Predisposing Factors for Venous Thromboembolism in HIV-infected Patients

Mark W. Tenforde[1], Robin M. Nance[1], Susan R. Heckbert[1], Kristina A. Crothers[1], Matthew J. Budoff[2], William B. Lober[1], William C. Mathews[3], Elvin Geng[4], Peter W. Hunt[4], Joseph J. Eron[5], Richard D. Moore[6], Michael J. Mugavero[7], James H. Willig[7], Greer Burkholder[7], Michael S. Saag[7], Mari M. Kitahata[1], Joseph A.C. Delaney[1], Heidi M. Crane[1]

[1]University of Washington, Seattle, WA, USA; [2]University of California, Los Angeles, Los Angeles, CA, USA; [3]University of California, San Diego, CA, USA; [4]University of California, San Francisco, CA, USA; [5]University of North Carolina, Chapel Hill, North Carolina, USA; [6]Johns Hopkins University, Baltimore, Maryland, USA; [7]University of Alabama Birmingham, Birmingham, Alabama

BACKGROUND

- The epidemiology and risk factors for venous thromboembolism (VTE) in people living with HIV (PLWH) in the era of widespread access to antiretroviral therapy (ART) is poorly understood
- HIV is associated with chronic inflammation and immune activation and increases the risk of VTE including deep venous thromboses (DVT) and pulmonary embolism (PE)
- VTEs are common with an incidence of ~1-1.7/1000 person-years among those without HIV
- While data among PLWH are more limited, particularly in the current era VTE risk is likely 1.5-10 times more common in PLWH than the general population
- Prior VTE studies in HIV populations have often lacked consistent central adjudication of clinical events and occurred in earlier treatment eras
- The impact of VTE is substantial in terms of both morbidity and mortality
- The impact may continue to increase with the aging of the population of PLWH
- We developed and implemented a robust verification process with centralized ascertainment and adjudication of VTEs in a large North American HIV cohort
- We conducted this study to better understand VTE risk among PLWH including traditional and HIV-related predisposing risk factors

METHODS

STUDY COHORT

- Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) is a well characterized longitudinal observational cohort of PLWH from clinical sites across the US
- Potential VTEs from 2005-2017 at 6 CNICS sites were identified through CNICS data repository

DATA SOURCES

- The CNICS Data Repository captures comprehensive clinical data from all outpatient and inpatient encounters for the CNICS cohort including:
  - Laboratory test results
  - Medication data
  - Diagnoses
- Reports from imaging tests such as venous duplex and CT angiography
- Historical clinical information collected at initial clinic visits by standardized intake process including prior ART use

CNICS VTE PROTOCOL

- We developed a centralized adjudication approach for VTE with ascertainment based on multiple criteria including diagnoses and procedures, followed by centralized adjudication of primary data

ASCERTAINMENT

- Potential events at clinical sites were identified in the centralized CNICS data repository. Case identification criteria included VTE diagnoses. In addition procedures such as inferior vena cava (IVC) filter placement and imaging such as lower extremity doppler tests were also included to optimize sensitivity of ascertainment for potential VTEs

Table 1. *Demographic and clinical characteristics of PLWH from multiple sites across the United States by type of venous thromboembolism*

Characteristic	DVT N=164 (46)	PE N=108 (30)	CAT N=35 (10)	Combo N=50 (14)	P-value
Sex					0.2
Female	30 (18)	29 (27)	11 (31)	12 (24)	
Age					0.2
<40	31 (19)	23 (21)	13 (37)	5 (10)	
40-49	56 (34)	34 (31)	11 (31)	16 (32)	
50-59	52 (32)	35 (32)	8 (23)	21 (42)	
60-69	18 (11)	15 (14)	3 (9)	5 (10)	
≥70	7 (4)	1 (1)	0 (0)	3 (6)	
Race/Ethnicity					0.3
White	77 (47)	37 (34)	12 (34)	20 (40)	
African-American	72 (44)	61 (56)	18 (51)	25 (50)	
Hispanic	12 (7)	10 (9)	3 (9)	4 (8)	
Other/unknown	3 (2)	0 (0)	2 (6)	1 (2)	
HIV Transmission Risk Factor					0.2
Heterosexual	42 (26)	42 (39)	10 (29)	14 (28)	
MSM	70 (43)	43 (40)	13 (37)	22 (44)	
IDU	44 (27)	15 (14)	10 (29)	13 (26)	
Other/unknown	8 (5)	8 (7)	2 (6)	1 (2)	
CD4 count closest to event (cells/μl)					0.8
0-200	54 (34)	31 (30)	13 (39)	13 (27)	
201-350	31 (20)	24 (23)	8 (24)	10 (20)	
>350	73 (46)	48 (47)	12 (36)	26 (53)	
HIV-1 RNA closest to event					0.4
<400	113 (72)	71 (69)	19 (58)	34 (71)	
Smoking status					0.5
Never	56 (34)	34 (31)	10 (29)	21 (42)	
Former	35 (21)	18 (17)	5 (14)	10 (20)	
Current	73 (45)	56 (52)	20 (57)	19 (38)	

- For each potential VTE, the site assembled de-identified packets that included physician notes, procedure results, imaging reports, lab results (e.g. d-dimer values), and medications (e.g. anticoagulants)
- Exposures such as antiretroviral medications were redacted from packets to allow reviews to be blinded to key covariates of interest

CENTRAL ADJUDICATION

- Two experts independently reviewed each packet, followed by a 3rd if discrepancies occurred
- Reviewers entered standardized data required to define a VTE into a web application such as imaging results, capturing all components, thus enabling the application of multiple operational definitions of whether a VTE occurred
- VTE classified by: Definite/probable, VTE type, and anatomic location
- Reviewers reviewed packets for predisposing risk factors for VTE such as bedrest and long plane rides

ANALYSES

- We conducted chi square tests and t-tests to compare demographic and clinical characteristics of individuals by VTE type
- Descriptive analyses including prevalence was used to describe predisposing factors
- Analyses were limited to initial VTE for those with recurrent events

RESULTS

- We included 357 PLWH with VTE: 208 (58%) deep venous thrombosis (DVT), 156 (44%) pulmonary embolus (PE), and 43 (12%) catheter-associated thrombosis events, including 50 (14%) with multiple types simultaneously (mostly DVT/PE)
- Two-hundred seventy-five (77%) patients were male; median age was 49 years old (interquartile range [IQR]: 41,56); and 146 (41%) were white, 176 (49%) black, and 29 (8%) Hispanic (Table 1)
- Median CD4 count was 319 cells/μL (IQR: 154,548) and 30% had a detectable viral load (≥400 copies/mL)
- One-hundred sixty-eight (47%) were current smokers
- Most patients had multiple predisposing factors (Table 2); mean 2.1 (standard deviation [SD] 1.5)
- Only 49 (14%) had no pre-disposing factor identified
- The most common predisposing factors identified included recent hospitalization (143, 40%), infection (142, 40%), or immobilization/bed rest (84, 24%) within the past 90 days, and current injection drug use (80, 22%)
- Eighty-eight (25%) had both hospitalization and infection in the past 90 days; 59 (17%) had both immobilization/bed rest and hospitalization

Table 2. *Predisposing factors for venous thromboembolism among PLWH from multiple sites across the United States*

Predisposing factor	Number (357 overall)	Percent
Hospitalization in the past 90 days	143	40%
Infection in the past 90 days	142	40%
Immobilization/bed rest in the past 90 days	84	24%
Injection drug use	80	22%
Malignancy, active in the past year	65	18%
Surgery in past 90 days	38	11%
Chronic obstructive pulmonary disease	34	10%
Chemotherapy in the past 90 days	25	7%
Estrogen and/or progestin or anabolic steroid use in last 30 days	26	7%
Dialysis	22	6%
Inherited or acquired thrombophilia (other than malignancy)	21	6%
Heart failure prior to event	18	5%
Major trauma including fracture in past 90 days	16	4%
Pulmonary hypertension	15	4%
Transfusion in past 30 days	17	5%
Long plane ride/prolonged sitting in the past 30 days	11	3%
Nephrotic syndrome	7	2%
Current pregnancy or within 3 months post-partum	2	<1%

CONCLUSION

- We conducted a robust adjudication process and examined predisposing factors for VTE among PLWH in a large North American cohort
- PLWH with VTE were relatively young and most had at least one identified traditional pre-disposing risk factor
- In addition, non-traditional risk factors, including injection drug use and recent infection, were common
- Almost one-third of patients had detectable viral loads, and almost half were active smokers, suggesting potential modifiable pro-thrombotic risk factors

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