Accepted Manuscript online: 2023-06-14 Article published online: 2023-07-25

Venous Thromboembolism in Patients with Human Immunodeficiency Virus

Kashyap Patel[1] Omaike Sikder[2] Nikhil Nair[3] Sean Wasserman[4,5] John W. Eikelboom[6]

[1] School of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[2] School of Nursing, McMaster University, Hamilton, Ontario, Canada
[3] Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada
[4] Division of Infectious Diseases and HIV Medicine, Groote Schuur Hospital, University of Cape Town, Rondebosch, Western Cape, South Africa
[5] Wellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Rondebosch, Western Cape, South Africa
[6] Thrombosis Service, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Address for correspondence John W. Eikelboom, MBBS, Department of Medicine, McMaster University, Thrombosis Service, HHS - General Division 237 Barton Street East, Hamilton, Ontario L9K1H8, Canada (e-mail: eikelbj@mcmaster.ca).

TH Open 2023;7:e226–e228.

At the end of 2020 there were an estimated 38.4 million people living with human immunodeficiency virus (HIV) worldwide, the majority in low- and middle-income countries.[1] Widespread implementation of effective antiretroviral therapies (ARTs) has transformed the natural history of HIV such that affected individuals now have a life expectancy approaching that of the general population. Despite highly effective ART patients living with HIV remain at increased risk of arterial vascular disease,[2] possibly mediated by chronic inflammation.[3] It is unclear whether they also remain at increased risk of venous thromboembolism (VTE).[4]

We searched PubMed for observational and randomized studies published since January 1, 2000, involving patients with HIV that reported event rates for VTE, including deep vein thrombosis (DVT) and/or pulmonary embolism (PE). The Supplementary Material details the search strategy (►**Supplementary Table S1**, online only) and the process of study selection (►**Supplementary Fig. S1**, online only). All 18 studies identified in our search reported VTE, whereas 12 separately reported DVT and 11 separately reported PE. Only 10 of the 18 studies reported the mean (or median) follow-up period, and use of ART was not consistently reported.

The mean age of patients enrolled in these studies was between 33.5 and 59 years. In pooled analyses, the crude incidence rates were: VTE 1.77% (interquartile range [IQR]: 1.40–2.14), DVT 1.44% (IQR: 0.98–1.89), and PE 0.43% (IQR: 0.21–0.64) (►**Table 1**). For studies that reported the duration of follow-up (10 studies, 28,139 patients), the pooled incidence rate for VTE per 1,000 person-years was 2.8 (IQR: 2.5–3.0) (►**Supplementary Table S2**, online only).

Our data have limitations related to the potential for selection and information biases and confounding. Additionally, estimates of the crude incidence of VTE in patients with HIV were dominated by a single study that included 2.429 million patients and accounted for 97% of patients included in our pooled estimates. The pooled rate of VTE per 1,000 patient-years did not include this study and may be more informative because it takes account of the risk exposure.

In the general population the incidence rate of VTE is 1 to 2 per 1,000 patient-years, but is highly age-dependent, ranging from 0.1 per 1,000 patient-years under the age of 30 to 10 per 1,000 patient-years in those over the age of 80.[4] A Danish nationwide cohort study reported that patients aged 30 to 60 have incidence rates for VTE ranging from 0.32 to 1.50 events per 1,000 person-years.[5] Our data confirm that even in the era of widespread use of highly active ART, patients with HIV have a risk of VTE that remains substantially elevated compared with the general population. For individuals, the risk of VTE will vary according to traditional risk factors (e.g., inherited hypercoagulable states, hospitalization, surgery) as well as the severity of HIV (e.g., CD4 count) and disease complications (e.g., Kaposi's sarcoma, non-Hodgkin lymphoma, tuberculosis) as well as diseases that are more common in long term survivors of HIV (e.g., cancer). Patients with HIV who have unexplained chest pain, dyspnea, or hypoxemia should be investigated for PE.

received
March 30, 2023
accepted after revision
June 7, 2023
accepted manuscript online
June 14, 2023

DOI https://doi.org/10.1055/a-2110-5884.
ISSN 2512-9465.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Table 1 Crude incidence rates for venous thromboembolism, deep vein thrombosis, and pulmonary embolism[a]

Study	Mean Age[b]	Venous thromboembolism			Deep vein thrombosis			Pulmonary embolism		
		Patients	Events	Crude incidence (%)	*N*	Events	Crude incidence (%)	*N*	PE	Crude incidence (%)
Saif et al 2001[6]	38.3	131	10	7.63	131	6	4.58	131	2	1.53
Saber et al 2001[7]	43[c]	4,752	36	0.76	4,752	33	0.69	4,752	3	0.06
Copur et al 2002[8]	–	362	14	3.87	362	9	2.49	362	5	1.38
Fultz et al 2004[9]	46.7	37,535	745	1.98	–	–	–	–	–	–
Majluf-Cruz et al 2004[10]	38.3	1,550	34	2.19	1,550	31	2.00	1,550	2	0.13
Jacobson et al 2004[11]	43	650	24	3.69	650	14	2.15	650	10	1.54
Lijfering et al 2008[12]	41	109	11	10.09	109	6	5.50	109	5	4.59
Matta et al 2008[13]	–	2,429,000	42,000	1.73	2,429,000	34,000	1.40	2,429,000	10,000	0.41
Jong et al 2010[14]	36.4	86	0	0	86	0	0	–	–	–
Rasmussen et al 2011[15]	36.4	4,333	148	3.42	–	–	–	–	–	–
Arab et al 2017[16]	–	1,997	25	1.25	–	–	–	–	–	–
Borjas-Howard et al 2017[17]	35	87	10	11.49	–	–	–	–	–	–
Howard et al 2019[18]	44	14,389	232	1.61	14,389	99	0.69	14,389	105	0.73
Castilho et al 2019[19]	36.9	6,206	44	0.71	–	–	–	–	–	–
Erbe et al 2003[20]	39	49	6	12.24	49	3	6.122	49	2	4.08
Stellbrink et al 2019[21]	33.5	657	1	0.15	–	–	–	657	1	0.15
Olson et al 2021[22]	53	110	4	3.64	110	3	2.727	110	1	0.91
Zimba et al 2021[23]	59	58	4	6.90	58	4	6.897	–	–	–
Pooled		*2,502,061*	*43,348*	*1.77 (1.40–2.14)*	*2,451,246*	*34,208*	*1.44 (0.98–1.89)*	*2,451,759*	*10,136*	*0.43 (0.21–0.64)*

Abbreviation: PE, pulmonary embolism.
[a]References are provided in the Supplementary Material.
[b]Some studies only reported age ranges.
[c]Average age reported only for patients with DVT.

Conflict of Interest
None declared.

References

1 WHO. HIV/AIDS [Internet]. World Health Organization. 2020. https://www.who.int/health-topics/hiv-aids#tab=tab_1
2 Bibas M, Biava G, Antinori A. HIV-associated venous thromboembolism. Mediterr J Hematol Infect Dis 2011;3(01): e2011030
3 Jackson BS, Pretorius E. Pathological clotting and deep vein thrombosis in patients with HIV. Semin Thromb Hemost 2019; 45(02):132–140
4 Kearon C. Epidemiology of venous thromboembolism. Semin Vasc Med 2001;1(01):7–26
5 Arnesen CAL, Veres K, Horváth-Puhó E, Hansen J-B, Sørensen HT, Brækkan SK. Estimated lifetime risk of venous thromboembolism in men and women in a Danish nationwide cohort: impact of competing risk of death. Eur J Epidemiol 2022;37(02): 195–203
6 Saif MW, Bona R, Greenberg B. AIDS and thrombosis: retrospective study of 131 HIV-infected patients. AIDS Patient Care STDS 2001;15(06):311–320
7 Saber AA, Aboolian A, LaRaja RD, Baron H, Hanna K. HIV/AIDS and the risk of deep vein thrombosis: a study of 45 patients with lower extremity involvement. Am Surg 2001;67(07):645–647
8 Copur AS, Smith PR, Gomez V, Bergman M, Homel P. HIV infection is a risk factor for venous thromboembolism. AIDS Patient Care STDS 2002;16(05):205–209
9 Fultz SL, McGinnis KA, Skanderson M, Ragni MV, Justice AC. Association of venous thromboembolism with human immunodeficiency virus and mortality in veterans. Am J Med 2004;116 (06):420–423
10 Majluf-Cruz A, Silva-Estrada M, Sánchez-Barboza R, et al. Venous thrombosis among patients with AIDS. Clin Appl Thromb Hemost 2004;10(01):19–25
11 Jacobson MC, Dezube BJ, Aboulafia DM. Thrombotic complications in patients infected with HIV in the era of highly active antiretroviral therapy: a case series. Clin Infect Dis 2004;39(08): 1214–1222
12 Lijfering WM, Sprenger HG, Georg RR, van der Meulen PA, van der Meer J. Relationship between progression to AIDS and thrombophilic abnormalities in HIV infection. Clin Chem 2008;54(07): 1226–1233
13 Matta F, Yaekoub AY, Stein PD. Human immunodeficiency virus infection and risk of venous thromboembolism. Am J Med Sci 2008;336(05):402–406
14 Jong E, Louw S, van Gorp ECM, Meijers JCM, ten Cate H, Jacobson BF. The effect of initiating combined antiretroviral therapy on endothelial cell activation and coagulation markers in South African HIV-infected individuals. Thromb Haemost 2010;104 (06):1228–1234
15 Rasmussen LD, Dybdal M, Gerstoft J, et al. HIV and risk of venous thromboembolism: a Danish nationwide population-based cohort study. HIV Med 2011;12(04):202–210
16 Arab K, Spence AR, Czuzoj-Shulman N, Abenhaim HA. Pregnancy outcomes in HIV-positive women: a retrospective cohort study. Arch Gynecol Obstet 2017;295(03):599–606
17 Borjas-Howard JF, Bierman WFW, Meijer K, van der Werf TS, Tichelaar YIGV. Venous thrombotic events in patients admitted to a tuberculosis centre. QJM 2017;110(04):215–218
18 Howard JFB, Rokx C, Smit C, et al; ATHENA observational HIV cohort investigators. Incidence of a first venous thrombotic event in people with HIV in the Netherlands: a retrospective cohort study. Lancet HIV 2019;6(03):e173–e181
19 Castilho JL, Escuder MM, Veloso V, et al. Trends and predictors of non-communicable disease multimorbidity among adults living with HIV and receiving antiretroviral therapy in Brazil. J Int AIDS Soc 2019;22(01):e25233
20 Erbe M, Rickerts V, Bauersachs RM, Lindhoff-Last E. Acquired protein C and protein S deficiency in HIV-infected patients. Clin Appl Thromb Hemost 2003;9(04):325–331
21 Stellbrink HJ, Arribas JR, Stephens JL, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet HIV 2019;6(06):e364–e372
22 Olson JJ, Schwab PE, Jackson J, Lange JK, Bedair HS, Abdeen A. HIV-positive patients are at increased risk of venous thromboembolism after total joint replacement. J Am Acad Orthop Surg 2021;29 (11):479–485
23 Zimba S, Nutakki A, Chishimba L, et al. Risk factors and outcomes of HIV-associated stroke in Zambia. AIDS 2021;35(13):2149–2155