Human Immunodeficiency Virus Infection and Risk of Venous Thromboembolism

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ABSTRACT: *Background:* The incidence of venous thromboembolism (VTE) in HIV-infected patients is uncertain, and the impact of protease inhibitors on the incidence of VTE is also uncertain, yet important to know to create a database for providing opinion regarding prophylaxis for the prevention of VTE. *Methods:* Data from the National Hospital Discharge Survey (NHDS) were analyzed from 1990 through 2005. International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9-CM) codes were used to identify illnesses. *Results:* Among 2,429,000 patients older than 18 years hospitalized with HIV infection, the incidence of pulmonary embolism (PE) was 0.4%, deep venous thrombosis (DVT) 1.4%, and VTE 1.7%. The relative risks compared with all hospitalized non-HIV patients of PE, DVT, and VTE were 0.91, 1.26, and 1.21. The incidence of VTE from 1990 to 1996 was 17,000 of 1,198,000 (1.4%) and after 1996 it was 25,000 of 1,230,000 (2.0) ($P < 0.0001$) (relative risk = 1.43). Among hospitalized patients who did not have HIV, the relative risk comparing incidences after 1996 with incidences before was 1.22. *Conclusion:* The incidence of VTE in patients with HIV infection was higher than in non-HIV patients. The incidence of VTE in patients with HIV in the postprotease inhibitor era (after 1996) was higher than in HIV patients before 1996, but the incidence was also higher in non-HIV patients after 1996. The higher incidence since 1996 is small, probably not clinically significant, and not necessarily because of protease inhibitors. **KEY INDEXING TERMS:** Pulmonary embolism; Deep venous thrombosis venous thromboembolism; HIV infection; Human immunodeficiency virus infection. **[Am J Med Sci 2008;336(5):402–406.]**

Patients with human immunodeficiency virus (HIV) infection often have a hypercoagulable state characterized by acquired protein S, protein C and antithrombin III deficiency,[1–4] particularly if the CD4 cell count is low.[5,6] Procoagulant factors, such as heparin cofactor II, plasminogen activator inhibitor I, tissue plasminogen activator, von Willebrand factor, and tissue factor may be increased as well[7] and antiphospholipid antibodies may also be present.[3] Opportunistic infections,[6] particularly cytomegalovirus disease[8] and malignancies[6] such as Kaposi's sarcoma[9,10] may also contribute to a hypercoagulable state. The progestational agent, megestrol, may also lead to VTE.[10–12] Even so, before 1992, it was thought that venous thrombosis was an infrequent problem in patients with HIV infection, although HIV-related hypercoagulability had been recognized.[10,13] Several case series, however, have now shown that the risk of venous thromboembolism (VTE) in patients with HIV infection is higher than in uninfected patients.[12–14] The incidence of VTE in patients with HIV infection has been reported by some to be increasing[15,16] but some showed a decreasing incidence.[17] An increasing incidence has been suggested to relate to the use of protease inhibitors.[15,16,18] Some suggested that VTE might relate specifically to indinavir.[12] It is important to know the incidence of venous thromboembolism (VTE) in HIV-infected patients to create a database for providing opinion regarding prophylaxis in hospitalized patients.[10] Therefore, to assess the incidence of VTE in HIV-infected patients, we analyzed the data from the National Hospital Discharge Survey.

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Methods

The number of patients 18 years of age or older discharged from short-stay non-Federal hospitals throughout the United States with a diagnostic code for HIV infection from 1990 through 2005 was obtained from the NHDS.[19] Among these patients the number with pulmonary embolism (PE) and/or deep venous thrombosis (DVT) was determined. The NHDS consists of data obtained annually from approximately 270,000 sampled inpatient abstracts from about 500 non-Federal short-stay hospitals in 50 states and the District of Columbia.[19] The NHDS samples about 8% of short stay non-Federal hospitals and about 1% of discharges.

The incidence of VTE in patients with HIV infection was compared with all hospitalized patients who did not have HIV

Table 1. Incidence and Relative Risk of Pulmonary Embolism, Deep Venous Thrombosis, and Venous Thromboembolism in Hospitalized Patients with and without HIV Infection

Age (yrs)	n/N (%) HIV	n/N (%) No HIV	Relative Risk (95% CI) HIV vs. No HIV
pulmonary embolism			
≥18	10,000/2,429,000 (0.4)	2,094,000/462,966,000 (0.5)	0.91 (0.89–0.93)
30–49	7,000/1,804,000 (0.4)	362,000/114,599,000 (0.3)	1.23 (1.20–1.26)
Deep venous thrombosis			
≥18	34,000/2,429,000 (1.4)	5,096,000/462,966,000 (1.1)	1.26 (1.25–1.28)
30–49	25,000/1,804,000 (1.4)	922,000/114,599,000 (0.8)	1.72 (1.70–1.74)
Venous thromboembolism			
≥18	42,000/2,429,000 (1.7)	6,602,000/462,966,000 (1.4)	1.21 (1.20–1.22)
30–49	31,000/1,804,000 (1.7)	1,196,000/114,599,000 (1.0)	1.65 (1.63–1.67)

All incidences comparing HIV with no HIV differed ($P < 0.0001$).

infection. The incidence in patients with HIV was also compared with the incidence in hospitalized non-HIV patients who were at high risk of VTE because of heart failure,[20] stroke,[21] or cancer.[22]

The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes used to identify HIV infection were 042, 043, and 044. The ICD-9-CM codes used for identification of patients with pulmonary embolism (PE) were 415.1, 634.6, 635.6, 636.6, 637.6, 638.6, 673.2. The codes used for deep venous thrombosis (DVT) were 451.1, 451.2, 451.8, 451.9, 453.2, 453.8, 453.9, 671.3, 671.4, 671.9. Those with VTE had ICD-9-CM discharge codes for PE and/or DVT. Five-digit codes, such as 451.11 (included under the code 451.1), were not listed, as they were included under the corresponding 4-digit codes. We compared the incidence of PE, DVT, and VTE in hospitalized patients with HIV infections to those without HIV infections. We also compared the incidences of PE, DVT, and VTE in patients who did not have HIV infections, but had heart failure (ICD-9-CM codes 428.0, 428.1, and 428.9) ischemic stroke (codes 434 and 436), hemorrhagic stroke (code 431), and cancer. Codes used for cancer were malignant neoplasms at the following sites: lip, oral cavity, and pharynx 140.0, 140.1, 140.3–140.6, 140.8, 140.9, 141.0–141.6, 141.8, 141.9, 144.0, 144.1, 144.8, 144.9, 145.0–145.6, 145.8, 145.9, 146.0–146.9, 147.0–147.3, 147.8, 147.9, 148.0–148.3, 148.8, 148.9, 149.0, 149.1, 149.8 and 149.9; esophagus 150.0–150.5, 150.8 and 150.9; stomach 151.0–151.6, 151.8 and 151.9; colon 153.0–153.9; rectum, rectosigmoid junction and anus 154.0–154.3 and 154.8; liver, gallbladder, intra- and extrahepatic bile ducts 155.0–155.2, 156.0–156.2, 156.8 and 156.9; pancreas 157.0–157.4, 157.8 and 157.9; trachea, bronchus and lung 162.0, 162.2–162.5, 162.8, 162.9; female breast 174.0–174.9; uterus 179, 182.0, 182.1 and 182.8; cervix 180.0, 180.1, 180.8 and 180.9; ovary 183.0; prostate 185; bladder 188.0–188.9; kidney 189,0, 189.1; brain 191.0–191.9; lymphoma (includes lymphosarcoma and reticulosarcoma) 200.0–200.2, 200.8, 201.0–201.7, 201.9, 202.0–202.6, 202.8, 202.9; leukemia 204.0–204.2, 204.8, 204.9, 205.0–205.3, 205.8, 205.9, 206.0–206.2, 206.8, 206.9, 207.0–207.2, 207.8, 208.0–208.2, 208.8, 208.9; and "other" lymphatic and hematopoietic tissues (includes myeloproliferative disease) 238.7. We also attempted to evaluate the incidence of VTE in patients hospitalized with HIV infection who had Kaposi's sarcoma (ICD-9 code 176) and cytomegalovirus infection (code 0785).

Recognizing that the incidence of VTE is age-related,[23] and 74% of the HIV patients were of age 30 to 49 years, we compared patients with HIV infections and VTE aged 30 to 49 years with patients who did not have HIV infections who were the same age. We also calculated rates of VTE before and after the introduction of protease inhibitor therapy, which was in 1996.[15]

χ^2 was used to compare proportions. Relative risks and 95% confidence intervals (CI) were calculated using calculator for confidence intervals of relative risk (www.sign.ac.uk/methodology/risk.xls).

Results

From 1990 through 2005, among 2,429,000 patients hospitalized with HIV infections, 12% were aged 18 to 29 years, 74% were aged 30 to 49 years and only 14% were aged 50 years or older. Among 462,966,000 hospitalized patients who did not have HIV infections, 16% were aged 18 to 29 years, 25% were aged 30 to 49 years and 59% were aged 50 or older.

Among 2,429,000 patients older than 18 years of age hospitalized with HIV infections the incidence of PE was 10,000 (0.4%), DVT 34,000 (1.4%) and VTE 42,000 (1.7%) (Table 1). Among 1,804,000 HIV patients aged 30 to 49 years, the incidences were the same. The relative risks of PE, DVT, and VTE compared with all hospitalized patients who did not have HIV infections among patients ≥18 years were 0.91, 1.26, and 1.21 (Table 1). Among patients aged 30 to 49 the relative risks were 1.23, 1.72, and 1.65, respectively (Table 1).

Regarding gender, among 1,766,000 men and 663,000 women ≥18 years hospitalized with HIV infection, the incidence of VTE was 1.6% in men and

Table 2. Relative Risk of Pulmonary Embolism, Deep Venous Thrombosis, and Venous Thromboembolism in Hospitalized Patients with HIV Infection (According to Gender and Race)

Age (yrs)	Relative Risk (95% CI) Male vs. Female	Relative Risk (95% CI) African American vs. White
Pulmonary embolism		
≥18	0.66 (0.64–0.69)	2.09 (1.99–2.20)
30–49	0.69 (0.66–0.72)	4.16 (3.87–4.48)
Deep venous thrombosis		
≥18	0.93 (0.91–0.96)	0.78 (0.76–0.80)
30–49	1.01 (0.98–1.04)	0.81 (0.79–0.83)
Venous thromboembolism		
≥18	0.84 (0.83–0.86)	0.95 (0.93–0.97)
30–49	0.90 (0.88–0.92)	1.08 (1.05–1.11)