIV as a potential risk factor, in addition to existing comorbidities, for the occurrence of VTE.

### Case Presentation

A 64-year-old woman with a medical history of left ventricular mural thrombus (LVT), coronary artery

disease, and heart failure with reduced ejection fraction, HIV, cerebrovascular accident, malnutrition with a percutaneous endoscopic gastrostomy tube, prediabetes, and substance abuse with cocaine was brought in by emergency medical services from a rehabilitation center with altered mental status and respiratory distress. In the emergency department, she was altered, not oriented to time, place and person, and unable to protect her airway, and she was hypotensive, hypoxic, and septic. The patient was intubated and mechanically ventilated. She received intravenous fluids, vasopressors, and antibiotics and was admitted to the intensive care unit. She had acute metabolic encephalopathy due to multi-organ damage secondary to septic shock and acute chronic heart failure with a reduced ejection fraction. Her home medications, including bictegravir + emtricitabine + tenofovir alafenamide 50-200-25 mg per day for the HIV infection and apixaban 5 mg twice daily for her history of LVT, were continued. A hematologist was consulted for the management of her AC dosage given her history of thrombectomy and embolectomy for LVT and established protein S deficiency. She was switched to enoxaparin (1 mg/kg) subcutaneously every 12 h. Bilateral venous Doppler ultrasonography (US) of the legs was negative. The laboratory results of the HIV showed the absolute CD4 helper cell count was 93/uL, HIV viral load by PCR on admission was <20 copies/ml, and hypercoagulability workup showed protein S deficiency. Coagulation parameters showed elevated prothrombin time (PT) of 16 seconds and international normalized ratio was 1.43, d-dimer was not done during this admission. After 17 days of continuous therapeutic enoxaparin, the patient developed bilateral leg swelling, more on the right than the left leg. Doppler US of the lower extremities revealed acute DVT in the right proximal peroneal vein. Because the patient had already received a therapeutic dose of anticoagulants, no changes were made. She had a guarded prognosis and survived for only 3 days after the VTE diagnosis due to complications of septic shock and multi-organ damage.

**DISCUSSION**

In HIV-infected populations, multiple mechanisms contribute to a hypercoagulable state. The two most reported associations are protein C and S deficiency and antiphospholipid antibody syndrome associated with chronic HIV infection[9,10]. Furthermore, the presence of comorbidities such as diabetes, hyperlipidemia, and malignancy further complicate thrombotic risk in this population[11]. The interplay among these factors contributes to a hypercoagulable state, making HIV-infected individuals more susceptible to blood clot formation. Effectively managing AC in HIV-infected patients presents a significant challenge, and there is a growing need for large-scale studies to better understand the long-term success rates of AC therapy and to determine optimal strategies for AC in this population.

In a case series (N=5) by Sule et al. (2013)[12], HIV-seropositive patients with venous thrombosis were analyzed and followed up for 3 years for hypercoagulable states. Two of the five patients had protein S deficiency, one had antithrombin III deficiency, and two had elevated levels of anti-cardiolipin IgG antibody and homocysteine. All patients received ART including nucleoside, non-nucleoside, and protease inhibitors. The absolute CD4 count ranged from 103 to 392 cells/UL. All the patients received AC therapy with either warfarin or enoxaparin. Only one of the patients (20%) had complete resolution of DVT after >6 months of treatment with a therapeutic dose of anticoagulants, whereas the remaining four patients (80%) were refractory to AC therapy. The incidence of failure to resolve DVT was very high in this case series compared to that in the general population (approximately 3%). In a case report by Dong et al., an 11-year-old child with HIV developed antiphospholipid antibody syndrome leading to DVT that responded to warfarin therapy[9]. These investigations seek to demonstrate that HIV is a risk factor for VTE and that managing this group of individuals presents a considerable challenge. Nevertheless, more extensive studies are essential to evaluate the success rate of AC in HIV-infected patients over a 6-month period and to establish the most suitable AC approach.

Another possible explanation for AC therapy failure is drug-drug interactions. To the best of our knowledge, no large clinical study has been conducted to assess the drug-drug interaction between HIV medications and AC. Initial studies on the approval of warfarin and direct oral anticoagulants did not include patients undergoing ART. Sabourin et al. (2021)[13] discussed drug-drug interaction based on pharmacokinetics and the effect of medicines on cytochrome P450 and concluded that non-nucleoside reverse transcriptase inhibitors and protease inhibitors may interact with anticoagulant metabolism and that nucleoside reverse transcriptase inhibitors (NRTIs) and integrase strand inhibitors (INSTIs) have no significant interaction (NRTIs and INSTIs were used in the patient discussed in the present case report). In a case study by Liedtke et al. (2012), an increased warfarin dose was required to maintain a therapeutic international normalized ratio after the initiation of ritonavir-boosted darunavir, etravirine, and raltegravir therapy for HIV[14]. However, only limited clinical data are available on drug-drug interactions between AC and ART in HIV-infected patients; therefore, no definite conclusions can be drawn.

## CONCLUSION

Based on our case report and literature review, it is crucial to meticulously manage AC therapy in individuals with HIV because of the heightened risk of VTE arising from various mechanisms. These findings underscore the necessity for targeted and comprehensive research initiatives focusing on both the prophylaxis and management of VTE, specifically in the HIV-infected population. This nuanced understanding is vital for developing tailored strategies to optimize AC protocols and improve outcomes for HIV-infected individuals facing these intricate challenges.

## CONFLICT OF INTEREST

All authors declare no conflict of interest.

## Ethical approval

Written consent has been obtained from the son who had power of attorney to publish the case and relevant images as case report.

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