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HIV infection as a permanent, acquired risk factor for VTE

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We read with great interest the Review by Martinelli *et al.* (Inherited risk factors for venous thromboembolism. *Nat. Rev. Cardiol.* **11**, 140–156 [2014]),[1] which highlighted the main causes of inherited thrombophilia, their clinical manifestations, and the implications for antithrombotic prophylaxis. The Review was highly appreciated. However, whereas venous thromboembolism (VTE) is a dynamic, multifactorial disorder that results from the interaction between acquired and inherited factors, some important evidence that supports a role of HIV infection as a permanent, acquired risk factor for VTE was not included. Therefore, we wish to discuss the important implications of HIV infection in the accurate assessment of the absolute risk of VTE in patients with inherited thrombophilia.

Current epidemiological data suggest that chronic HIV infection is associated with a twofold to tenfold increase in the risk of VTE.[2,3] Furthermore, this elevated risk was confirmed in a large cohort study, with the highest rate in patients with both hepatitis C virus (HCV) and HIV.[4] The pathogenesis of this infection-associated hypercoagulable state is associated with both the ongoing, unresolved, chronic inflammation and the chronic immune activation.[5] Indeed, several experimental studies have shown upregulation of tissue factor owing to direct or indirect monocyte activation, increased thrombin generation, increased platelet production and activation, severe endothelial dysfunction and reduced nitric oxide production, and a cytokine-induced decline in liver function resulting in a procoagulant state.[2,5,6] Treatment of HIV with combination antiretroviral therapy (cART) improves coagulation homeostasis and reduces viral replication, inflammation, and immune activation. cART often restores the peripheral $CD4^+$ T-cell count and reduces viral replication, but inflammation, immune dysfunction, and coagulation abnormalities persist and strongly predict the risk of non-AIDS disorders.[7,8] The risk of VTE also depends on the treatment of specific co-infections frequently observed in these patients, such as tuberculosis, *Cytomegalovirus*, and HCV, which contribute to the inflammatory environment during cART.[9]

Increasing age is one of the main acquired risk factors for VTE.[1] Interestingly, the profile of HIV-associated changes in markers of inflammation and coagulation are very similar to those reported with ageing and increased frailty in the general population (including a decline in endothelial nitric oxide production; increased platelet activation; and increased levels of D-dimer, factors VIII, IX, and XI, fibrinogen, IL-6, and von Willebrand factor).[5,10–12] Considerable attention should be given to the evidence that patients with HIV infection age more rapidly than individuals without HIV infection.[13] The phenomenon of accelerated immune ageing is also supported by the observation of earlier onset of age-related morbidities in those with HIV infection, including VTE, than in individuals without HIV infection.[8,13,14] Furthermore, the risk of cardiovascular events is expected to increase substantially as patients with HIV infection live to older ages. Taken together, the hypercoagulable state associated with HIV infection and with other chronic infections, such as tuberculosis and HCV, must be considered as a permanent risk factor for VTE. Finally, in our view, many patients with mild thrombophilia, considered to be at low risk of VTE on the basis of chronological age and inherited risk factors, should be considered to be at increased risk when infected with HIV, particularly if chronically co-infected with HCV, with important implications for prophylaxis and extended treatment of VTE.

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Competing interests
The authors declare no competing interests.

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