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Markers of coagulation and inflammation often remain elevated in ART-treated HIV-infected patients

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Abstract

Purpose of review—Current antiretroviral therapies have dramatically changed the disease course of HIV infection. While antiretroviral therapy (ART) is effective at decreasing viral replication and preserving CD4+ T cell numbers, low-level immune activation and inflammation persist in virally suppressed HIV-infected patients. This chronic immune activation/inflammation may contribute to an increased risk for venous and arterial thrombosis.

Recent findings—Several markers of coagulation and inflammation are increased in HIV-infected patients. The Strategies for the Management of Antiretroviral Therapy (SMART) study reported that plasma D-dimer levels, a marker of fibrinolysis, independently predicted morbidity in HIV-infected patients. Increased plasma and cell surface levels of the procoagulant tissue factor (TF) have also been reported in patients with HIV disease. Fibrinogen, von Willebrand factor (vWf), and P-selectin are likewise increased in plasma samples of HIV-infected patients; all of these markers suggest HIV-infection results in a pro-coagulant state. Treatment with antiretroviral therapy reduces, but does not always normalize, levels of biomarkers associated with inflammation and coagulation in HIV+ patients.

Summary—HIV-infected patients are at greater risk for both venous and arterial thrombosis. Chronic immune activation and inflammation in these patients appears to contribute to coagulation risk. Antiretroviral therapy reduces viral replication, immune activation, and markers of coagulation, but these indices do not always return to normal, even after several years of viremic control.

Keywords

coagulation; D-dimer; antiretroviral therapy; inflammation

Introduction

Coagulation is the result of a complicated series of enzymatic reactions, regulated by multiple positive and negative factors, and can be driven, in part, by activation of the innate

immune system and through inflammation (1). The coagulation cascade is often separated into the intrinsic and extrinsic pathways; damage to a blood vessel is often an initiator of the intrinsic coagulation system. Tissue factor (TF), a transmembrane glycoprotein that can be expressed on cell surfaces or in circulation within microparticles, can initiate the extrinsic clotting pathway, and TF plays a well-documented role in thrombosis (2, 3). Activation of either the extrinsic or intrinsic coagulation cascades can result in the formation of a stable fibrin clot. Inappropriate clot formation can lead to blood vessel occlusion, and depending on the location and size of the clot, may result in thrombotic pathologies including deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, or myocardial infarction (MI).

Human immunodeficiency virus (HIV) infection is often associated with an increased risk of venous (4–7) and arterial thrombosis (8–11). Before the widespread use of combination antiretroviral therapy (ART), deficiencies in protein C (12) and protein S (13, 14), molecules involved in the inactivation of the procoagulant molecules factor Va and VIIIa, were recognized contributors to venous thrombotic risk in patients with advanced HIV disease/AIDS. Due to widespread use of antiretroviral therapy, HIV-infected patients are no longer succumbing to AIDS-defining morbidities, including deaths related to opportunistic infections, and instead, more patients are suffering catastrophic thrombotic events, including myocardial infarction and stroke (15–17). The mechanism(s) related to thrombotic risk in HIV-infected patients have not been fully elucidated. Even under suppressive antiretroviral therapy, many HIV-infected patients maintain increased levels of immune activation and inflammation compared to these indices in uninfected controls (18–21). Inflammation is often thought of as an initiator of coagulation, but several recent studies suggest that the relationship between coagulation and inflammation is bidirectional (22–24). Inflammation can contribute to endothelial cell activation (25) and tissue factor expression (26) activating coagulation cascades; several coagulation intermediates can also induce inflammation (22–24, 27). The focus of this review will be to discuss the evidence for abnormal coagulation in HIV disease, the relationship between inflammation and coagulation in HIV-infection, and how antiretroviral therapy may modulate the risk for thrombosis.

Increased Coagulation Biomarkers in HIV disease

Studies suggest that HIV-infected patients are at a 2-fold to 10-fold greater risk for a venous thromboembolic event (VTE) (7, 28, 29) and an approximately 2-fold greater risk for myocardial infarction (11) than are uninfected controls. Several groups have attempted to identify biomarkers that may be predictive of adverse thrombotic events and non-AIDs defining mortalities in HIV disease. The Strategies for the Management of Antiretroviral Therapy (SMART) study, where patients were placed on continuous ART or T cell count guided treatment interruptions, initiated much of the recent interest in HIV-related coagulation (30). The SMART study demonstrated that plasma markers of inflammation (C-reactive protein, interleukin-6) and coagulation (D-dimer) were predictive of all-cause mortality (30), and cardiovascular events (31) in HIV-infected patients. Plasma D-dimer levels are a marker of fibrinolysis, and increased levels are reported in patients with several thrombotic conditions, including DVT and PE. Study participants in SMART with the highest quartile of D-dimer levels had a 2.14-fold greater risk for cardiovascular disease (CVD) events than patients in the lowest quartile (31). When D-dimer levels among HIV-

infected participants in SMART and levels from HIV-uninfected donors in the Multi-Ethnic Study of Atherosclerosis (MESA) study were compared, the reported D-dimer levels from SMART patients were 94% higher than the levels in MESA participants, indicating increased coagulation in these HIV+ patients. Even among SMART participants with suppressed viremia (<400copies/mL), D-dimer levels were still 49.1% higher than levels measured in the general population (20). Results from a study of HIV-infected patients on ART, the Veterans Aging Cohort study (VACs), confirmed the predictive value of D-dimer levels on mortality in HIV-infected patients (32). In two retrospective case-control studies, plasma D-dimer levels were independently associated with venous thromboembolic events (33) and CVD events (34) in HIV-infected patients; providing another link between D-dimer levels and venous and arterial thrombosis in HIV-infection.

Fibrinogen

Another biomarker that may be predictive of mortality in HIV-infected patients is fibrinogen; an acute phase reactant involved in the coagulation cascade that has been associated with platelet aggregation and atherosclerosis (35, 36). Fibrinogen can also induce proinflammatory cytokine production and NF- κ B activation through interactions with Mac-1 (CD11b/CD18) on myeloid cells (37, 38). The Fat Redistribution and Metabolic Change in HIV infection (FRAM) study found that HIV-infected patients have increased levels of fibrinogen compared to levels in uninfected controls (39). During a 5 year follow-up study, patients from FRAM with the highest tertile of fibrinogen levels had a 2.6 fold higher adjusted odds ratio of death than did patients in the lowest tertile (40).

von Willebrand factor

Elevated levels of von Willebrand factor (vWf), a marker of endothelial cell damage, have also been reported in patients with HIV disease (18, 41) compared to levels in controls, and these increased levels may represent ongoing endothelial cell dysfunction/activation. While this marker has not been directly associated with mortality in HIV disease, vWf may enhance clot formation on blood vessel walls by contributing to platelet adhesion. Plasma levels of vWf are directly related to viremia and inversely related to CD4+ T cell counts and levels of vWf are reduced with ART (41).

Potential Drivers of Coagulation in HIV disease

Plasma markers of inflammation and coagulation appear to be increased in HIV-infected patients, but what is driving expression of these markers, even under suppressive ART, and how they may be mechanistically related to thrombosis, has not been fully elucidated. Patients undergoing ART-treatment interruptions in SMART were at greater risk for morbidity than patients who maintained suppressive ART, suggesting HIV replication, or the profound inflammatory and immune response related to uncontrolled viremia, may contribute to coagulation risk (30). Several cross-sectional studies have suggested that ART lowers plasma levels of coagulation and inflammation (19, 42–47) and these studies have been widely confirmed by longitudinal studies (18, 41, 48, 49). The likely mechanisms that link inflammation, coagulation, and thrombotic risk in HIV disease are complex and may involve multiple cell types and both the intrinsic and extrinsic clotting pathways.

Activation of the intrinsic pathway often occurs on damaged/activated endothelial cells. Several studies have reported evidence of endothelial cell dysfunction and activation, including altered vascular tone and increased expression of adhesion molecules (ICAM and VCAM), in HIV-infected patients (50–54). As mentioned above, increased levels of vWf in HIV-infected patients likely represents endothelial cell damage. Activated/damaged endothelial cells can serve as a substrate for clot initiation by activated platelets; proportions of which are also increased in HIV disease (55, 56). Plasma D-dimer levels have also been independently associated with endothelial dysfunction in HIV-infected patients, providing a potential link between endothelial dysfunction and coagulation in chronic HIV-infection (57).

Activation of the extrinsic clotting cascade begins with tissue factor (TF) binding to factor VIIa, which catalyzes factor X to Xa, resulting in activation of the prothrombin complex and generation of thrombin. Thrombin can then convert fibrinogen to fibrin, resulting in clot formation. Increased expression of TF, on monocytes (43, 44), platelets (56) and in the circulation (33, 43, 45), has been reported for HIV-infected patients. The proportion of monocytes that express TF remains elevated in patients receiving ART compared to the proportion in controls (43, 44), and this proportion correlates with viremia, soluble CD14, a monocyte activation marker that independently predicts mortality in HIV-infected patients (21), and plasma D-dimer levels (43), linking TF expression to coagulation. Bioactive TF+ microparticles, likely derived from activated monocytes, are also associated with plasma levels of D-dimer, IL-6, and vWf; providing another link between inflammation and coagulation in HIV-disease (45).

Tissue factor and activation of the extrinsic clotting pathway may also be contributing to inflammation through protease-activated receptors (PARs) (27, 58). The TF:factor VIIa complex can bind to PAR-2, inducing pro-inflammatory cytokines and adhesion molecule expression on endothelial cells and monocytes (22, 23, 27). Thrombin can activate PARs 1, 3, and 4, also inducing pro-inflammatory cytokine production (59, 60).

Tissue factor expression can be driven by multiple mechanisms including exposure of cells to inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), and through the direct activation of innate immune receptors, including Toll-like receptors (TLRs) (3, 26). HIV can directly activate TLR7 and 8 and exposure of monocytes to replication incompetent HIV-1 leads to increases in monocyte cell surface TF expression (44, 61). Damage to the gastrointestinal tract of HIV-infected patients results in increased levels of circulating microbial products, including LPS and bacterial DNAs (42, 62–64), that can also induce TF expression, monocyte activation (44, 65), and increased levels of proinflammatory cytokines (66). Interventional studies aimed at reducing microbial translocation and immune activation/coagulation in HIV-infected persons are underway. A recent study in simian immunodeficiency virus (SIV) infected monkeys provides preliminary mechanistic details linking circulating LPS, sCD14, and D-dimer levels, to cardiovascular lesions in these animals (67).

Recently, Baker et al measured pro- and anti-coagulant factors involved in clot formation in samples from a subset of patients in SMART in order to model thrombin generation and

coagulation potential (68). This study suggests HIV replication results in decreases in several anti-coagulant factors (including antithrombin), and increases in many procoagulant factors (including FVIII). Computational modeling suggests these changes result in a net procoagulant state. Antiretroviral therapy improved these changes, and the authors suggest that hepatic function and inflammation may contribute to thrombotic risk in HIV disease (68).

Administration of ART decreases inflammation, immune activation, and microbial translocation, potentially lowering coagulation risk, but these indices do not often normalize (18–21, 45). Multiple treatment strategies have been evaluated for effectiveness at reducing plasma markers of coagulation and immune activation, however, some studies have reported that ART may directly contribute to the increased risk for thrombosis in HIV-infected patients. An extensive description of this literature is outside the scope of this review, but treatment strategies involving Abacavir (ABC) or protease inhibitors (PI) warrant mention.

Abacavir

Treatment of HIV-disease with an abacavir (ABC) containing regimen has been associated with increased risk for arterial thrombosis in some (69, 70), but not all (71), studies. The mechanisms for the potential increased MI-risk following ABC exposure have not been elucidated, but may be related to endothelial cell dysfunction (52) or increased platelet reactivity (72, 73). In both a retrospective study (74) and a randomized controlled trial (75), patients receiving ABC did not have increased levels of plasma coagulation markers (including D-dimer, fibrinogen, and vWf) compared to patients who did not receive an ABC containing regimen.

Protease inhibitors

The effects of protease inhibitor (PI) treatment on the risk for venous and arterial thrombosis are also unclear. Several studies report an increased risk of arterial thrombosis associated with PI use (6, 76–78). Combination ART, including regimens containing a PI, lower, but do not normalize, levels of vWf, D-dimer, and fibrinogen (18, 39). Results from the FRAM study report that patients receiving any PI had increased fibrinogen levels compared to patients not receiving a PI (39). In a relatively small retrospective study of 465 HIV infected patients (17 thrombotic events), there was no association between PI-use and thrombosis (28). Protease inhibitor use may alter lipid levels in HIV-infected patients and contribute to endothelial dysfunction (50), and this could contribute to increased risk for thrombotic events. In a recent study, where patients switched to the HIV-integrase inhibitor raltegravir from a PI-boosted regimen, while maintaining the same nucleoside reverse transcriptase inhibitors (NRTIs) a decrease in D-dimer levels following raltegravir initiation was reported (79). While some classes of antiretroviral therapies may potentially contribute to increased thrombotic risk, the mechanisms behind which should be explored; overall, antiretroviral therapy is effective at reducing AIDS-related morbidity and mortality, and prolonging the lifespans of patients with chronic HIV disease (80, 81).

Complications

HIV-infection is widely believed to result in a pro-coagulant state; yet, the field is complicated and many questions remain. Not every study has found increased D-dimer levels and heightened coagulation in HIV-infected patients. Hsue et al report little difference in plasma levels of D-dimer, TF, and prothrombin fragment 1+2 (F1+2) between HIV+ patients and controls (82). This study also reports that both ART-treated and untreated HIV-infected patients have increased levels of antithrombin and decreased rates of thrombin generation, suggesting decreased, rather than increased, clot formation in HIV+ patients versus controls (82). Haugaard et al recently reported increased D-dimer levels in untreated HIV infected patients, but reduced platelet aggregation and clot initiation in treated and untreated HIV+ patients, compared to these indices in uninfected controls (83). This study also reported an inverse relationship between plasma LPS and platelet aggregation (83). In order to resolve these conflicting reports, clinical endpoint studies, with carefully selected HIV-infected and uninfected populations of similar demographics, that assess a wide panel of pro- and anti-thrombotic factors, and take into consideration the ART regimens, CD4+ T cell nadir, and duration of treatment, will be needed to properly evaluate thrombotic risk in ART-treated HIV disease.

Conclusions

Markers of coagulation are predictive of all-cause mortality in HIV infected patients (30, 31, 39) and in retrospective studies, D-dimer levels were independently associated with VTE (33) and CVD events (34) in this population. Inflammation and coagulation are closely linked, and while ART reduces the levels of several biomarkers of these processes, levels are not always lowered to those measured in HIV-uninfected donors (18–21, 45). The mechanisms responsible for chronic inflammation and altered coagulation in treated HIV disease may include low level viral replication in tissues (84), copathogens such as cytomegalovirus (85), microbial translocation (63), and pro-inflammatory lipids (86). These potential “drivers” could be linked to coagulation in HIV disease through induction of tissue factor expression on platelets (56), monocytes (43, 44), and on circulating microparticles (45); as well as through activation/damage of the vascular endothelium (18, 41) (Figure 1). One must also consider the increased prevalence of traditional coagulation risk factors, including smoking, dyslipidemia, hypertension, and diabetes, found within the HIV-infected population (11, 87) when assessing overall thrombotic risk in this group. Several interventions, including treatment with statins, aspirin, and other immunomodulatory molecules, are being tested in HIV-infected patients in order to reduce chronic inflammation and alter the procoagulant phenotype often measured in these patients. Long-term studies, with clinical endpoints, that include careful measurement of both pro-and anti-coagulant molecules will be required to assess the overall risk for thrombosis in chronic HIV infection.

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Bullet points

Markers of coagulation (D-dimer, fibrinogen) and inflammation (IL-6, C-reactive protein) are predictive of all-cause mortality, including deaths related to cardiovascular events, in HIV-infected patients.

Several markers of coagulation are increased in HIV infected patients, and in many studies, these markers do not normalize with ART.

A better characterization of multiple pro- and anti-thrombotic factors and clinical endpoint studies will be needed assess thrombotic risk in HIV-infected patients compared to the risk in uninfected controls.

Figure 1. Coagulation and Inflammation are connected in HIV disease

Many HIV-infected patients, even under suppressive antiretroviral therapy, have increased levels of plasma biomarkers that are related to coagulation and inflammation. The mechanisms contributing to this procoagulant state may include: low level viral replication, copathogens such as cytomegalovirus, microbial products translocated from the gastrointestinal tract, or proinflammatory lipids. Not only can inflammation contribute to coagulation, but coagulation products can activate inflammation through multiple receptors, including the protease activated receptors (PARs 1–4).