persons receiving antiretroviral treatment (ART) have also been shown to exhibit greater atherosclerotic disease compared with their HIV-negative counterparts. Cardiovascular disease is likely to increase with enhanced longevity in HIV-positive persons on highly active antiretroviral therapy.

The mechanisms by which HIV infection causes thrombosis are multifactorial and complex.[3] HIV-associated factors, as opposed to traditional risk factors (eg, smoking, immobility, family history, hospitalization), are believed to be central to the pathogenesis of thrombosis. Several coagulation abnormalities have been reported among HIV-infected patients including the presence of antiphospholipid antibodies, increased levels of von Willebrand factor, elevated homocysteine, and deficiencies of protein C, protein S, antithrombin III, and heparin cofactor II.[2] Previous studies suggest that ART, in particular HIV protease inhibitors, negatively impacts the cardiovascular system.[2] However, there are also several publications in which patients reported to manifest with VTE did not receive ART.[2] Advanced HIV disease may be another risk factor for the development of thromboses, perhaps due to an increased inflammatory state or the presence of concurrent comorbidities, such as infections.[2]

In the Strategies for Management of Antiretroviral Therapy (SMART) trial, mortality from non-AIDS events such as cardiovascular disease was found to be higher for participants randomized to intermittent, CD4-guided ART (drug conservation arm) than to continuous ART (viral suppression arm).[4] This resulted in researchers stopping the trial prematurely. An increased risk of death was associated with higher levels of high-sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), and D-dimers. IL-6 and D-dimer increased at 1 month by 30% and 16%, respectively, in the drug conservation arm but by only 0% and 5%, respectively, in the viral suppression arm ($P < .0001$). Moreover, the increases in these inflammatory/thrombotic markers in the drug conservation arm were related to HIV RNA levels at 1 month ($P < .0001$). These findings led the investigators to suggest that HIV-induced activation of inflammation and a hypercoagulable state increases the risk of death among HIV-positive patients, and that interrupting ART further increases this risk.[5]

Funderburg et al suggest that the increased risk for coagulation in HIV-infected persons may be related to increased expression of the procoagulant tissue factor (TF, thromboplastin). They further demonstrate that monocyte expression of TF correlates with HIV RNA and D-dimer levels in plasma. A total of 60 HIV-infected patients in this study were analyzed, whom the investigators subdivided into viremic (28 patients) and aviremic (32 patients) groups, depending on whether their HIV viremia was above or below 400 copies/mL of HIV RNA. Although they mention that 13 of their patients (46%) in the viremic group were on highly active antiretroviral therapy, their paper failed to report whether ART in this subgroup in any way influenced their findings.

Recent findings suggest that, in addition to HIV viral replication, other factors (eg, microbial translocation) could drive immune activation.[6] Accordingly, it is of great interest that Funderburg et al demonstrate that the bacterial Toll-like receptor, ligands lipopolysaccharide from *Escherichia coli* and flagellin from *Salmonella typhimurium*, induced monocyte TF expression in vitro. On the basis of their findings, these investigators propose that direct activation of monocytes by microbial products (eg, via bacterial translocation from the gut) may be a key player in promoting thrombosis in HIV infection.[1]

The findings of Funderburg et al bring us ever closer to elucidating the mechanism by which HIV infection promotes thrombosis. More work in this field is needed, including the use of TF^+ monocytes as a potential thrombotic marker (eg, for DVT prophylaxis) among HIV-infected patients, and the justification for using immunomodulators as adjuvant therapy to ART.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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● ● ● PLATELETS & THROMBOPOIESIS

Comment on Mumford et al, page 363

A bleeding disorder is born

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In this issue of *Blood*, Mumford and colleagues report a D304N variant of the thromboxane A_2 receptor (TxA_2 R) in a patient with a bleeding diathesis.[1] In their report, they describe the exciting path of a research journey initiated by a clinical observation, and leading to a discovery of a novel mechanism of a bleeding disorder: a mutation in the TxA_2 R gene, leading to a D304N substitution. This mutation leads to a loss of function of the receptor due to reduced ligand binding.

Searching for the cause of a bleeding disorder may become quite frustrating in patients who have normal screening tests of coagulation and platelet function. Many such cases are left with the presumptive diagnosis of an "undefined bleeding disorder," with general hemostatic support as the only therapeutic modality.

Our current screening tools for investigating primary hemostasis-related bleeding disorders are limited to platelet aggregometry (usually induced by ADP, epinephrine, collagen, ristocetin, and arachidonic acid), as well as testing von Willebrand factor antigen and activity. This limitation explains the quite frequent event of a "final"

Computed 3-dimensional structure of the human TxA_2 receptor. Adapted from Chou.[6]

diagnosis of undefined primary hemostatic disorder. Only highly qualified centers where more specific tests are available may take on the task of further evaluation. The platelet physiology subcommittee of the International Society of Thrombosis and Haemostasis (ISTH) has dedicated its work during recent years to searching for ways to improve and standardize platelet function testing, applying platelet aggregometry, the PFA-100 device, and a proteomics approach.[2-4]

This report also raises the issue of the gap between genotype and phenotypic expression in hereditary diseases. The D304N substitution was observed in the index patient, who presented with mild bleeding symptoms, and in his father, who had no history of bleeding. As in other cases, a search for modifier genes and for other factors might shed light on this differential phenotypic expression. Thus, the genetic background of a disease does not always explain all phenotypes, and a search for genetic and environmental modifiers should be considered for a more comprehensive understanding of this entity.

Improved understanding of the complex, multiple pathways of platelet activation is significantly contributing to the development of new antiplatelet drugs. Antiplatelet drug therapy is currently undergoing a dramatic revolution, including novel observations on platelet drug resistance, more refined dose adjustment, and development of more potent and safer new drugs.[5] One such example is the development of new TxA_2 R inhibitors. Such inhibitors are potentially more effective than aspirin because of their inhibitory effect on endothelial cell TxA_2 R as well.

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● ● ● THROMBOSIS & HEMOSTASIS

Comment on Moore et al, page 379

aHUS: a disorder with many risk factors

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In this issue of *Blood*, Moore and colleagues demonstrate that the presence of anti–factor H autoantibodies in aHUS may be associated with the deletion of the *CFHR1* gene. In addition, Moore et al provide data further supporting the model that the concurrence of multiple risk factors influences the onset of aHUS.

Intense research in recent years has demonstrated that atypical hemolytic uremic syndrome (aHUS), a rare but devastating disorder characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure, is associated with mutations and polymorphisms in various components and regulators of the complement alternative pathway (AP) including factor H, factor I, membrane cofactor protein (MCP), factor B, and C3. Mutations altering the C3b/polyanions-binding site located at the C-terminal region of factor H, specifically impairing the capacity of this complement regulator to protect host cells, are the prototypical genetic risk factor associated with aHUS.[1] In addition to the genetic alterations in complement proteins, it has been shown that 5% to 10% of aHUS patients present