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# Venous Thromboembolism in Patients With HIV/AIDS *A Case-Control Study*

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## Abstract

**Background—**Retrospective cohort studies of HIV-infected patients suggest an incidence of venous thromboembolism (VTE) of 1% to 2%, which is 10 times that expected among people without HIV. We investigated the prevalence of established risk factors for VTE in this population and explored novel risk factors.

**Methods—**We conducted a case-control study using patients in the Johns Hopkins University AIDS Service cohort. We used conditional logistic regression and paired *t* tests to test for covariates significantly associated with VTE.

**Results—**We identified 160 patients with VTE diagnosed radiologically or with a clinical course consistent with VTE; 23% of the cases of VTE were diagnosed in hospitalized patients. The incidence of VTE was approximately 0.5% per patient-year. Patients with VTE and control patients did not differ by gender, but black patients were overrepresented among those with VTE (odds ratio [OR] = 1.9, 95% confidence interval [CI]: 1.11 to 3.08) and patients with VTE were older than controls (mean: 39 vs. 37 years; $P = 0.001$). Patients with VTE had lower CD4 counts (229 vs. 362 cells/mm$^3$; $P < 0.0001$), higher HIV RNA titers (120,254 vs. 71,262 copies/mL; $P = 0.013$), and lower hemoglobin concentrations (11.4 vs. 12.7 g/dL; $P < 0.0001$) preceding the event than those without VTE. The use of highly active antiretroviral therapy was not associated with VTE. In multivariate analyses, independent risks for VTE were age, hospitalization in the past 3 months (OR = 13, 95% CI: 6.4 to 27), central venous catheter use in the past 3 months (OR = 6.0, 95% CI: 2.3 to 16), and a CD4 count <500 cells/mm$^3$ (OR = 3.0, 95% CI: 1.2 to 7.8).

**Conclusions—**The incidence of VTE in our cohort is similar to that reported in other cohorts of patients with HIV. Recent hospitalization was the risk factor most strongly associated with VTE.

### Keywords

AIDS; HIV; incidence; risk factors; venous thromboembolism

Increasingly, patients with HIV are being recognized as patients at risk for deep venous thrombosis (DVT) and pulmonary embolism (PE). Significant morbidity is associated with venous thromboembolism (VTE), including cardiopulmonary compromise, postphlebitic syndrome, and bleeding complications from treatment. Thirty-day mortality rates in the general population are 6% for initial DVT and 12% for initial PE.[1] In the past decade, potent highly active anti-retroviral therapy (HAART) has increased the life expectancy of patients with HIV/AIDS; complications of chronic HIV infection, including VTE, pose new clinical challenges, however.

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Several studies suggest a 2- to 10-fold increased incidence of VTE among patients with HIV/AIDS compared with the general population, with estimates ranging from 0.3% to 2% per year.[2] Klein et al[3] systematically reviewed the literature on the epidemiology of VTE among patients with HIV/AIDS through 2004 and reported an incidence of DVT of 0.26% per year. The reasons for thrombophilia in this population are uncertain; this population may be enriched with traditional risk factors for VTE or may have novel risks.

We hypothesized that patients with HIV infection have novel clinical risk factors that raise the incidence rate of VTE to greater that seen in the HIV-uninfected population. In this case-control study, we aimed (1) to establish the incidence of VTE in a cohort of patients with HIV infection in the current era of HAART, (2) to determine the prevalence of established risk factors for VTE in this population and the odds of VTE associated with these risk factors, and (3) to identify novel clinical risk factors for VTE in this patient population.

## METHODS

### Cohort

Since 1989, clinical data have been captured on >99% of patients with HIV treated by the Johns Hopkins University AIDS Service. There are no inclusion or exclusion criteria for enrollment in the cohort except willingness to participate in clinical research and to receive longitudinal care in the clinic. The clinic-based medical record maintains information on all confirmed medical and surgical diagnoses; hospitalizations; laboratory information; fatalities; and prescribed therapy by medication name, dose, and number of refills. An observational database, established for research purposes, has been maintained on these clinic patients. Trained monitors use structured data collection forms to extract extensive demographic, clinical, laboratory, pharmaceutic, and psychosocial data from patient charts and from the hospital's automated databases at baseline and every 6 months thereafter.[4] Maintenance of this database and use of its contents are approved by the Institutional Review Board of the Johns Hopkins University School of Medicine.

### Study Design

We conducted a nested case-control study using participants in this cohort. Patients with diagnosed VTE were identified by International Classifications of Disease-9-Clinical Modification (ICD-9-CM) codes 325, 415.xx, 452, 451.xx, 453.xx, 671.x, and 673.xx. As a preliminary validation step, the electronic medical records were reviewed on 33 patients with these ICD-9-CM codes and on 32 patients from the cohort without a code indicating VTE. In this sample, the positive predictive value for this code was 73% and the negative predictive value was 100%. Given the poor specificity of these codes in this population, we verified all diagnoses by reviewing the electronic medical records and radiology reports of all patients identified in the administrative data.

### Validation Procedure

For each patient with an appropriate ICD-9-CM code, a single reviewer (AA) extracted clinical information from the medical records. We captured data on dates of admission and discharge and on radiologic procedures during that admission. Radiologic tests that we considered acceptable for a definitive diagnosis of VTE are listed in Table 1. If there was no evidence of VTE in the radiology reports, we reviewed the discharge summary for mention of VTE and the discharge medication list for an anticoagulant (warfarin, heparin, or low-molecular-weight heparin). If the discharge summary reported a history of VTE, earlier records were reviewed to find the earliest documentation of a thrombotic event.

### Case-Control Study

We defined the index visit as the most recent clinic visit preceding the diagnosis of VTE in the cases. Control patients were frequency-matched to the case patients at a ratio of 4:1 by duration of enrollment in the cohort and index visit date. For the control patients, the time since enrollment in the cohort must have been within 6 months of the case patient's enrollment date and the index visit must have been within 4 weeks preceding the case patient's index visit. We abstracted data from the cohort database, including concomitant diagnoses, major and minor surgical procedures, medications, pregnancy history, opportunistic infections, and laboratory data.

### Statistical Analyses

We used a matched-pairs *t* test to test for differences in continuous variables between the group with VTE and the group without VTE.[5] We calculated odds ratios (ORs) for putative risk factors for VTE with conditional logistic regression. Covariates significant in bivariate analyses were entered into multivariate conditional logistic models to assess the independent association of these covariates with VTE. Model fit was tested with likelihood ratio tests, and interaction terms were tested.

We calculated a yearly incidence rate by dividing the number of patients with confirmed VTE in that year by the number of person-years contributed to the cohort that year. The years 1990 through 1995 were pooled in this calculation. We calculated a weighted average of the yearly estimates by weighting each yearly estimate by the inverse of the SE of the point estimate for each year, obtained from the binomial distribution. We used direct adjustment to calculate an age-adjusted incidence of VTE, adjusted to the US population. We used STATA 9 (StataCorp LP; College Station, TX) for our analyses.

## RESULTS

### Validation Study

The search of the cohort database yielded 337 admissions with an ICD-9-CM code indicating thrombosis for 230 unique patients. Chart review revealed that 65 of these patients had no event that could be considered VTE, and these were considered to be false-positive ICD-9-CM codes. One patient was eliminated from our set because his thrombosis was documented as being clearly induced by a central venous catheter. An additional patient was eliminated because his incident event occurred before enrollment in the AIDS cohort, without documentation. This left 163 patients with incident VTE diagnosed since enrollment in the AIDS cohort. The positive predictive value for the ICD-9-CM codes we used was 71% (163 of 228 patients). In other words, we could not identify VTE in the medical record for 29% of the patients coded with an ICD-9-CM code indicative of VTE (Fig. 1).

Of these 163 incident venous thromboembolic events, 148 were confirmed by imaging. The additional 15 events had discharge summaries that were consistent with a diagnosis of VTE. Detailed historical clinical information was not available on 3 patients, leaving 160 case patients for the case-control analyses.

The weighted average incidence of VTE over the 15 years of observation of this cohort was 0.54% (95% confidence interval [CI]: 0.39 to 0.73) per patient-year. Because the VTE incidence rate varied little by age strata, the incidence adjusted to the age distribution of the US population was similar at 0.56% per year.

### Case-Control Study

By design, we had 544 control subjects for our analyses. The case patients and control patients were all enrolled in the AIDS cohort between January 1989 and June 2004. The index visit occurred after a median of 2.9 years. Twenty-nine of the incident VTE events occurred before formal enrollment in the AIDS cohort, but documentation confirming the diagnosis was available in the electronic medical record. Among the case patients who were hospitalized, laboratory values are from a clinic visit a median of 134 days (interquartile range [IQR]: 102 to 198 days) preceding hospitalization. Unavoidably, for those case patients whose first contact with our institution was for admission with VTE, we have no earlier laboratory data. Laboratory data were available on 129 of 160 case patients and on 411 of 544 control patients.

Thirty-nine PEs were diagnosed, along with 109 DVTs. Thirty percent of diagnosed DVTs were of the upper extremity. The 17 thromboses occurring in other places included portal, hepatic, and mesenteric vein thromboses. Computed tomography and duplex ultrasonography were the most frequently used imaging modalities (see Table 2).

The demographic and clinical characteristics of the patients with VTE are summarized in Table 3. Patients with VTE were largely middle-aged black men (reflecting the demographics of the patients in the cohort). Nearly three quarters (69%) of these patients had been hospitalized in the previous 3 months. The distribution of CD4 cell counts and HIV-1 RNA levels suggested that this was a population of moderately sick patients, although the proportion of patients on HAART was not high (33%).

In bivariate analyses, relative to the control patients, the case patients were more likely to be black (OR = 1.85, 95% CI: 1.11 to 3.08) and to be older than 36 years (OR = 1.85, 95% CI: 1.21 to 2.83). Case patients were more likely than control patients to have a CD4 count <500 cells/$mm^3$ (OR = 5.0, 95%, CI: 2.4 to 10) and to have a hemoglobin concentration <12 g/dL (OR = 3.34, 95% CI: 2.2 to 5.0). Patients with VTE were more likely to have been hospitalized in the preceding 3 months (OR = 21, 95% CI: 11 to 35), and were more likely to have been hospitalized for lymphoma in the previous year (OR = 18, 95% CI: 4.0 to 83) than patients without VTE. Additionally, the case patients with VTE were much more likely to have used a central venous catheter in the preceding 3 months (OR = 17, 95% CI: 8.6 to 32) and to have received mechanical ventilation in the previous 3 months (OR = 9.6, 95% CI: 3.73 to 25). Few of the case patients had undergone knee or hip surgery or were recently pregnant.

In our multivariate analyses, age remained a predictor of VTE. Hospitalization within the previous 3 months was strongly independently associated with VTE (adjusted OR = 13, 95% CI: 6.4 to 27), as was recent use of a central venous catheter (OR = 6.0, 95% CI: 2.3 to 16) (Table 4). There was an interaction between these 2 risk factors, such that having been hospitalized and having a central venous catheter further raised the odds of VTE. A CD4 count <500 cells/$mm^3$ was associated with VTE with an OR of 3.0 (95% CI: 1.2 to 7.8), with no dose-response relation lower than this level. Hemoglobin was no longer independently significant because it was highly correlated with hospitalization status. Neither viral load nor use of antiretroviral drugs was associated with VTE.

## DISCUSSION

We report an incidence of VTE of 0.54%, comparable to what has been reported in the literature.[6–8] Klein et al[3] systematically reviewed the literature on the epidemiology of VTE among patients with HIV infection. The 10 studies reviewed varied greatly in quality. The largest, a multisite US study, reported results from medical record abstraction on 42,935 patients between 1990 and 1998 and found an incidence of DVT of 0.26%.[9] A high-quality study using Veterans Affairs hospital administrative data reported a 2% incidence of DVT, PE, phlebitis, and

thrombophlebitis in the 13,549 studied men.[9] Another study looking at PE among 3792 patients admitted to an HIV service between 1993 and 1997 documented an incidence of 0.26%.[10] These studies had varying rigor regarding the requirements for objective documentation of thrombosis, and most were restricted to identifying thromboses diagnosed in inpatients. We suspect that the use of administrative data may have overestimated the incidence rate in some studies. Despite their limitations, the incidences are fairly comparable across studies and are around 1%, a rate approximately 10 times what would be expected in a population of comparable age without HIV.

In several of the studies described previously, investigators sought to identify risk factors for VTE in this population, noting that the population of patients with HIV/AIDS has a disproportionately high prevalence of many of the traditional risks for VTE, including frequent hospitalization.[11,12] In our cohort, independent risks for VTE included age, hospitalization in the past 3 months, recent central venous catheter use, and a CD4 count <500 cells/$mm^3$.

Several groups have aimed to identify unique risk factors for VTE among patients with HIV/AIDS. In a large study by Sullivan et al,[13] age older than 45 years, cytomegalovirus infection, other opportunistic illness, hospitalization, and use of megestrol acetate or indinavir were identified as risks for VTE. Similar to our findings, Saif et al[14] found a higher prevalence of thrombosis in patients with CD4 counts <200 cells/$mm^3$ relative to patients with higher CD4 counts. Many other hypotheses about thrombotic risk factors in this population have been proposed, including activation of endothelial cells from infections such as cytomegalovirus, herpes, and possibly HIV itself or formation of thrombotic microparticles from platelets or CD4 lymphocytes as a consequence of HIV infection.[15] Alterations in natural anticoagulant proteins have been observed in patients with HIV; most commonly reported is a reduction in protein S.[15–18] Much has been reported on the prevalence of antiphospholipid (APL) antibodies in this population, as reviewed in detail by Uthman and Gharavi.[19] The prevalence of lupus anticoagulants has been estimated as high as 53% to 70% and that of anticardiolipin antibodies as high as 44% to 90%. Despite these associations, the clinical relevance of these antibodies is unclear.[19,20]

Although a prospective study in which risk factors can be identified before the event is optimal, there are several strengths to our study. We were able to nest this case-control study in an existing cohort established in 1990. With this study design, data were collected without knowledge of the outcome of interest. An additional strength of this study is that we verified each case of VTE by medical record review. We demonstrated that the use of administrative data from ICD-9-CM codes alone may be risky in this population; the specificity was low in our cohort. As with any case-control study, there are limitations, including the variable length of time between the laboratory measures, particularly CD4 cell count and HIV RNA level, and the outcome. The choice of controls can also strongly affect the estimates in a case-control study, and matching on duration of enrollment in the cohort eliminated this as a variable that we could investigate. We consider the results of this study to be hypothesis generating, because the CIs surrounding our ORs are wide and should be more thoroughly investigated prospectively.

Future studies should involve further clarification of the risks for VTE in this population. The rate is 10 times higher that what would be expected in the general population and is expected to increase as this population ages. Mechanistic work is essential to identify the common pathway to thrombosis in this population, which originates from these rather disparate risk factors. With this understanding, appropriate prophylactic measures can be instituted, which may include universal VTE prophylaxis with heparin or low-molecular-weight heparin on hospitalization or possibly anti-inflammatory or antiplatelet agents for high-risk outpatients. The mortality from PE is high, and the morbidity from DVT is great. With the tremendous

recent gains in life expectancy for patients with HIV/AIDS, addressing the threat of VTE is increasingly appropriate.

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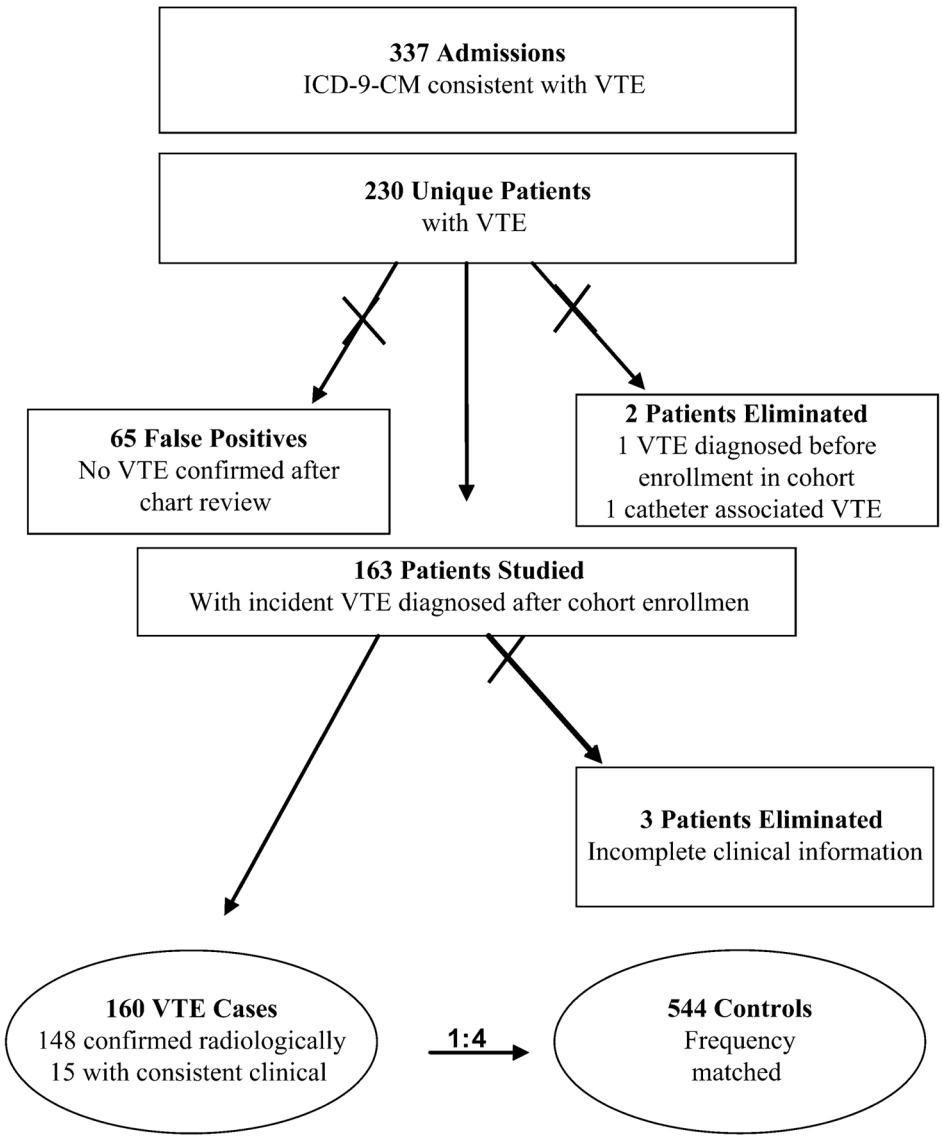


**FIGURE 1.**
Validation scheme.

**TABLE 1**

Confirmatory Tests for Diagnosis of VTE for This Study

| Anatomic Site | Diagnostic Test |
|---|---|
| DVT | Extremity venous sonography showing noncompressible vein, computed tomography venography, MR venography, contrast venography |
| PE | Ventilation/perfusion scan with a moderate- or high-probability scan, high-resolution computed tomography, pulmonary angiography |
| Portal, hepatic or mesenteric vein thrombosis | Duplex ultrasound, computed tomography, contrast venography |
| Cerebral venous sinus thrombosis | Computed tomography angiography, MR venography/MR angiography, conventional contrast angiography |

MR indicates magnetic resonance.

**TABLE 2**

Thromboses Imaged During the Index Admission (145 Unique Individuals)

| Diagnostic Test | Summary of Findings | Diagnostic Test | Summary of Findings |
|---|---|---|---|
| Computed tomography, angiography/venography | 6 upper extremity DVTs<br>8 lower extremity DVTs<br>3 high probability PEs<br>4 portal vein thromboses<br>5 other | Conventional contrast angiography | 1 upper extremity DVT |
| High-resolution thoracic CT | 15 high-probability PEs<br>3 moderate-probability PEs<br>1 upper extremity DVT<br>4 other | Duplex sonography | 16 upper extremity DVTs<br>60 lower extremity DVTs<br>2 portal vein thromboses |
| Ventilation/perfusion scan | 8 high-probability PEs<br>5 intermediate-probability PEs | MR venography | 1 lower extremity DVT |

CT indicates computed tomography; MR, magnetic resonance.

**TABLE 3**

Clinical Characteristics of Patients With VTE (n = 160)

| Characteristic | n (%) or Median [Range] |
|---|---|
| Mean age, y | 39 [22 to 67] |
| Male | 100 (63%) |
| Race | |
| African American | 134 (84%) |
| White | 24 (15%) |
| Other | 2 (1.8%) |
| HIV risk factor (more than 1 answer possible) | |
| IDU | 99 (62%) |
| MSM | 30 (19%) |
| High-risk heterosexual sex | 36 (23%) |
| Hospitalization within past 3 months | 111 (69%) |
| Central venous catheter within past 3 months | 60 (38%) |
| Mechanical ventilation in previous 3 months | 16 (10%) |
| Hospitalization in previous 12 months for other diagnoses | |
| Congestive heart failure | 9 (6%) |
| Lymphoma | 9 (6%) |
| Nephrotic syndrome | 3 (2%) |
| Kaposi sarcoma | 2 (1%) |
| Median white blood cell count preceding diagnosis of VTE (cells/$mm^3$) (n = 129) | 4460 [IQR: 3180 to 6300] |
| Median platelet count preceding diagnosis of VTE (×109/mL) (n = 129) | 211 [IQR: 149 to 291] |
| Median hemoglobin preceding diagnosis of VTE (g/$dL_)$ | 11.5 [IQR: 10 to 12.7] |
| CD4 cell count preceding diagnosis of VTE (cells/$mm^3$) (n = 119) | |
| <50 | 34 (29%) |
| 50 to 200 | 37 (31%) |
| 200 to 500 | 36 (30%) |
| >500 | 12 (10%) |
| HIV-1 RNA level preceding diagnosis of VTE ($log_{10}$/mL) (n = 101) | |
| <4.0 | 45 (45%) |
| 4.0 to 5.0 | 23 (23%) |
| >5.0 | 34 (34%) |
| No. on HAART preceding VTE | 52 (33%) |
| Blood type | |
| A | 46 (31%) |
| AB | 9 (6%) |
| B | 28 (19%) |
| O | 66 (44%) |

IDU indicates intravenous drug use; MSM, men who have sex with men.

## TABLE 4

Clinical Predictors of VTE

| Covariates | Adjusted OR* (95% CI) |
|---|---|
| Age (for every 1-year increase) | 1.05 (1.01 to 1.09) |
| Hospitalization in previous 3 months | 13 (6.4 to 27) |
| Central venous catheter use in previous 3 months | 6.0 (2.3 to 16) |
| CD4 count <500 cells/mm$^3$† | 3.0 (1.2 to 7.8) |

*Adjusted for other covariates in the table; there was a significant interaction term for the interaction between hospitalization and central venous catheter use; however, inclusion of this term substantially changed the classification of only 6 patients as to their predicted probability of VTE (adjusted ORs are presented without inclusion of this interaction term).

†Relative to >500 cells/mm$^3$.