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Venous Thromboembolism Requiring Extended Anticoagulation Among HIV-Infected Patients in a Rural, Resource-Constrained Setting in Western Kenya

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Abstract

Background: HIV-infected patients are at an increased risk of developing venous thromboembolism (VTE), and minimal data are available to describe the need for extended treatment. **Objective:** To evaluate the frequency of and determine predictive risk factors for extended anticoagulation of VTE in HIV-infected patients in rural, western Kenya. **Methods:** A retrospective chart review was conducted at the Anticoagulation Monitoring Service affiliated with Moi Teaching and Referral Hospital and the Academic Model Providing Access to Healthcare. Data were collected on patients who were HIV-infected and receiving anticoagulation for lower-limb deep vein thrombosis. The need for extended anticoagulation, defined as receiving ≥7 months of warfarin therapy, was established based on patient symptoms or Doppler ultrasound–confirmed diagnosis. Evaluation of the secondary outcomes utilized a univariate analysis to identify risk factors associated with extended anticoagulation. **Results:** A total of 71 patients were included in the analysis; 27 patients (38%) required extended anticoagulation. The univariate analysis showed a statistically significant association between the need for extended anticoagulation and achieving a therapeutic international normalized ratio within 21 days in both the unadjusted and adjusted analysis. Patients with a history of opportunistic infections required an extended duration of anticoagulation in the adjusted analysis: odds ratio = 3.42; 95% CI = 1.04-11.32; $P = 0.04$. **Conclusions:** This study shows that there may be a need for increased duration of anticoagulation in HIV-infected patients, with a need to address the issue of long-term management. Guideline recommendations are needed to address the complexity of treatment issues in this population.

Keywords

HIV, venous thromboembolism, warfarin, Sub-Saharan Africa, extended anticoagulation

Background

In 2015, the global population of HIV-infected individuals reached 36 million.[1] Treatment with highly active antiretroviral therapy (HAART) has significantly prolonged the life expectancy of HIV-infected patients. Increased lifespan as a result of improved treatment regimens and immune response has led to an increased prevalence of non–AIDS-related deaths, with cardiovascular disease being among the leading causes.[2-4]

The increased risk of venous thromboembolism (VTE) in HIV-infected patients is among the rising concerns for treating cardiovascular disease in this population. The incidence of VTE in HIV-infected patients ranges from 0.19% to 7.63% per year, with reports suggesting that there is a 2- to 10-fold higher risk of VTE when compared with the general population.[5,6] In addition to traditional risk factors, coagulation abnormalities seen in this population, such as deficiencies in protein C, protein S, and antithrombin III; the presence of antiphospholipid antibodies; and increases in von Willebrand factor, fibrinogen, and D-dimers may contribute to the increased risk of developing VTEs.[5,7] Furthermore, a case-controlled study in HIV-infected patients revealed that elevated levels of interleukin-6 and

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D-dimer were associated with an increased risk of all-cause mortality, with increases in these markers relative to HIV viral load.[8] Patients presenting with low CD4+ counts, high viral loads, and opportunistic infections, may also be at increased risk of developing VTEs.[5-7,9] In addition to the increased risk associated with various biomarkers, the risk of VTE can also increase with age. It has been observed that HIV-infected patients present with a higher risk of VTE at a younger age when compared with the general population.[7,10] Although many studies have reported on the various risk factors present in HIV-infected patients for developing a VTE, there are limited published guidelines or studies directing the management and prevention of VTE in this patient population.

Data from the developed world have shown prevalence rates of recurrence or a second episode of VTE in HIV-infected patients of 7.8% and 15%, respectively.[7,10] Among the global population of people living with HIV, 70% live in Sub-Saharan Africa. With the prevalence of AIDS-related deaths decreasing and the potential for higher rates of cardiovascular disease than that seen in the developed world, it is important that we understand VTE and its treatment-related concerns in this understudied setting.[1,11]

This study describes the unique interaction of HIV and VTE in a cohort of HIV-infected patients with lower-limb deep vein thrombosis (DVT) attending the Moi Teaching and Referral Hospital (MTRH) Anticoagulation Monitoring Service (AMS) in western Kenya. The objective of this study is to evaluate the rate at which HIV-infected patients with lower-limb DVT required >6 months of anticoagulation and to assess predictive risk factors for requiring extended anticoagulation.

Methods

Study Site

The study was conducted as a retrospective chart review of patients who had been enrolled in the AMS and the Academic Model Providing Access to Healthcare (AMPATH) outpatient HIV clinics. AMPATH, based in western Kenya, has provided comprehensive HIV care for more than 150 000 HIV-infected patients throughout a catchment area of more than 3.5 million people. AMPATH is a partnership between MTRH (the second largest referral hospital in Kenya), Moi University College of Health Sciences, and a consortium of North American universities, with the stated goal of delivering comprehensive health care in partnership with the Kenyan government.[12,13] The AMS is a pharmacist-managed clinic at MTRH. The clinic has served more than 2000 patients, whose common anticoagulation indications include rheumatic heart disease, atrial fibrillation, and VTE. Despite being in a resource-constrained setting, the clinic has been able to provide high-quality care that meets the recommended performance metrics established for anticoagulation care in resource-rich settings.[14]

At each visit, clinic personnel conduct a comprehensive patient interview, monitor international normalized ratio (INR) using the i-STAT (Abbott Labs) device, create a management plan, and fill pill boxes to maximize adherence. Patients with VTE are seen on a weekly basis for the first 4 weeks to ensure that their INR is within the therapeutic range of 2 to 3. At the time of the study, the aim of care was to provide parenteral anticoagulation as a method of bridging prior to achieving a therapeutic INR. Because patients may be diagnosed in a hospital setting, hospital staff are responsible for starting anticoagulation care, including parenteral bridging, prior to referral to the outpatient clinic. Because of resource constraints in our setting, bridging with parenteral anticoagulation is not always possible for reasons of availability of the medication and cost to the patient. In the study period, the clinic based its treatment decisions on the American College of Chest Physicians (ACCP) Antithrombotic Therapy and Prevention of Thrombosis Evidence-Based Clinical Practice Guidelines (8th edition).[15] The guidelines recommended 3 months of treatment with a vitamin K antagonist and suggested the need to balance the risk of recurrent VTE and bleeding in patients with a first unprovoked DVT as a method of determining the need for indefinite therapy. Because HIV is a permanent risk factor and no direct guideline recommendations are available for treatment of this population, the clinic staff and management have adopted a standard treatment duration of 6 months in patients to ensure that the primary clot is adequately treated. On treatment completion, patients are evaluated for signs and symptoms of residual clot, including lower-limb swelling, calf pain, and/or calf circumference difference of 3 cm or more. Patients with concerns for residual clot are requested to obtain an ultrasound to document its presence. Because the clinic is located in a resource-constrained setting, patients are often unable to pay for transport, clinic fees, and diagnostic tests. These issues, coupled with limited radiology and laboratory infrastructure, result in clinic staff opting to extend treatment based on clinical judgment to ensure optimal therapy.

Patient Population

Patients were included in the study if they were enrolled in the clinic between February 2009 and April 2013, were HIV infected, were enrolled in HIV care at AMPATH, and were receiving anticoagulation for a lower-limb DVT. Patients were excluded if they had any of the following characteristics: follow-up <6 months in the AMS, lack of access to the HIV outpatient medical chart, or another indication for anticoagulation.

Data Collection

In the AMS medical charts, study personnel collected patient demographics, duration of anticoagulation with warfarin, dosages, INRs, bleeding events and severity, self-reported adherence and pill counts, travel time to the clinic, self-reported ability to pay for clinic fees, availability of a caretaker, results of radiological tests, and the presence of symptoms and diagnoses consistent with unresolved clots or recurrence. Data from the AMPATH HIV outpatient clinic were retrieved from the AMPATH Medical Record System and patient medical charts. We collected CD4+ counts, antiretroviral (ARV) medications, self-reported adherence to ARVs and clinic visit attendance, and history of current or historical opportunistic infections. At the time of the study, viral load testing was not routinely done, and CD4+ counts were used for monitoring patient response to ARV treatment. Viral loads were only ordered when treatment failure was suspected. Thus, these data were not collected because most of our patients would likely not have a documented viral load value.

Data Analysis

In the primary analysis, descriptive statistics were used to describe the frequency and indication for HIV patients requiring extended anticoagulation beyond 6 months. Extended anticoagulation was defined as receiving anticoagulation for ≥7 months to account for the lag time between the end of treatment ultrasound and return to clinic. The 95% CIs were calculated around the proportion of patients requiring extended anticoagulation.

In the secondary analysis, both non–HIV-specific risk factors and HIV-specific risk factors were assessed to identify associations among patients requiring extended anticoagulation. Risk factors analyzed included patient demographics, time to reach therapeutic range, time in therapeutic range (TTR), presence of a minor bleeding event, adherence to warfarin, socioeconomic status, distance to the clinic, availability of a caretaker, CD4 count, current or historical opportunistic infections, and concomitant use of ARV or tuberculosis medications. An analysis was done to compare the risk of requiring extended anticoagulation between patients <40 years and ≥40 years of age.

A therapeutic INR was defined as an INR, within the range of 2 to 3, achieved for 2 consecutive clinic appointments. Based on past evaluations of our clinic, patients typically need approximately 7 to 21 days to reach a therapeutic INR with weekly monitoring; it was considered extended if it was reached after 21 days or not attained during the treatment period. TTR is the amount of time the patient spends within the goal INR range of 2 to 3. TTR is calculated using the linear interpolation method described by Rosendaal et al[16] and weighted by the duration of follow-up of each patient. The standard desired performance metric of anticoagulation clinics in resource-rich settings have a TTR of 63.5%, and this was utilized as the cut-point for analysis.[17]

Self-reported adherence and pill counts were assessed at each clinic visit, with nonadherence being defined by clinic staff as missing ≥1 dose of warfarin between clinic visits. The study evaluated any level of nonadherence to warfarin as a predictor of extended anticoagulation. Because socioeconomic status and distance to the clinic may affect adherence to appointments and treatment, we evaluated the patient's ability to pay for clinic visits and hours needed to travel to the clinic.

To test whether immunosuppression was a predictor of extension of anticoagulation in HIV-infected patients, we looked at patients with CD4+ cell counts below 200 cells/mm^3, 201 to 500 cells/mm^3, and above 500 cells/mm^3 at different time points. Information was also collected on the patient's history of opportunistic infections. Nonadherence to ARVs was defined as more than 2 reports of missed ARV doses or 2 missed clinic appointments.

For each of these potential risk factors, a univariate analysis using Fischer's exact test or the χ^2 test was performed to identify potential variables for requiring extended anticoagulation. For any risk factor with a P value less than 0.2, the variable was inserted into a logistic regression model to provide the adjusted odds ratio (OR). Analyses were performed at an α level of 0.05. To identify relevant trends with these risk factors, they were subdivided with clinically relevant reference points to facilitate better characterization of the associations seen.

Both local and international institutional review board and ethics committee approvals were received prior to starting the study.

Results

A total of 96 patients were evaluated for eligibility, with 71 patients meeting inclusion and exclusion criteria (Figure 1). Included patients had a mean age of 40 (SD = 9.91) years and were mostly female. The median CD4+ count on diagnosis of DVT in this population was 208 cells/mm^3. Overall, the patients included in this study remained within the therapeutic INR range 59% of the evaluated period of time. Additional patient characteristics are described in Table 1.

In the analysis of the primary end point, 27 (38%) patients (95% CI = 27%-49%) required extended anticoagulation (Table 2). Of these, 25 patients had an unresolved clot based on symptoms or compression ultrasound confirmation, whereas 2 patients had a new clot after being discharged from the clinic. These 2 patients were diagnosed with new clots at 22 and 18.5 months after completion of initial therapy. Seven (25.9%) of the 27 patients in the extended anticoagulation treatment group experienced minor bleeding events (total = 10 events).

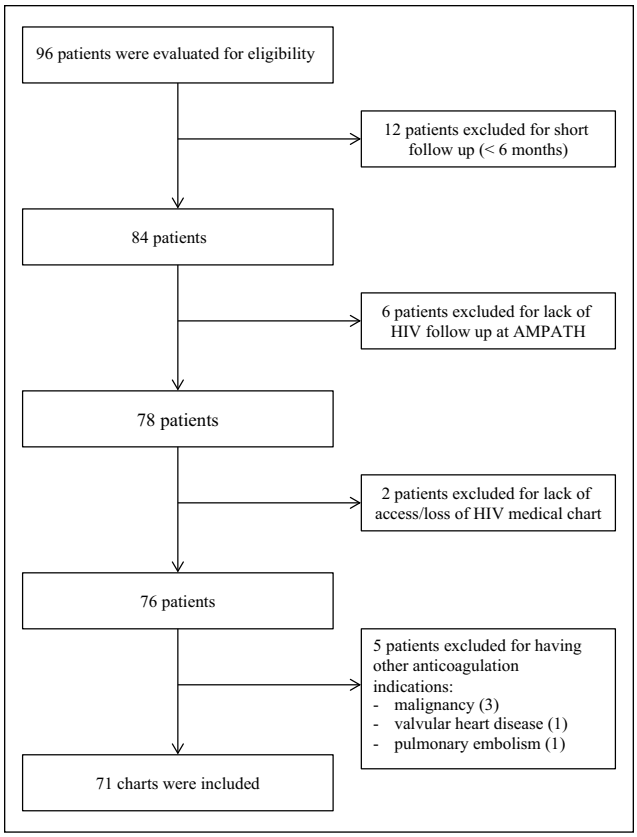

Figure 1. Patient enrollment.
Abbreviation: AMPATH, Academic Model Providing Access to Healthcare.

Seventeen (38.6%) of the 44 patients in the standard duration anticoagulation group experienced minor bleeding events (total = 25 events). No patient experienced major bleeding events.

The univariate analysis conducted to evaluate the risk factors associated with need for extended anticoagulation showed a statistically significant association with time to reaching a therapeutic INR and history of opportunistic infection (Table 3). Patients who reached a therapeutic INR in less than 21 days after being started on warfarin had an increased risk of requiring extended anticoagulation in both the unadjusted and adjusted analyses: unadjusted OR = 8.84, 95% CI = 1.75-45.65, $P < 0.02$; adjusted OR = 10.31, 95% CI = 1.62-65.59, $P < 0.02$. Reaching a therapeutic INR in greater than 21 days after starting warfarin treatment reduced the risk of requiring extended anticoagulation: OR = 0.11, 95% CI = 0.02-0.58, $P < 0.01$; adjusted OR = 0.09, 95% CI = 0.02-0.57, $P < 0.02$. In all, 17 patients (24%) were not able to meet the definition of reaching a therapeutic INR and were thus classified as reaching a therapeutic INR in greater than 21 days. Also, 18 patients, 9 per group, were utilizing rifampin therapy, and none of these patients was able to reach a therapeutic INR within 21 days.

Table 1. Patient Demographics.

Characteristic	n (%)
Gender	
Male	11 (15%)
Female	60 (85%)
Age	
<40 years	30 (42%)
≥40 years	41 (58%)
Active patients	17 (24%)
Inactive patients	
Completed therapy	48 (68%)
Deceased as a result of HIV	6 (8%)
Patients on antiretroviral therapy	69 (97%)
Patients not on antiretroviral therapy	2 (3%)
Median CD4+ count	208 cells/mm^3

Table 2. Primary Analysis of Patients Requiring Extended Anticoagulation.

Characteristic	n (%)
Patients requiring extended anticoagulation	27 (38%) [95% CI = 27%-49%]
Indications for extended anticoagulation	
Unresolved clot	
Diagnosis by signs or symptoms (no Doppler ultrasound)	16 (59.3%)
Doppler ultrasound confirmation of unresolved clot	9 (33.3%)
New clot after completion of 6 months of anticoagulation	2 (7.4%)

Patients with a positive history of opportunistic infections were found to have a statistically significantly increased risk of requiring extended anticoagulation as a result of unresolved or recurrent clots in the adjusted analysis but not in the unadjusted analysis: unadjusted OR = 1.98, 95% CI = 0.75-5.25; $P = 0.167$; adjusted OR = 3.42, 95% CI = 1.04-11.32, $P = 0.04$. Analysis of specific opportunistic infections did not reveal any statistically significant associations with extended anticoagulation.

Age ≥40 years, TTR, adherence to warfarin, self-reported socioeconomic status, distance to clinic, CD4+ count, concurrent use of ARVs or medications for tuberculosis or both, and adherence to ARVs were not associated with the need for extended anticoagulation.

Discussion

This study population represents one of the largest HIV-infected populations to be evaluated for the use of extended

Table 3. Univariate Analysis of Risk Factors for Extended Anticoagulation.

Potential Complicating Risk Factor	Extended Anticoagulation Group (N = 27), n (%)	Standard Duration Anticoagulation Group (N = 44), n (%)	Unadjusted Odds Ratio of Requiring Extended Anticoagulation	*P* Value	Adjusted Odds Ratio of Requiring Extended Anticoagulation[a]	*P* Value
Age less than 40 years	14 (52%)	16 (36%)	1.86 (0.71-4.99)	0.202		
Caretaker availability	25 (93%)	41(93%)	0.91 (0.14-5.86)	0.925		
Distance from clinic (less than 2 hours)	24 (89%)	27 (61%)	1.28 (0.35-4.73)	0.714		
Self-reported ability to pay for testing						
Unable to afford any test or medication	13 (48%)	16 (36%)	1.63 (0.61-4.30)	0.328		
Can afford up to 500 ksh (~$6)	6 (22%)	14 (32%)	0.61 (0.20-1.85)	0.385		
Can afford up to 1000 ksh (~$12)	8 (30%)	14 (32%)	0.93 (0.31-2.77)	0.901		
Anticoagulation-related risk factors						
Was the therapeutic range reached?	23 (85%)	31 (70%)	2.41 (0.70-8.36)	0.165	2.21 (0.27-6.51)	0.31
Time to therapeutic range						
Less than 21 days	8 (30%)	2 (4.5%)	8.84 (1.71-45.65)	0.009	10.31 (1.62-65.59)	0.02
Greater than 21 days	19 (70%)	42 (95%)	0.11 (0.02-0.58)	0.009	0.09 (0.02-0.57)	0.02
Percentage of time spent in the therapeutic range						
Less than 30%	4 (15%)	7 (16%)	0.91 (0.24-3.49)	0.902		
Between 30% and 63.5%	4 (15%)	18 (41%)	0.36 (0.11-1.13)	0.081	0.23 (0.05 -1.07)	0.06
Greater than 63.5%	19 (70%)	19 (43%)	2.4 (0.89-6.50)	0.085	2.47 (0.59-10.4)	0.21
Adherence to warfarin (missing <3 days or perfect adherence?)	23 (85%)	36 (82%)	1.28 (0.35-4.73)	0.714		
Presence of a minor bleeding event	7 (26%)	17 (39%)	0.585 (0.203-1.68)	0.436		
HIV-related risk factors						
Highest CD4+ count reached						
Less than 200	4 (15%)	10 (23%)	0.66 (0.18-2.39)	0.524		
Between 201-500	11 (41%)	17 (39%)	1.35 (0.51-3.60)	0.548		
Greater than 500	12 (44%)	17 (39%)	0.96 (0.36-2.54)	0.926		
Lowest CD4+ count reached						
Less than 200	16 (59%)	33 (75%)	0.44 (0.155-1.25)	0.124	0.34 (0.05-2.13)	0.25
Between 201 and 500	10 (37%)	8 (18%)	2.57 (0.86-7.69)	0.091	3.15 (0.48-20.67)	0.23
Greater than 500	1 (3.7%)	2 (4.5%)	0.79 (0.068-9.14)	0.849		
CD4+ count on initial diagnosis of HIV						
Less than 200	14 (52%)	29 (66%)	0.52 (0.19-1.40)	0.195	0.46 (0.06-3.73)	0.47
Between 201 and 500	11 (41%)	10 (23%)	2.27 (0.80-6.44)	0.124	1.72 (0.34-8.67)	0.50
Greater than 500	2 (7.4%)	4 (9%)	0.78 (0.12-4.58)	0.783		
CD4+ count on initial diagnosis of DVT						
Less than 200	8 (30%)	23 (52%)	0.47 (0.18-1.29)	0.147	0.96 (0.23-4.1)	0.96
Between 201 and 500	11 (41%)	16 (36%)	1.28 (0.48-3.45)	0.622		
Greater than 500	8 (30%)	5 (11%)	2.16 (0.64-7.30)	0.216		
What type of HIV regimen has the patient received						
No medications	1 (4%)	0 (0%)	1.65 (0.099-27.59)	0.726		
First-line NNRTI regimen only	24 (89%)	42 (95%)	0.605 (0.04-10.09)	0.726		
Both NNRTI and a second-line PI-based regimen	2 (7.4%)	2 (4.5%)	1.68 (0.22-12.68)	0.615		
Has the patient ever had an OI?	15 (56%)	17 (39%)	1.98 (0.75-5.25)	0.167	3.42 (1.04-11.32)	0.04
Adherence to ARVs?	20 (74%)	36 (82%)	0.64 (0.20-2.01)	0.440		
Concurrently on TB therapy	6 (22%)	9 (20%)	1.11 (0.35-3.57)	0.859		
Concurrently on TB and ARV therapy	5 (19%)	8 (18%)	0.68 (0.19-2.26)	0.552		

Abbreviations: NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; OI, opportunistic infection; ARV, antiretroviral; DVT, deep-vein thrombosis; TB, tuberculosis.

[a]An adjusted odds ratio was calculated using a fixed-effects model if the *P* value in the unadjusted odds ratio was less than 0.20.

anticoagulation in the management of DVT in Sub-Saharan Africa. Our data show that approximately one-third of the population who were HIV infected and being treated at the MTRH AMS clinic for a DVT required extended anticoagulation. Very few studies have evaluated the risk of recurrence of VTE in an HIV-infected population. Based on the retrospective nature of our study, it remains difficult to determine the necessary treatment duration of VTE in HIV-infected patients. Future prospective studies are needed to evaluate the duration of anticoagulation needed, the recurrence rates of VTE, methods of preventing VTE, and how laboratory parameters and biomarkers such as CD4+ count, viral load, interleukin-6, and D-dimer affect the treatment recommendations in the HIV-infected population.

With HIV becoming a chronic disease through the increased availability of HAART, providers will face these challenges more often, especially the question of duration of anticoagulation in VTE. The MTRH AMS is not alone in prolonging VTE treatment beyond guideline recommendations. A recent study was conducted to evaluate "real-life" clinical practice of VTE treatment duration.[18] Approximately half of all patients with either an unprovoked VTE, transient risk factor associated VTE, or cancer-related VTE were treated for 12 months, which was not in alignment with guideline recommendations at the time.[19] Recently published ACCP Antithrombotic Therapy and Prevention of Thrombosis Evidence-Based Clinical Practice Guidelines (10th edition) provide recommendations on the provision of extended anticoagulation (indefinite) for patients who present with a first unprovoked VTE and have a low or moderate bleeding risk, in order to prevent recurrence.[20]

The use of indefinite anticoagulation may not be feasible in our resource-constrained setting. Lack of sustained access to the necessary monitoring infrastructure for vitamin K antagonists would limit their use in rural Sub-Saharan Africa. One possible solution is the use of aspirin as thromboprophylaxis after completion of treatment for VTE. Two studies—the ASPIRE trial and the WARFASA study—evaluated the use of aspirin in populations with a first-ever, unprovoked VTE for the prevention of recurrence.[21,22] Their combined results showed a statistically significant 32% reduction in the rate of recurrence of VTE and a 34% reduction in the rate of major vascular events without an increase in major bleeding when compared with placebo.[23] Although the use of aspirin has not been studied for prevention of recurrence of VTE in the HIV-infected population, its ability to decrease recurrence without increasing major bleeding risk and the lack of laboratory monitoring for management makes it an attractive option for patients in a resource-constrained setting. As a result of these studies, in 2013, the AMS decided to recommend the use of aspirin as thromboprophylaxis to HIV-infected patients with a prior history of VTE (completed therapy) and no contraindications, which is a recommendation supported by current guidelines for patients with unprovoked VTE who are unable to continue indefinite anticoagulation.[20]

Understanding the risk factors that predispose HIV-infected patients to developing VTE and recurrence of VTE may also help in management of this challenging population. In our study, 2 factors were associated with increased need for extended anticoagulation: time to reaching therapeutic range and a history of opportunistic infection.

Unexpectedly, reaching a therapeutic INR within 21 days of starting warfarin was associated with an increased likelihood of requiring extended anticoagulation, whereas those who took more than 21 days had a reduced likelihood of requiring extended anticoagulation. A small number of patients (10 patients) reached therapeutic INR within 21 days as opposed to those who took more than 21 days to reach therapeutic INR (61 patients). This phenomenon is not unusual because therapeutic anticoagulation in HIV-infected patients may be difficult to achieve and maintain as a result of other comorbidities and drug-drug interactions with ARVs.[24] Because of the small sample size of this study, the characteristics evaluated had wide CIs, increasing the likelihood of type 1 errors when performing subgroup analyses. One plausible explanation of this finding is that patients who achieved therapeutic INRs within 21 days were more likely to exhibit better care-seeking behaviors and would be more likely to report symptoms of VTE and require prolonged anticoagulation. One piece of evidence that may support this explanation is that all the patients on rifampin-based therapy for treatment of tuberculosis did not reach a therapeutic INR within 21 days. By having almost all the patients receiving tuberculosis treatment in one group, it starts to depict the picture of poorer health metrics as described in the prior example.

In this study, having a history of an opportunistic infection was predictive of requiring extended anticoagulation. The most common opportunistic infections reported were tuberculosis, cryptococcal meningitis, herpes, candidiasis, and *Pneumocystis jiroveci* pneumonia. Data showing an association between opportunistic infections and risk of VTE are not uncommon and may be a result of possible proinflammatory or hypercoagulable states.[5,7,9,10]

Variables tested in the univariate analysis, including age, CD4+ count, TTR, adherence, ARV or tuberculosis treatment, and socioeconomic status, were not associated with extended anticoagulation. It is possible that if we had compared an older age or had a larger population of patients in our study, we would have seen a higher risk, as expected. It is not surprising that we did not see a difference in the need for extended anticoagulation based on which ARVs a patient was utilizing because previous data have shown conflicting evidence to support ARV association with increased VTE risk.[7] If this study contained a larger sample size, it may have been possible to identify other factors that placed patients at a higher risk of needing extended anticoagulation.

The conclusions drawn from this study may be limited by its retrospective nature, small sample size, and the lack of a comparison group. Because patients were not followed up after being discharged from the clinic, we may have missed some patients who, after completing 6 months of therapy, may have needed to be re-enrolled as a result of recurrent clots. The lack of a standard diagnostic method for all patients, such as compression ultrasound, may have also led to bias. It is important to note that only a third of patients could afford a confirmatory radiological test of the unresolved clot. Because guideline recommendations do not support reimaging patients after treatment of DVT, it is uncertain whether our findings should indicate that all patients with HIV and DVT receive imaging after treatment

and how a repeat compression ultrasound should be interpreted and applied to the treatment duration. Because of data collection methods in the clinic, we were unable to label DVTs as provoked or unprovoked. In addition, the study was unable to determine whether or not patients received parenteral anticoagulation until they reached a therapeutic INR. Because most patients were referred to the clinic after being diagnosed in the inpatient setting, it is possible that they received parenteral anticoagulation prior to discharge. Lack of parenteral anticoagulation could have increased their chances for needing extended anticoagulation. Obtaining a more thorough medical history outside of HIV would have been helpful in determining other risk factors. However, in this setting, regular outpatient follow-up for chronic conditions in the public sector is not common. Additionally, patients were treated empirically for 6 months versus the guideline-recommended 3 months, creating difficulty in adequately evaluating the current recommendations for this patient population. Despite these limitations, the current study describes one of the largest cohorts of HIV-infected patients requiring VTE treatment.

This study represents one of the only investigations looking specifically at a resource-constrained Sub-Saharan African population and highlights the heightened requirement for extended anticoagulation. However, larger studies are needed to support standard guidelines for discerning the ideal duration of anticoagulation in HIV-infected patients, which considers the unique factors that can modulate the risk for recurrent clots in this population.

Authors' Note

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References

1. UNAIDS. Fact sheet November 2016. http://www.unaids.org/en/resources/fact-sheet. Accessed September 21, 2016.
2. Palella FJ Jr, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr*. 2006;43:27-34.
3. Farahani M, Mulinder H, Farahani A, Marlink R. Prevalence and distribution of non-AIDS causes of death among HIV-infected individuals receiving antiretroviral therapy: a systematic review and meta-analysis [published online February 10, 2016]. *Int J STD AIDS*. doi:10.1177/0956462416632428.
4. Crum NF, Riffenburgh RH, Wegner S, et al. Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. *J Acquir Immune Defic Syndr*. 2006;41:194-200.
5. Bibas M, Biava G, Antinori A. HIV-associated venous thromboembolism. *Mediterr J Hematol Infect Dis*. 2011;3:e2011030.
6. Klein SK, Slim EJ, de Kruif MD, et al. Is chronic HIV infection associated with venous thrombotic disease? A systematic review. *Neth J Med*. 2005;63:129-136.
7. Crum-Cianflone NF, Weekes J, Bavaro M. Review: thromboses among HIV-infected patients during the highly active antiretroviral therapy era. *AIDS Patient Care STDS*. 2008;22:771-778.
8. Kuller LH, Tracy R, Belloso W, et al; INSIGHT SMART Study Group. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med*. 2008;5:e203. doi:10.1371/journal.pmed.0050203.
9. Kiser KL, Badowski ME. Risk factors for venous thromboembolism in patients with human immunodeficiency virus infection. *Pharmacotherapy*. 2010;30:1292-1302.
10. Sullivan PS, Dworkin MS, Jones JL, Hooper WC. Epidemiology of thrombosis in HIV-infected individuals. The Adult/Adolescent Spectrum of HIV Disease Project. *AIDS*. 2000;14:321-324.
11. Wester CW, Koethe JR, Shepherd BE, et al. Non-AIDS-defining events among HIV-1-infected adults receiving combination antiretroviral therapy in resource-replete versus resource-limited urban setting. *AIDS*. 2011;25:1471-1479.
12. AMPATH. Leading with care. http://www.ampathkenya.org. Accessed January 24, 2014.
13. Einterz RM, Kimaiyo S, Mengech HN, et al. Responding to the HIV pandemic: the power of an academic medical partnership. *Acad Med*. 2007;82:812-818.
14. Manji I, Pastakia SD, Do AN, et al. Performance outcomes of a pharmacist-managed anticoagulation clinic in the rural, resource-constrained setting of Eldoret, Kenya. *J Thromb Haemost*. 2011;9:2215-2220.

15. Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest*. 2008;133:454S-545S.
16. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;69:236-239.
17. Kaatz S. Determinants and measures of quality in oral anticoagulation therapy. *J Thromb Thrombolysis*. 2008;25:61-66.
18. Ageno W, Samperiz A, Caballero R, et al. Duration of anticoagulation after venous thromboembolism in real world clinical practice. *Thromb Res*. 2015;135:666-672.
19. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e419S-e494S.
20. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. *Chest*. 2016;149:315-352.
21. Brighton TA, Eikelboom JW, Mann K, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med*. 2012;367:1979-1987.
22. Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med*. 2012;366:1959-1967.
23. Simes J, Becattini C, Agnelli G, et al. Aspirin for the prevention of recurrent venous thromboembolism: the INSPIRE collaboration. *Circulation*. 2014;130:1062-1071.
24. Anderson AM, Chane T, Patel M, Chen S, Xue W, Easley KA. Warfarin therapy in the HIV medical home model: low rates of therapeutic anticoagulation despite adherence and differences in dosing based on specific antiretrovirals. *AIDS Patient Care STDS*. 2012;26:454-462.