Incidence of Venous Thromboembolism in Patients Living with HIV: A Cohort Study

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To the Editor:

SEVERAL STUDIES RAISED suspicions about risk of venous thromboembolism (VTE) in patients with HIV. Incidence of VTE in the general population has been estimated at 1–1.8 per 1000 person-years.¹ In a systematic review, Klein et al. report higher incidence of VTE in HIV, ranging from <1% to 18% in one small study of 60 HIV-positive patients.² Several risk factors have been described for VTE in HIV, such as antiretroviral medication,^{3,4} chronic low-level inflammation,⁵ opportunistic infections, AIDS status, and cancer.^{6,7}

To our knowledge, there is no population-based study estimating both outpatient and inpatient incidence of VTE in HIV-positive versus a comparable population of HIV-negative patients. We hypothesized that HIV-infected patients would have a higher incidence rate of both inpatient and outpatient VTE, after excluding events linked to intravenous drug use.

We conducted a retrospective cohort study using the administrative health care database of the province of Québec (RAMQ database), Canada. The database contains data on medical billing claims, hospitalization discharge summaries, and prescription drug dispensations for subscribers to the public pharmaceutical insurance (40% of Québec population).

HIV infection was identified using ICD-9 (*International Classification of Diseases*, Ninth Revision) codes in physician billing claims and pharmaceutical dispensation of at least one HIV-specific antiretroviral drug. Date of first dispensation for HIV-specific drug was defined as cohort entry date. Each HIV-positive patient was matched to up to four HIV-negative patients by age, gender, and cohort entry date. Exclusion criteria were as follows: age <20 years at cohort entry date, no public insurance drug coverage for a year before cohort entry, and a diagnosis of atrial fibrillation or intravenous drug use in the year before cohort entry. Patients were followed into the cohort until occurrence of (1) death, (2) end of pharmaceutical insurance coverage, or (3) end of study. The study period was from January 1, 1996 to December 31, 2011.

The primary outcome was occurrence of either inpatient or outpatient VTE. Outpatient thromboembolism was defined as a new treatment with any anticoagulation drug within 15 days

after a radiological test used to diagnose VTE. Inpatient thromboembolism was defined as a new diagnostic code in a hospital discharge summary. Diagnostic codes for superficial vein thrombosis and varicose veins were excluded. Thromboses were considered to be provoked if they happened (1) 30 days following discharge after major surgery; (2) current treatment with hormone replacement therapy; (3) pregnancy and postpartum period or (4) presence of active cancer. Events that did not fulfill those conditions were classified as unprovoked.

Crude and adjusted hazard ratio (aHR) of VTE were modeled using Cox proportional hazard models. All potential confounders listed in Table 1 were included in the multivariable model as time-dependent variables. All analyses were performed using SAS software version 9.3.

This research project was approved by the ethics review board of our institution.

We identified 4424 adults with HIV matched to 16,350 controls. Prevalence of each exclusion criteria was higher in the HIV-positive group; 0.5% versus 0.3% had prior diagnosis for atrial fibrillation, 1.0% versus 0.6% were anticoagulated at baseline, 2.1% versus 0.3% had prior VTE, and 11.6% versus 0.8% used intravenous drugs. The final cohort included 3820 HIV-positive and 16,074 HIV-negative participants.

Table 1 shows baseline characteristics of the study participants. Overall, mean age was 42 years and 76% were men. Cardiovascular diseases, chronic obstructive pulmonary disease, and active cancer were more prevalent in HIV-positive patients. A total of 224 incident events of VTE occurred, 87 in HIV-positive (3.59/1000 person-years, 95% confidence interval [CI] 2.84–4.35), and 137 in HIV-negative patients (1.79/1000 person-years, 95% CI 1.49–2.09). Overall, 121 (54.0%) of events were diagnosed and treated on an outpatient basis. This proportion varied from 41.4% outpatient events in the HIV-positive to 62.0% in the HIV-negative.

Table 2 presents the results of the univariable and multivariable analyses. The aHR for VTE associated to HIV infection was 1.48 (95% CI 1.11–1.98). Other factors independently associated with VTE were age (aHR 1.26,

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TABLE 1. BASELINE CHARACTERISTICS OF STUDY PARTICIPANTS

Characteristic	HIV-positive (n = 3820)	HIV-negative (n = 16,074)
Age, years		
Mean (SD)	41.76 (0.17)	41.90 (0.08)
Median (min–max)	41.00 (20.00–86.00)	41.00 (20.00–87.00)
Male, n (%)	2979 (78.0)	12,156 (75.6)
Follow-up duration, years		
Mean (SD)	6.34 (0.08)	4.76 (0.03)
Median (IQR)	4.69 (2.32–10.41)	3.58 (1.34–7.31)
Comorbidities, n (%)		
Hepatitis-C infection	73 (1.91)	36 (0.22)
Alcohol abuse	96 (2.51)	154 (0.96)
Cardiovascular disease	96 (2.51)	239 (1.49)
Chronic obstructive pulmonary disease	217 (5.68)	448 (2.79)
Chronic kidney disease	47 (1.23)	44 (0.27)
Hypertension	152 (3.98)	777 (4.83)
Type 2 diabetes	96 (2.51)	463 (2.88)
Active cancer	240 (6.28)	199 (1.24)
Medications, n (%)		
Female hormone therapy	104 (2.72)	765 (4.76)
Testosterone replacement therapy	63 (1.65)	27 (0.17)
Antiplatelets	13 (0.34)	48 (0.3)
Number of hospitalizations, mean (SD)	0.55 (0.01)	0.12 (0.00)

Characteristics are measured in the year before cohort entry date.
IQR, interquartile range; SD, standard deviation.

95% CI 1.11–1.43 for each 10-year increase in age), cardiovascular disease (aHR 1.53, 95% CI 1.02–2.29), chronic kidney disease (aHR 2.41, 95% CI 1.42–4.11), active cancer (aHR 4.99, 95% CI 3.35–7.43), current exposure to female hormone therapy (aHR 2.99, 95% CI 1.57–5.69), and being within 30 days of a surgery (aHR 49.99, 95% CI 34.09–73.3).

We found that HIV infection was associated to a 1.48 (95% CI 1.11–1.98) increase in the incidence of inpatient and outpatient VTE, compared with an age- and gender-matched HIV-negative population. Other factors independently associated with an increased risk of VTE in our cohort were age, being diagnosed with cardiovascular disease, chronic kidney disease, active cancer, being exposed to female hormone therapy, and postsurgical period.

These results are consistent with prior data. Rasmussen et al. examined the risk of inpatient VTE in people living with HIV compared with matched HIV-negative patients. They found an incidence rate ratio of 3.84; 95% CI 2.99–4.93 associated with HIV infection.⁸ Fultz et al. reported standardized incidence ratios for VTE in HIV patients of 1.39; 95% CI 1.26–1.52 before 1996 (inpatient events only) and 1.33; 95% CI 1.24–1.43 after 1996 (both inpatient and outpatient).⁹ Malek et al. reported odds ratios for VTE in HIV-positive patients of 1.43; 95% CI 1.39–1.46.¹⁰ Other studies that also reported increased risk of VTE in HIV were mainly case reports, case series, and reviews of hospital discharge databases.^{4,10–12}

Key limitations of our study include data limitations. We had no access to laboratory data (viral load and CD4 count). Although this would have allowed us to characterize further the pathways that lead to increased thrombotic risk in patients living with HIV, it does not interfere with the interpretation of our results. Data on some potentially important confounders are lacking, such as smoking and obesity. Unmeasured confounders could explain some of the association found. Our study was

conducted using the administrative health care databases of the province of Québec, Canada. This is a developed country setting with universal health care coverage. The external validity of our results might be low in other socioeconomic settings.

Strengths of this study include its large sample size, its control group, and the inclusion of both inpatients' and outpatients' events. Because outpatients' codes are generated as part of physician's billing, it is possible that a physician would write down the code for thrombophlebitis for a suspicion of thrombophlebitis, creating falsely high event rates (false positives). To avoid this, we used a stringent outpatient event definition, requiring an imaging test used for VTE diagnosis, followed by initiation of anticoagulation. This will limit the possibility of false positive events. Inpatient diagnostic codes are generally more valid, as they are written by the treating physician at the time of hospital discharge, after complete investigation. We are, therefore, confident that our outcome definition is valid, and that any outcome misclassification would not be differential in the HIV-positive and HIV-negative.

In conclusion, we found that HIV infection was associated with increased risk of VTE, even after adjustment for confounders. Medical practitioners should be aware of that association when diagnosing and treating thromboembolic disease.

Declaration

M.D. and T.D. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Authors' Contributions

M.D. wrote the scientific protocol, planned and oversaw the analysis. M.D. and L.S. wrote the article's first draft. T.D. and Y.J. reviewed the scientific protocol, participated in

TABLE 2. UNIVARIABLE AND MULTIVARIABLE HAZARD RATIOS FOR FIRST VENOUS THROMBOEMBOLISM (OUTPATIENT AND INPATIENT) ACCORDING TO HIV STATUS AND COVARIATES

<i>Characteristic</i>	<i>Number of events (n = 224)</i>	<i>Crude hazard ratio (95% CI)</i>	<i>Adjusted hazard ratio (95% CI)</i>
HIV			
Positive	87	2.01 (1.57–2.55)	1.48 (1.11–1.98)
Negative	137	Referent	Referent
Sex			
Male	175	1.03 (0.78–1.36)	1.17 (0.82–1.67)
Female	49	Referent	Referent
Age (per 10 years increase in age)	N/A	1.39 (1.25–1.54)	1.26 (1.11–1.43)
Hepatitis C infection ^a			
Positive	12	2.51 (1.53–4.14)	1.58 (0.85–2.92)
Negative	212	Referent	Referent
Alcohol abuse ^a			
Present	23	2.26 (1.55–3.3)	1.2 (0.76–1.91)
Absent	201	Referent	Referent
Cardiovascular disease ^a			
Present	38	2.65 (1.92–3.66)	1.53 (1.02–2.29)
Absent	186	Referent	Referent
Chronic obstructive lung disease ^a			
Present	39	1.93 (1.41–2.64)	1.34 (0.92–1.94)
Absent	185	Referent	Referent
Chronic kidney disease ^a			
Present	18	4.27 (2.71–6.72)	2.41 (1.42–4.11)
Absent	206	Referent	Referent
Hypertension ^a			
Present	41	1.43 (1.04–1.96)	0.95 (0.65–1.39)
Absent	183	Referent	Referent
Type 2 diabetes ^a			
Present	19	1.37 (0.92–2.04)	0.65 (0.39–1.08)
Absent	205	Referent	Referent
Active cancer ^b			
Present	63	16.15 (12.09–21.58)	4.99 (3.35–7.43)
Absent	161	Referent	Referent
Antiplatelet medication ^b			
Present	9	3.02 (1.53–5.95)	0.84 (0.33–2.12)
Absent	215	Referent	Referent
Female hormone therapy ^c			
Present	17	2.54 (1.61–4.0)	2.99 (1.57–5.69)
Absent	207	Referent	Referent
Testosterone replacement therapy ^c			
Present	11	1.89 (1.0–3.58)	0.66 (0.24–1.81)
Absent	213	Referent	Referent
Postsurgical period ^d			
Present	67	93.48 (69.03–126.59)	49.99 (34.09–73.3)
Absent	157	Referent	Referent

^aDefined as time-dependent variables during the entire follow-up time, once present, presence of the characteristic is considered irreversible for remainder of follow-up time.

^bOne-year period after any diagnostic code for cancer.

^cDefined as current use of medication: dispensation date+duration of dispensation +30 days.

^dDefined as 30 days after hospitalization discharge for a surgical procedure either intra-abdominal or orthopedic of lower limb or spine, proximal to and including ankle.

CI, confidence interval.

analysis planning, conducted the data analysis, and reviewed the article. M.L. and C.T. reviewed the protocol and article for important intellectual content.

relate to this study. She receives honorarium or research funding from Merck, VIIV, and Gilead in form of research grants, speaker, and advisory board member.

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M.D., T.D., L.S. and M.L. have no conflict of interest to declare. C.L.T. has no conflict of interest to declare that

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