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Review

Thromboses among HIV-Infected Patients during the Highly Active Antiretroviral Therapy Era*

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Abstract

Venous thrombotic events (VTEs) may occur at higher rates among patients with HIV; some studies suggest that highly active antiretroviral therapy (HAART) may increase the risk for these potentially life-threatening events. We performed a retrospective study among patients with HIV to evaluate the incidence and risk factors for VTEs during the HAART era. A literature review was performed examining VTEs in the pre- and post-HAART eras. Seventeen (3.7%) of 465 patients with HIV experienced a VTE. The overall incidence rate of deep VTEs among HIV-positive persons was 377 cases per 100,000 person–years, a fourfold higher rate compared to age-matched males in the general population. The median age at VTE was 36 years (range, 27–68). Patients with a thrombosis compared to those without had significantly lower current CD4 (153 versus 520 cells/mm^3, $p < 0.001$) and nadir (76 versus 276 cells/mm^3, $p < 0.001$) CD4 counts, higher viral loads (3.6 versus 1.7 $\log_{10}$ copies per milliliter, $p = 0.003$), and more likely to have a diagnosis of AIDS (76% versus 32%, $p < 0.001$); there were no differences in demographics, hyperlipidemia, current use of HAART, the duration of HAART or protease inhibitor (PI) exposure. A review of the literature noted 129 VTE cases; mean age was 40 years, mean CD4 count was 181 cells/mm^3, the majority of patients were not receiving HAART, and the most common risk factor was an ongoing infection. Thrombotic events are occurring among patients with HIV despite their relatively young ages. Advanced HIV disease is a risk factor for development of thromboses, possibly due to an increased inflammatory state or the presence of concurrent comorbidities such as infections. HAART or PI therapy does not appear to play a significant role in the occurrence of VTEs.

Introduction

HIV-infected persons are experiencing increasing life spans since the era of highly active antiretroviral therapy (HAART).[1,2] As the risk of fatal opportunistic infections and other AIDS-defining events have decreased, other causes of morbidity and mortality among HIV patients have emerged.[3–6] Subsequent to the advent of HAART, the rate of venous thrombotic events (VTEs) among HIV-infected persons has reportedly been on the rise,[7,8] yet little is known about the risk factors or the specific impact of antiretroviral drugs.

Some studies have suggested that HIV-related factors, rather than traditional risk factors (such as age, smoking, immobility, family history, and hospitalization), may be more important in the pathogenesis of clot formation among this population.[7,9–12] Patients with HIV may be at particular risk of thromboses by several mechanisms. Various abnormalities in coagulation pathway have been described among patients with HIV including: the presence of antiphospholipid antibodies, such as anticardiolipin antibodies and lupus anticoagulants; increased levels of von Willebrand factor, fibrinogen, and D-dimers; and deficiencies of protein C, protein S, antithrombin III, and heparin cofactor II.[13–22] In addition, HIV itself may induce the release of tumor necrosis factor (TNF)-α, which in turn, causes plasminogen acti-

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vator inhibitor 1 to be expressed by endothelial cells.[21,23] Furthermore, HIV may cause the expression of von Willebrand factor and tissue factor by the endothelium and smooth muscle cells.[24,25]

Some studies have noted that patients with low CD4 counts (< 200 cells/mm^3) or end-stage disease are at higher risk for coagulation abnormalities and thromboses[12,14,26,27]; however, other studies have refuted this association.[10] Concurrent opportunistic infections (e.g., cytomegalovirus, *Pneumocystis jiroveci* pneumonia, and Mycobacteria) have been epidemiologically linked to VTEs.[9,28] The pathogenesis may be due to induction cytokine production (TNF-α, interleukin [IL]-1, IL-6) which subsequently activates endothelial cells that are typically maintained in a resting, anticoagulant state. Although inflammation and cytokine production is known to activate the coagulation pathway, we are unaware of any studies that have examined the levels of TNF-α or IL-6 during VTEs among patients with HIV.

Medications utilized by HIV-infected patients may also augment the development of VTEs. Examples include megestrol acetate as well as erythropoietin.[9,29–31] Additionally, the receipt of HAART has been a proposed risk factor for VTEs. Supporting evidence includes studies suggesting the rate of VTEs has increased since the introduction of HAART[8] and reports noting a temporal association between the development of VTEs after the initiation of protease inhibitors (PI), especially indinavir.[9,12,32,33] Further potential support for this association is the relationship between PIs and arterial thrombotic events such as myocardial infarctions, the pathogenesis of which is likely related to endothelial cell dysfunction and the development of hyperlipidemia.[34,35] Other studies propose that PIs may have procoagulant activity by increasing plasminogen activator inhibitor.[21]

Most reports regarding venous events, however, have been small case series, and to our knowledge, no study has provided a detailed comparative HAART and PI use among those with and without VTEs. To clarify the risk factors and the impact of antiretroviral therapy on the development of VTEs, we evaluated the incidence rate and predictors of these events among a cohort of HIV-infected persons and performed a literature review of VTE cases to date.

Materials and Methods

We conducted a retrospective study of active HIV patients at a large U.S. clinic to evaluate the incidence of VTEs during the HAART era (January 1, 1996 to June 30, 2007). All patients were military beneficiaries (active duty members, retirees, or dependents) who received their HIV care at the Naval Medical Center San Diego, California. Cases included in this study occurred after documented HIV seroconversion, and only first-time incident events were utilized. Cases were identified by review of medical charts and radiology results.

VTEs consisted of deep and superficial thromboses, visceral vein thromboses, and pulmonary emboli (PE). Diagnostic studies to confirm the clot included venous ultrasounds for peripheral clots, abdominal computed tomography (CT) scans for visceral thrombosis, and high resolution chest CT scans for PE. Medical records were examined, and the data collected included last HIV seronegative test; first HIV seropositive test; demographics (age, gender, and race); CD4 cell count and HIV viral load at diagnosis of VTE or last available for those without VTE (controls); concurrent medical conditions; lipid values; the receipt of antiretroviral therapy/HAART at time of VTE or at the last clinic visit; and the duration of HAART use in months. In addition, we calculated the percentage of time of HIV infection in which the patient was receiving HAART; this was calculated as months on HAART divided by the duration in months of HIV infection. All patients in the study had free, open access to all antiretroviral medications. HAART was defined as two or more nucleoside reverse transcriptase inhibitors (NRTIs) in combination with at least one PI or one non-nucleoside reverse transcriptase inhibitor (NNRTI); one NRTI in combination with at least one PI and at least one NNRTI; or an abacavir or tenofovir containing regimen of three or more NRTIs. In addition, medical records were reviewed for the clinical presentation, complications, laboratory evaluation for causes of the thrombosis, use of tobacco, and hospitalization for each case of VTE. The study was approved by the Institutional Review Board.

Statistics included descriptive characteristics of the population. Incidence rates were calculated as first time thrombotic events divided by the number of active HIV clinic patients per year. We compared demographics, HIV-specific data, and HAART use among HIV patients with and without VTE using Fisher's exact and rank sum tests. Analyses were repeated examining only patients with deep VTEs. Significant variables at a p value < 0.10 in the univariate tests were examined using backward-stepwise multivariate logistic regression. Similar methods were utilized to compare VTE cases in the pre- and post-HAART eras in the medical literature. A p value of < 0.05 was considered statistically significant. All analyses were conducted using STATA 9.0 (College Station, TX).

Results

Seventeen (3.7%) of 465 patients with HIV experienced a thrombotic event during the study period. The median age of our entire study population was 41 years (range, 21–74 years); 93% were male, and race was reported as 50% Caucasian and 29% African American (Table 1). The median CD4 cell count of the cohort was 514 cells/mm^3 (range, 9–1200) with a median viral load of 1.7 $\log_{10}$ copies per milliliter (1.7–5.2); 71% were receiving HAART.

The total number of thrombotic events was 19; 2 patients experienced a clot recurrence at novel sites. Fifteen were deep venous thrombosis, 13 of these involved the extremities and 2 were located in the vasculature of the gastrointestinal tract (splenic and portal veins). There was one case of pulmonary embolism (PE) with an unknown originating site. Three cases involved the superficial vasculature. Overall, four (23%) patients with VTE experienced a PE.

The overall incidence rate of a thrombotic event was 454 cases per 100,000 person–years (PY) of follow-up; the rate was higher during the late (2002–2007) versus early (1996–2001) HAART eras (514 versus 374 per 100,000 PY, respectively), although this was not statistical significant ($p = 0.26$.). The overall incidence of deep VTEs was 377 cases/100,000 PY. Compared to age-matched males in the general population[36], HIV positive persons in our study had a fourfold higher rate of deep VTEs.

Table 1. Study Data

Characteristic	*Total population* n = *465*	*Thrombosis*[a] n = *17*	*No thrombosis*[a] n = *448*	p *value*
Age, median (range), years	41 (21–74)	36 (27–68)	41 (21–74)	0.84
Gender, sex; male	430 (92.5%)	15/17 (88.2%)	415/448 (92.6%)	0.37
Race				
Caucasian	232 (49.9%)	10/17 (58.8%)	222 (49.6%)	0.77
African American	135 (29.0%)	4/17 (23.5%)	131 (29.2%)	
Hispanic	61 (13.1%)	3/17 (17.6%)	58 (12.9%)	
Other	37 (8.0%)	0/17 (0%)	37 (8.3%)	
AIDS diagnosis[b]	158 (34%)	13/17 (76.4%)	145/448 (32.4%)	<0.001
CD4 nadir, median (range), cells/mm^3	268 (0–762)	76 (1-762)	276 (0–539)	<0.001
Duration of HIV, median (range), years	10.5 (1–22.5)	10 (1–18)	10.5 (1–22.5)	0.34
CD4 count, median (range), cells/mm^3	514 (9–1200)	153 (9–762)	520 (14–1200)	<0.001
Viral load, median (range), $\log_{10}$ copies/mL	1.70 (1.7–5.2)	3.64 (1.7–5.2)	1.70 (1.7–5.2)	0.003
Undetectable viral load (< 400 copies/mL)	309 (66.5%)	7/17 (41.1%)	302/448 (67.4%)	
HAART (y/n)	331 (71.2%)	10/17 (58.8%)	321/448 (71.7%)	0.28
Duration of HAART (months)	58.5 (0–160)	95 (0–132)	57 (0–160)	0.17
Duration of PI (months)	26.0 (0–160)	54 (0–129)	26 (0–160)	0.15
Percentage of Time with HIV Infection Receiving HAART[c]	47.8% (0–100%)	47.9% (0–90.1%)	47.6% (0–100%)	0.70
Percentage of time with HIV infection receiving PI[c]	20.4% (0–100%)	28% (0–89.6%)	20% (0–100%)	0.35
Diabetes mellitus	18 (3.9%)	2/17 (11.8%)	16/448 (3.6%)	0.14
Hypertension	185 (39.8%)	9/17 (52.9%)	176/448 (39.2%)	0.32
Lipid Data, mg/dL				
Median (range)				
Cholesterol	183 (67–303)	177 (67–272)	183 (111–303)	0.53
Triglycerides	134 (29–1092)	131 (45–371)	133 (29–1092)	0.82
HDL	39 (14–119)	33 (16–107)	39 (14–119)	0.40
LDL	112 (12–263)	105 (58–184)	113 (12–263)	0.30

[a]Data for the thrombosis cases is at time of diagnosis and for controls at last available clinic visit.
[b]AIDS was based solely on CD4 nadir < 200 cells/mm^3.
[c]Defined as the months receiving HAART divided by the duration in months of HIV infection. Percentage of time of PI use defined similarly.
HAART, highly active antiretroviral therapy; PI, protease inhibitors; HDL, high density lipoprotein; LDL, low density lipoprotein.

When examining only first-time events, the median age at the time of the thrombosis was 36 years (range, 27–68 years), and 88.2% of cases occurred in males which was similar to our overall study population. Ten of the patients presenting a thrombotic event were Caucasian, four were African American, and three were of Hispanic descent. The median duration of HIV infection at the time of thrombosis was 10 years (range, 1–18 years). The CD4 cell count at the time of VTE was a median of 153 (range, 9–762) cells/mm^3, median CD4 nadir of 76 (1–762) cells/mm^3, median viral load of 3.64 (1.7–5.2) $\log_{10}$ copies per milliliter, and 59% were receiving HAART. Overall, 41% had an undetectable viral load (< 400 copies per milliliter) at the time of the thrombotic event.

Regarding concurrent medical illnesses, 52% of those with VTE had a diagnosis of hypertension and 12% had diabetes mellitus. Hypercholesterolemia (>200 mg/dL) was noted among 31%, hypertriglyceridemia (>150 mg/dL) among 31%, low high density lipoprotein (HDL;< 35 mg/dL) among 53%, and elevated low density lipoprotein (LDL; >130 mg/dL) among 20% of those with VTEs.

All patients with a VTE had potential risk factor(s) for clot development. The most common was a concurrent active infectious process that occurred among 59% of the VTE patients. Active infections included *Staphylococcus aureus* bacteremia, coccidioidomycosis, *Streptococcus pneumoniae* bacteremia and pneumonia, *Cryptococcus neoformans* meningitis, disseminated histoplasmosis, suspected *Mycobacterium avium* complex infection, varicella zoster virus reactivation, necrotizing fasciitis, and pyomyositis.

Other potential risk factors for VTE among cases included peripherally inserted central catheter (PICC) (29%), neuropathy (24%), current hospitalization (18%), tobacco use

(12%), a family history of thrombosis (12%), decreased ability to ambulate (12%), cancer (non-Hodgkin's lymphoma) undergoing chemotherapy (6%), recent surgical procedure (6%), recent initiation of oral contraceptives (6%), and trauma (6%); some patients had multiple risk factors. Two patients were also receiving megestrol acetate and two others were on erythropoietin. No patient was receiving aspirin or other anticoagulants at the time of the VTE, and only one patient was on an antilipid medication. A hypercoagulability workup was performed among six (35%) patients: one patient had the G20210A prothrombin gene mutation, and two patients were positive for lupus anticoagulant.

Anticoagulant therapy was administered in 13 VTE (76%) cases. The 4 who were not treated included 2 patients with superficial thromboses and 2 with visceral thromboses. Of note, 1 patient with superficial clots had multiple recurrent events that were extremely painful; the patient improved after administration of coumadin. Coumadin therapy was given from 2.5 months to lifelong therapy; the most common duration was six months. Three patients (18%) were given lifelong therapy due to an underlying hypercoagulabilty state or due to recurrent embolic events; one patient received an inferior vena cava (IVC) filter.

HIV-infected persons with a thrombotic event compared to those without VTE in the univariate analyses had significantly lower CD4 cell counts (153 versus 520 cells/mm^3, $p < 0.001$), nadir CD4 cell counts (76 versus 276 cells/mm^3, $p < 0.001$), and higher HIV viral loads (3.6 versus 1.7 $\log_{10}$ copies per milliliter, $p = 0.003$) and were more likely to have a diagnosis of AIDS (76% versus 32%, $p < 0.001$); there were no differences in demographics, duration of HIV infection, hypertension, or diabetes (Table 1). Hyperlipidemia was examined both in terms of continuous and categorical approaches (data not shown), and no significant association was noted.

We evaluated the potential relationship between HAART use among those with a thrombosis at the time of clot formation (59%) compared to HAART use among those without thrombosis (72%) and found no significant association ($p = 0.28$). Only 5 of /17 (29%) of patients with VTE were receiving a PI at time of clot development for a median of 24 months (range 1–32 months) duration. We also evaluated the duration of HAART use, duration of PI use, percentage of time receiving HAART in relation to the duration of HIV infection, and the percentage of time on PIs in relation to the duration of HIV infection and found no significant relationships (Table 1).

All statistically significant variables in the univariate models were highly correlated with each other ($p < 0.05$), except for last HIV viral load and AIDS diagnoses. In the multivariate model, low CD4 cell count ($p < 0.001$) and high HIV viral load ($p = 0.045$) at VTE diagnosis or last visit remained significant. The odds ratio for the CD4 cell count was 0.57 per 100 cells; for each increase of 100 CD4 cells, the risk of VTE decreased 43%. Analyses were repeated, including only deep VTEs with no significant alterations in the results.

Review of the Literature

We searched the English literature for cases of venous thrombotic events among HIV-infected persons using EMBASE and MEDLINE (1981 to present). Our search words included "thrombosis," "thromboses," or "thrombophlebitis," and "HIV" or "AIDS." We also utilized the references of papers reviewed to identify additional cases. Reports that did not include detailed individual data were excluded.[7–9,29–31,37–43] Cases that simply mimicked venous occlusive disease, but were due to another etcology, were excluded.[44,45]

Our search yielded 129 cases, including our 17 cases.[10,16,17,20,22,26,31–33,46–81] Forty-eight of the cases occurred prior to HAART (published before 1997 accounting for the lag time of publication) with the first cases being reported in 1986[46,47]; 81 cases have been reported in the literature after the widespread availability of HAART (1997–2007). The mean and median age of the VTE was 39.8 years and 37 years, respectively (range, 22–70 years), and of those reporting gender, 84.9% were among males, likely related to the demographics of HIV-infected persons in the developed world from which the majority of cases were reported. Comparing the post- versus pre-HAART periods, the mean age was slightly higher (41.5 versus 36.6 years, $p = 0.03$), as was the percentage of cases among females (22.5% versus 5.4%, $p = 0.4$). Most (100/129; 77.5%) cases were single VTE events, whereas multiple sites of clot occurrence were present in 22.5%. Recurrent events over time occurred among 7.8% of patients with an initial VTE. The most common location was the lower extremity ($n = 50$), lung/pulmonary embolus ($n = 42$), upper extremity ($n = 11$), retinal vein ($n = 10$), abdominal viscera most commonly involving the portal vein ($n = 9$), inferior vena cava ($n = 6$), central nervous system ($n = 4$), dermal vessels ($n = 3$), and neck vessels ($n = 2$); the site was not specified in 10 cases. Some cases had multiple locations of VTEs.

A potential risk factor for the occurrence of the VTE was reported in 106 of 129 (82.2%) of cases. Most commonly, these were infections ($n = 48$), especially cytomegalovirus (CMV; $n = 20$), *Pneumocystis carinii* pneumonia (PCP; $n = 13$), *Mycobacteria* ($n = 11$), and pneumonia ($n = 5$); but a wide range of microorganisms were potentially implicated, including cryptococcus, histoplasmosis, coccidioidomycosis, herpes, and bacteremia. Infections at the time of VTE were more frequently noted in the pre- versus post-HAART era (60.4% versus 23.5%, $p < 0.01$).

Other commonly described risk factors for the development of a venous clot included cancer ($n = 23$), medication use ($n = 13$; megesterol [$n = 8$], erythropoietin [$n = 3$], and hormones [$n = 2$]), hospitalization ($n = 8$), intravenous line ($n = 7$), family history ($n = 5$), and illicit drug use ($n = 5$). Several reports noted abnormalities in thrombotic factors, including anticardiolipin antibodies ($n = 13$), lupus anticoagulant ($n = 7$), antiphospholipid syndrome ($n = 5$), decreased protein S ($n = 11$) and C ($n = 4$) levels, high factor VIII ($n = 4$), antithrombin III deficiency ($n = 2$), and elevated homocysteine ($n = 3$), von Willebrand factor ($n = 3$), and fibrinogen ($n = 1$).

Of cases reported after 1996, 38 (52.1%) of 73 which reported medication information were receiving HAART at the time of the VTE. A protease inhibitor was part of the regimen in 71% of these cases; there was a wide distribution of the type of PI: indinavir, $n = 6$; saquinavir, $n = 5$; ritonavir, $n = 5$; lopinavir, $n = 3$; nelfinavir, $n = 2$; atazanavir, $n = 2$. A variety of nucleoside agents were utilized, most commonly including lamuvidine, zidovudine, stavudine, tenofovir, emtricitabine, and didanosine, in decreasing order.

The mean and median CD4 cell count at the time of the VTE was 181 cells/mm^3 and 118 cells/mm^3, respectively (range, 1–800), and was higher in the post- versus pre-HAART era (203 versus 97 cells/mm^3, $p = 0.01$). Viral loads were only available in the HAART era, with a mean and median of 4.9 and 3.6 $\log_{10}$ copies per milliliter, respectively (range, 1.7–5.9). Forty-two percent of patients had a viral load less than 1000 copies per milliliter at the time of the VTE.

Treatment of the VTE typically utilized coumadin therapy ($n = 57$); heparin was utilized in 12 cases and low molecular weight heparin in 3 patients. An inferior vena cava filter was placed among 6 cases, and surgery was performed in another 6 patients. Several reports ($n = 40$) did not name the therapy administered. Overall, 82 (79.6%) of patients survived, and 21 (20.4%) died; 26 had no follow-up recorded. The majority of patients succumbed to AIDS-related causes and not the VTE itself. In the post-HAART era, 84% survived compared to 65% in the pre-HAART era ($p = 0.05$), which was likely secondary to the decline in the overall mortality rates after the advent of HAART.

Discussion

The current study demonstrates that venous thrombotic events may complicate HIV infection even among relatively young patients. In addition to classic risk factors, our research revealed that HIV-infected persons have additional predictors for the development of VTEs, including markers of advanced disease, such as low CD4 counts, high HIV viral loads, and concurrent infections. Unlike prior studies, we did not find an association between HAART or PI use and the development of venous thrombotic events.

The overall incidence rate of deep VTEs in the general population is approximately 1 case per 1000 PY, but this rises varies considerably with age: for example the rate is 0.1 per 1000 PY for males at 20 years of age, 0.9 at 40 years, 1.6–3.2 per 1000 PY at 60 years and 6.5 at 70 years.[36,82–84] Our study noted 3.8 deep VTEs per 1000 person–years, a fourfold higher rate compared to age-matched controls from the general population.[36] Other studies among HIV-infected persons have shown similar incidence rates of 1.9–7.6 per 1000 PY,[9,10,27,37,40] with the largest study of over 40,000 patients showing an incidence of 2.6 cases per 1000 PY.[9] A systematic review of the literature from 1991 to 2004 found that VTEs were 2 to 10 times more common among HIV-infected persons compared to the general population.[85]

These findings are somewhat paradoxical, given that most patients with HIV with VTEs were relatively young, and it is known that clots are associated with aging. All of the reviewed literature reported lower median ages among HIV positive individuals than in the general population.[8,10,26] The median age at VTE in our study was 36 years, and for the literature review, it was 37 years. Two autopsy studies also confirm that VTEs occur commonly in HIV patients and often at younger ages than expected.[86,87]

Regarding risk factors, our study noted an association between VTEs and low CD4 cell counts and high HIV viral loads. Although the CD4 nadir and most recent CD4 count were both predictive in the univariate models, the strongest predictor in our multivariate models was the CD4 cell count at the time of the VTE. The median CD4 count in our study among those with clot formation was 153 cells/mm^3. Other studies have also shown that low CD4 cell counts are associated with an increased thrombotic state.[12,14,26,88] For example, one study showed that patients with a CD4 count less than 200 cells/mm^3 had a 30-fold higher rate of VTE.[26] Although most cases occur at low CD4 cell counts, thromboses may occur over a broad range of CD4 cell counts (range, 1–800 cells/mm^3) suggesting that the risk is not completely confined to those with end-stage disease.

The association between low CD4 cell counts and VTEs may be related to an increasing hypercoaguable state found with progressive immune suppression. For example, studies have shown that protein S and C deficiencies are more common with lower CD4 cell counts.[13,14,17,89] Levine et al.[89] noted progressive decreases in protein S comparing HIV-negative women to those with asymptomatic HIV to those with clinical AIDS ($p < 0.0001$). There were similar stepwise increases in factor VIII. In addition, high HIV viral loads have been associated with hypercoagulable state.[89] These findings suggest that advanced HIV may lead to thrombosis by immune/inflammatory activation inducing a hypercoagulable state. Another potential explanation is the association of end-stage AIDS with an increased risk of infections, cancers, or other medical illnesses[9,12,26]; these conditions and their treatments often amplify the risk for VTEs. Similar to VTEs, thrombotic microangiopathy (TMA) also occurs at elevated rates among patients with HIV, is associated with advanced stages of HIV infection, and may be related to increased plasma inflammatory factors; however, unlike VTEs, TMA has marked decreased since the advent of HAART suggesting diverse pathogenic mechanisms.[90,91]

We noted that all our VTE cases occurred among patients with potential risk factors for clot development. The most common was an active infectious process. Our review of the literature also demonstrated this finding. Infections may lead to activation of endothelial cells and a procoagulant state.[12,26,28,36,52,92] In addition, often these patients require intravenous lines and hospitalization, both known risk factors for venous thromboses.

Dyslipidemia is a well-described risk factor for arterial events such as myocardial infarctions; however, its relationship with VTEs has been less clear. Some studies have found a high prevalence of hyperlipidemia; nonetheless, its role in the pathogenesis of clot formation has not been demonstrated.[10,11] Our study did not find a relationship between lipid levels (total cholesterol, triglycerides, HDL, or LDL) and an increased risk of VTEs.

Several retrospective studies have suggested that antiretroviral medications, particularly PIs, may play a role in the increased incidence of VTEs seen in the HAART era.[8,9,12,32,33] Two studies have found that the incidence of VTEs increased sharply since the introduction of PIs,[8,33] yet, another study reported no significant increase.[40] Some case reports and series described a temporal relationship between PI initiation and clot development,[32,33] while others did not.[11] One large study showed that indinavir was predictive of VTEs, but not other PIs.[9] A recent review concluded that any relationship between HAART and VTEs is weak.[85] Since patients receive antiretroviral regimens for long durations of time, further study has been advocated to better define possible relationships.[10]

We examined the current use of HAART, the duration of HAART, and the percentage of time with HIV infection on

HAART and found no differences among those with and without a VTE. Similar analyses were conducted for PI use, and no relationship was found. Only a minority of our cases and those described in the literature occurred among patients receiving a PI. These data suggest that if ART plays a role in VTEs, it is certainly not necessary for such events; whether ART has a permissive or additive effect is unclear, although our study did not find such a relationship.

The majority of our patients did not undergo a hypercoagulable work-up largely due to the presence of concurrent predisposing conditions. However, of the patients who had an evaluation, 50% had an abnormal finding, including the G20210A prothrombin gene mutation and lupus anticoagulant. Many other studies have shown that a procoagulant state frequently exists among patients with HIV, including the presence of antiphospholipid antibodies, anticardiolipin antibodies, and lupus anticoagulants; increased levels of von Willebrand factor and D-dimers; and deficiencies of protein C, protein S, antithrombin III, and heparin cofactor II.[13–22] These alterations toward a hypercoagulable state may be due to HIV itself, or also have been linked to the presence of coinfections with opportunistic infections.[16] For instance, CMV may induce the presence of antiphospholipid antibodies.[93,94] Although these abnormalities in coagulation factors are often noted among patients with HIV, they are frequently present without causing clinical manifestations,[16,17,47,78] suggesting that this may not be sufficient alone in causing VTEs. Their presence, however, may add an additional risk among patients with other risk factors for venous clots.

Clinically, deep vein thromboses most commonly involve the popliteal and/or femoral veins[10,36] followed by pulmonary emboli. In addition, abdominal involvement may occur as portal or splenic vein thromboses.[32,68,80] HIV-infected persons may experience recurrences; the literature review of case reports showed an 8% recurrence rate, while another large study found second VTEs among 15% of patients with HIV.[9] Management of VTEs among HIV patients is similar to that of the general population.[70]

Limitations of this study include its retrospective design. We advocate that prospective, controlled studies be conducted to establish temporal associations between hypothesized risk factors and VTEs. In addition, our study sample was small, so potential associations could have been missed. Larger, multicenter studies are needed, owing to the overall low incidence rate of VTEs. For example, the collection of VTE data could be an addition component of medication or to natural history studies. We did conduct a comprehensive review and analysis of the literature to supplement data on VTEs. Our study's strengths included its well-defined study population with meticulous recording of medical conditions and medication use as part of the military health benefit system.

In summary, thrombotic events are four times more common among HIV-infected persons than the general population, and often occur among relatively young patients. Advanced HIV disease is a risk factor for development of thromboses, possibly due to an increased inflammatory/hypercoagulable state and the presence of concurrent comorbidities. Our study found no relationship between the receipt of antiretroviral medications, specifically protease inhibitors, and the development of venous clots. DVT prophylaxis should be strongly considered among HIV patients with thrombotic risk factors, and thrombotic events in young patients with HIV risk factors may suggest the possibility of AIDS.

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