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Chronic HIV Disease and Activation of the Coagulation System

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Abstract

With current effective antiretroviral treatment, the spectrum of morbidity and mortality during chronic HIV disease has shifted away from AIDS defining clinical events. Persistent abnormalities in coagulation appear to contribute to excess risk for a broad spectrum of non-AIDS defining complications, including, but not limited to, venous and arterial thrombotic disease. Mechanisms specific to HIV disease, antiretroviral therapy, and lifestyle or behavioral factors contribute to a pro-coagulant state, in part, through increased tissue factor activity coupled with a paradoxical decline in the anti-coagulant response. Alterations in coagulation biology in the context of HIV disease appear to be largely a consequence of persistent systemic immune activation, micro- and macro-vascular disease, and, potentially, impaired hepatic synthesis of coagulation factors. The clinical consequences of HIV-related changes in coagulation biology, the degree to which they are unique to HIV disease, and whether they can be mitigated through adjunct treatments, remains a focus of current research.

Coagulation and Disease Risk in the Era of Effective Antiretroviral Treatment

Current antiretroviral therapy (ART) treatment now effectively and durably suppresses HIV replication. The well-described immune recovery and improved survival associated with effective ART has also motivate recent research that expands our understanding of the hematologic complications of HIV disease. The classic hematologic complications described early in the HIV/AIDS treatment era largely constituted thrombocytopenia, anemia, and neutropenia attributable, in part, to increased consumption, concurrent infections, bone marrow suppression and/or ART drug toxicity (e.g., zidovudine) [1]. More widespread use of less toxic ART has reduced cytopenias among an HIV population that is now largely treated with corresponding viral suppression where access to antiretroviral therapy is present [2, 3].

The spectrum of HIV-related clinical disease risk now more commonly includes non-AIDS defining disease such as atherosclerotic cardiovascular disease (CVD) and cancer, and rates for these diseases are typically higher than for uninfected populations [4-6]. A series of recent epidemiologic studies have demonstrated that inflammatory and coagulation biomarkers are both elevated with HIV infection and strongly predict risk for a broad

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spectrum of non-AIDS defining end-organ diseases (e.g., CVD, cancer, and liver and renal disease) [7-14]. Plasma levels of the coagulation biomarker D-dimer are approximately 50% elevated, and the increase clinical risk associated with elevated levels are more extreme, among treated HIV positive patients with viral suppression when compared with uninfected controls [7, 8, 13, 15]. Furthermore, the increased risk for subsequent CVD and all-cause mortality associated with elevated D-dimer levels is robust, is present over 5-8 years of follow-up, and is not present for AIDS-defining events [16, 17].

Although both venous and arterial thrombotic diseases as well as cancer appear to be increased in treated HIV disease, these complications still occur only at modest rates and may take years to manifest clinically [5, 6, 11, 17-20]. The focus of this review is then to explore the pro-coagulant mechanisms during chronically treated HIV disease (Figure 1), given the potential implications for excess long-term non-AIDS defining morbidity and mortality.

Persistent Systemic Inflammation

Inflammation, in general terms, modulates thrombotic responses by up-regulating procoagulants, down-regulating anticoagulants and suppressing fibrinolysis [21]. Viral replication may non-specifically activate coagulation via cell injury and apoptosis leading to tissue factor activation, and, potentially, through altered hepatic production of coagulation factors [21-26]. Tissue damage, with associated release of cytokines and cellular products (e.g., histones) can also activate endothelial surfaces to increase TF expression, reduce endogenous anti-coagulant signals, and promote leukocyte infiltration [21, 27-30]. Conversely, thrombin itself can feedback and stimulate innate immune responses via protease-activated receptor 1 (PAR-1) signaling, leading to inflammatory cytokine production and enhanced interferon mediated anti-viral responses [31, 32]. Furthermore, thrombin has been shown to enhance the adaptive immune response by activating memory CD8+ T-cell subsets from HIV patients (also via PAR-1 signaling), and facilitating their migration to sites of tissue injury [33]. These data highlight the intrinsic interconnectedness of coagulation biology with the immunopathogenesis of inflammatory conditions such as HIV disease.

Immune dysfunction, activation of lymphocytes and monocytes, and elevated levels of inflammatory cytokines are hallmarks of untreated HIV infection. Most of these immunologic abnormalities improve with effective ART, but remain impaired compared to HIV uninfected persons [8, 34, 35]. The precise mechanisms driving high level immune activation during treated HIV disease are not entirely clear, but appear to involve both a persistent anti-HIV response (even with HIV RNA at low levels) and a more generalized immune activation (e.g., cytokine release) [36]. Specifically, HIV disease factors that may contribute to excess inflammation include: *a)* excess burden of co-pathogens such as CMV and other herpes viruses; *b)* HIV-mediated destruction of mucosal epithelium in the gut, which may lead to chronic translocation of bacterial products even after ART-related immune recovery; *c)* loss of key regulatory cells such as Th17 and perhaps T regulatory cells *d)* insulin resistance and metabolic abnormalities; and *e)* residual HIV replication during apparently effective ART [37-44]. Importantly, the consequences of these factors for

innate immunity (e.g., monocyte activation in blood) has received increasing attention due the potential contribution to CVD and other non-AIDS disease risk [11, 13, 14, 35, 45-47]. Ultimately, the implication is that in the current era treated HIV disease is characterized by a state of persistent systemic inflammation with corresponding activation of coagulation.

Activation of Tissue Factor Pathways

Blood thrombosis is primarily initiated and perpetuated by local activation of tissue factor (e.g., the extrinsic pathway). Circulating TF exists on cell surfaces (e.g., activated monocytes), as soluble cell-free TF in plasma (where it is largely inactive in coagulation), and on cell-derived microparticles or vesicles released from activated or apoptotic cells that contain functionally active proteins from the parent cell [48]. Though TF-positive microparticles constitute only a small fraction of circulating TF, they likely represent a functionally active form of TF given their origin from activated cells (e.g., released form monocytes in response to endotoxemia) [48, 49]. We have demonstrated that ART treatment is associated with reductions in microparticle TF pro-coagulant activity, when compared to untreated HIV infection [50]. Furthermore, among ART-treated patients with viral suppression, microparticle TF pro-coagulant activity is associated with D-dimer levels [50].

Funderburg and colleagues have conducted a series of sentinel studies characterizing TF expression on monocytes among HIV infected patients [26, 46]. They reported that monocyte TF expression is increased among HIV infected versus uninfected persons, and was correlated directly with HIV viral load [26]. In that study, monocyte TF expression also correlated with D-dimer levels and with soluble CD14 (sCD14), a monocyte inflammatory marker and co-receptor for bacterial lipopolysaccharide (LPS) [26]. HIV pathogenesis studies postulate that increased translocation of microbial products across intestinal surfaces, a consequence of permanent damage to the mucosal lymphatic tissue, may contribute to monocyte activation, tissue factor expression, and pathogenic hypercoagulation [40, 42, 51]. Funderburg and colleagues when on to demonstrate that among treated HIV positive patients with suppressed viral loads, LPS levels were associated with increases in activated monocyte phenotypes (CD14++/CD16+) that also expressed TF to a greater degree when compared to the classical monocyte phenotype (CD14++/CD16−) [46]. This pattern of monocyte activation and TF expression was not present for HIV uninfected controls but was apparent among patients with acute coronary syndrome [46]. In another retrospective case-control study, soluble TF levels were elevated among HIV-infected patients preceding a CVD event, versus controls who did not have a CVD event [12]. However, to date, studies have been unable to fully assess whether increases in functionally active TF account for the epidemiologic associations between D-dimer and clinical risk [8, 9, 12, 13].

Finally, injury to vascular surfaces is well known to stimulate a number of pro-thrombotic mechanisms, including expression of TF [29, 52]. Within the context of macro-vascular disease, TF is typically expressed on vascular smooth muscles cells and macrophages within atherosclerotic plaques [53-55]. Atherosclerotic vascular disease, including coronary heart disease events, occur more frequently with HIV infection due to reasons that are multifactorial and have been reviewed elsewhere [5, 56-58]. Although TF is not typically expressed on inner endothelial surfaces under normal conditions, injury and damage to the

endothelium can lead to TF expression throughout the microvasculature [29, 52, 59]. HIV infection is also associated with micro-vascular dysfunction, and HIV studies have reported associations between D-dimer levels and impaired small vessel elasticity, endothelial dysfunction, and biomarkers of endothelial activation [60-63]. Ultimately, the degree to which HIV-mediated injury and dysfunction of endothelial surfaces up-regulates TF-mediated coagulation is unclear, and more likely involves multiple mechanisms that influence coagulation biology.

Altered Composition of Coagulation Factors

We recently studied the influence of HIV replication and ART treatment specifically on the composition of extrinsic (TF) pathway coagulation factors [64]. In addition to the expected increases in some pro-coagulants (e.g., factor VIII and von Willebrand factor) as a consequence of systemic inflammation, we also observed that untreated HIV replication led to declines in all major anticoagulants (e.g., antithrombin, protein C and protein S) as well as other pro-coagulants dependent on hepatocyte function (e.g., fibrinogen, prothrombin, and factor VII). Through computational modeling to estimate thrombin generation based on the composition of extrinsic pathway factors developed by Brummel-Ziedins and colleagues, we demonstrated the net effect of HIV replication was to increase coagulation potential. Initiation of HIV treatment with ART subsequently led to reciprocal changes, including reduced inflammation (e.g., factor VIII levels), improved hepatocyte production of anticoagulants (e.g., antithrombin, protein C and protein S), and declines in thrombin generation potential.

A recent review on the coagulopathy of liver disease highlights data that declining liver function initially results in a pro-coagulant state until later end-stage disease, where the almost complete lack of coagulation factors results in hemorrhage [65]. Data from HIV studies also support a hypothesized HIV-mediated reduction in hepatocyte synthetic function. Levels of C-reactive protein (CRP), an acute phase reactant released by hepatocytes, were modestly higher among HIV mono-infected individuals and actually lower among those with HIV/HCV co-infection, when compared to uninfected controls [66]. In addition, while IL-6 and D-dimer levels decline with initiation of ART, CRP levels fail to improve or actually increase in some studies [67, 68]. Finally, HIV-1 appears to have the capacity to replicate in hepatocytes [69-71], and the FIB-4 index, a non-invasive estimate of hepatic fibrosis, correlates with the degree of HIV replication[72, 73]. In summary, recent observations and experimental data suggest that HIV infection may have a pro-coagulant effect, in part, through its effects on hepatocyte synthesis of coagulation factors. A critical unanswered question is whether these HIV-related changes in the profile of coagulation factors has direct long-term implications for disease pathogenesis.

Platelet Activation

Platelets provide an additional link between HIV-mediated inflammation and hypercoagulation, as they are activated at sites of infection or injury and interact with monocytes, lymphocytes and endothelial cells [74-76]. HIV-1 binds, and is highly associated, with platelets in the blood, which has been postulated to facilitate clearance

and/or dissemination of the virus [77, 78]. Among patients with untreated HIV infection, thrombocytopenia is a classic hematologic abnormality that worsens with advancing HIV disease but typically normalizes with ART treatment [79].

When compared to uninfected persons, platelets from HIV positive persons demonstrate greater activation, chemokine release, and reactivity to epinephrine [80, 81]. Even after effective ART treatment with viral suppression, levels of platelet microparticles remain elevated, and more frequently express CD62P and TF, when compared with uninfected controls [82, 83]. Finally, platelet-monocyte complexes are another measure of platelet activation that has been shown to be more frequent among HIV infected versus uninfected persons [84]. In contrast, a recent study showed that untreated HIV infection was associated with paradoxical reductions in functional measures of platelet aggregation and delayed clot initiation despite having elevated D-dimer levels [85].

Data on platelet toxicity related to specific antiretroviral medications is limited, though exposure to abacavir has been associated with platelet hyperactivity in 2 studies providing a potential biologic explanation for the increased risk for myocardial infarction reported with this medication [86-88]. To some degree, methodological challenges in assessing platelet activation and function have limited data that characterize the effects from HIV infection, and the clinical implications, in the context of untreated and treated disease.

Treatment Strategies to Reduce Hypercoagulation in Treated HIV Disease

The need for adjunct disease modifying treatment strategies (given concurrently with ART) to target excess inflammation and coagulation activation is an area of active research that has been recently reviewed [89, 90]. A major challenge to conducting initial trials evaluating the potential benefits of candidate treatments is that intermediate measures of inflammation and/or coagulation have not been validated as surrogate markers in this population. Most preliminary studies to date have leveraged off-target properties of established cardioprotective medications such as aspirin, statins, and angiotensin receptor blockers [91-93]. In addition to the well-established anti-platelet benefits, aspirin has broad anti-inflammatory properties and has demonstrated potential to reduce T-cell activation, monocyte activation, and platelet activation in a pilot study of treated HIV patients [92]. The effects of rosuvastatin were recently studied in a randomized trial of 147 ART-treated HIV positive patients with evidence of increased immune activation at baseline [93]. In this study, rosuvastatin reduced TF expression on activated monocyte phenotypes and plasma markers of monocyte activation, but did not reduce D-dimer levels. The implications of these treatment effects for clinical risk and other aspects of coagulation biology are not yet clear.

No large-scale clinical trials are underway specifically studying an anticoagulant medication as primary prevention for ART-treated HIV positive patients. The new generation of oral anticoagulant medications (e.g., direct inhibitors to thrombin and factor Xa) would represent a highly novel approach to target hypercoagulation during chronic HIV disease, but would face significant challenges. Bleeding risks are predictable and become a major deterrent when considering a treatment strategy of primary prevention over decades for a population

where clinical event rates remain modest (even if in excess of the general population). Furthermore, significant drug-drug interactions with antiretrovirals exist through hepatic metabolism via CPY-3A4 pathway (e.g., the factor Xa inhibitors such as rivaroxaban) as well as via inhibition of P-glycoprotein transportation.

Conclusion

Recent data have demonstrated that the coagulation system may be persistently activated during chronic HIV infection despite effective ART treatment. Alterations in coagulation biology associated with HIV specific factors (whether due to antiretroviral toxicity, the virus itself, or permanent damage to the immune system) are similar to that described in other states of chronic inflammation, and are characterized by a concurrent up-regulation of tissue factor pathways and reduction in the anti-coagulant response. While the increase in pro-coagulant potential may be modest, epidemiologic associations with plasma D-dimer levels suggest increased coagulation may contributed to excess risk across a broad spectrum of non-AIDS defining clinical diseases that manifests over years [7, 9, 12, 13, 17, 20, 64]. However, elevated D-dimer levels during chronic HIV infection may also reflect the convergence of multiple pathways and overall disease burden. For example, the profile of HIV-related changes to inflammatory and coagulation factors are similar to changes seen with aging and frailty in the general population (e.g., IL-6, D-dimer, von Willebrand factor, factor VIII, and factor VII) [7, 8, 64, 94]. Future research should focus on understanding the similarities and differences in altered coagulation biology during treated HIV disease compared to other disease states, as well as the clinical consequences and potential prevention strategies.

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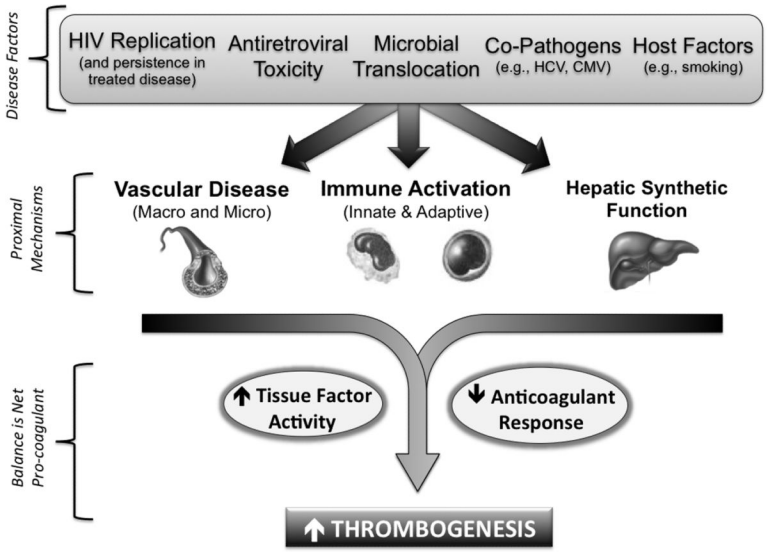

Figure 1. Pro-Coagulant Mechanisms During Chronic HIV Disease

Presented is a conceptual model whereby factors specific to HIV itself, antiretroviral therapy, and lifestyle contribute to a pro-coagulant state. In addition, permanent damage to the immune system during chronic HIV disease despite effective ART treatment also contributes, including: a) decreased integrity of the mucosal lymphatic barrier, with corresponding endotoxemia, and b) a loss of T-cell regulatory function combined with excess antigen stimulus from co-pathogens. This contributes to a state of persistent immune activation (characterized by both T-cell and monocyte abnormalities), injury to endothelial surfaces with micro-vascular dysfunction, premature atherosclerosis, and potentially, impaired hepatic synthesis of coagulation factors. The end-result may increased thrombogenesis due to both an up-regulation of tissue factor activity, as well as alterations in extrinsic pathway factor levels with notable declines in the anticoagulant response (e.g., antithrombin and protein C).