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HIV-Infected Patients and Potential Impact on Thrombotic Events

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1. Introduction

There is increasing evidence that infection with HIV may be associated with a hypercoagulate state.

The incidence of thrombotic events in Human Immunodeficiency Virus (HIV)-infected patients is rising as suggested in recent retrospective cohort studies (1%- 2%, which is 10 times that expected among people without HIV) [1], but the underlying etiology remains uncertain.

2. Procoagulant mechanisms underlying HIV infection

Several mechanisms associated with HIV infection that may lead to predispose to a hypercoagulate state, in the absence of classic thrombophilic risk factors [2], are emerging.

More than one "hit" seems to be involved [3]:

2.1. Host risk factors

2.1.1. Age

HIV-infected patients are older than their chronological age, experiencing the so-called "*premature aging* ", with persistent immunological defects and inflammation, even after years of treatment mediated viral suppression (similar to those seen in normal ageing, but they occur at an earlier age than normal): low CD4: CD8 ratio, low *naïve*: memory cell ratio and reduced responsiveness to vaccines. In addition, longevity and life expectancy is increasing due to effective antiretroviral therapy (ART), making HIV infection a chronic disorder.

In a Nederland cohort [4] of 109 patients with HIV, the annual incidences of venous and arterial thrombosis were 5- to 16-fold higher and 2- to 8-fold higher, respectively, than in the healthy population. The median age at the onset of venous thrombosis was 45 years, 17 years earlier than the median age of onset for venous thrombosis in non-HIV- infected patients; and the median age for arterial thrombosis onset was 53 years, a decade earlier than that documented in the Framingham study.

2.1.2. Hypercoagulate state - Primary prothrombotic abnormalities boosted by direct effect of HIV

- Protein S (PS) deficiency (27-76%): decreased synthesis by the endothelial cells, hepatocytes and megakariocytes injured in HIV infection; antibodies to PS and low levels of circulating free antigen; tumor necrosis-factor alpha (TNF α) can lower the levels of active protein S, down-regulating the protein S synthesis in the endothelial cells; and loss of protein S in urine in HIV-related nephropathy [5].
- Protein C (PC) deficiency (0-14%): altered synthesis and metabolism of PC, as well as low-grade disseminated intravascular coagulation (DIC) with consumptive coagulopathy, in the setting of HIV infection with severe immunosuppression [5].
- Presence of Factor V Leiden (activated protein C resistance) [6].
- Antithrombin deficiency: decreased protein synthesis (liver diseases and malnutrition), protein-losing nephropathies or enteropathies, consumptive states (malignancy, surgery, DIC).
- Antiphospholipid antibodies: Anticardiolipin antibodies (aCL) and lupus anticoagulant (LA) have been reported in HIV-infected patients with a prevalence ranging from 7 to 94% and 0 to 72%, respectively. They have been implicated with antiphospholipid syndrome features (mainly avascular bone and cutaneous necrosis) or playing a limited role beside the multifactorial origin of HIV-related thrombosis [7]. HIV infection induces destruction of CD4 lymphocytes, which leads to polyclonal stimulation of B cells and hypergammaglobulinemia, resulting in antibodies against damaged endothelial cells (phospholipids exposed) and inhibition of protein S synthesis [5]. It is thought that LA activity in these patients might be an epiphenomenon secondary to chronic immune stimulation in HIV infection and no pathogenic correlation has been found with thromboses.
- Tissue Factor (TF): TF expression on circulating monocytes has been postulated in the setting of driving immune activation by translocation of microbial products through the damaged gut. In addition, HIV- associated gp120 causes release of TF via activation of arterial smooth muscle cells [2].
- Microparticles (MP): The MP are generated from endothelial cells, platelets and apoptotic CD4 lymphocytes.
- HIV-associated autoimmune haemolytic anemia has been related with an increased risk of thromboembolism during the acute phase of hemolysis [5].
- Homocysteine: Mild to moderate hyperhomocysteinemia (11-29%), related to a homozygous C677T mutation of the methylenetetrahydrofolate reductase gene [8],

especially in the setting of ART. It is not sufficient alone to cause thrombosis, but it may add an additional risk among patients with other risk factors for venous clots.

- Endothelial dysfunction: A dysfunctional venous endothelium, induced by HIV, may express heparin cofactor II deficiency and increased amounts of P-selectin, von Willebrand factor, TF, plasminogen activator inhibitor-1 and factor V, all of which may promote blood clotting. Biomarkers of endothelial dysfunction [9] (P-selectin, D-dimer and hyaluronic acid), coagulation, and tissue fibrosis may help identify HIV-infected patients at elevated risk of venous thromboembolism (VTE). Other endothelial dysfunction biomarker is asymmetric dimethylarginine (ADMA), a competitive inhibitor for endothelial nitric oxide synthase (eNOS) which seems to be related to an increased immune activation pathways in HIV-1 infection [10].

  In addition, intravenous drug use (IDU) can induce endothelial injury [11]. From a Danish HIV cohort [12], the 5-year risk of VTE was 8.0% [95% confidence interval (CI) 5.78-10.74%] in IDU HIV-infected patients, 1.5% (95% CI 1.14-1.95%) in non-IDU HIV-infected patients and 0.3% (95% CI 0.29-0.41%) in the population comparison cohort. In non-IDU HIV-infected patients, adjusted incidence rate ratios (IRRs) for unprovoked and provoked VTE were 3.42 (95% CI 2.58-4.54) and 5.51 (95% CI 3.29-9.23), respectively, compared with the population comparison cohort. In IDU HIV-infected patients, the adjusted IRRs were 12.66 (95% CI 6.03-26.59) for unprovoked VTE and 9.38 (95% CI 1.61-54.50) for provoked VTE. Low CD4 cell count had a minor impact on these risk estimates, while ART increased the overall risk (IRR 1.93; 95% CI 1.00-3.72).

- High density lipoprotein (HDL). A prospective study from South Africa [13] compared thrombotic profiles of 30 HIV-positive and 30 HIV-negative patients with acute coronary syndrome (ACS). Patients with HIV were younger; and besides smoking (73% vs 33%) and low HDL (0.8 ± 0.3 vs 1.1 ± 0.4), they had fewer traditional risk factors. Thrombophilia was more common in HIV-positive patients with lower protein C (PC; 82 ± 22 vs 108 ± 20) and higher factor VIII levels (201 ± 87 vs 136 ± 45). Patients with HIV had higher frequencies of aCL 47% vs 10%) and antiprothrombin antibodies (87% vs 21%).

  In addition to promoting cholesterol efflux from lipid-filled macrophages (foam cells) and reverse cholesterol transport, HDL protects low density lipoprotein (LDL) from oxidation and decreases expression of adhesion molecules on endothelial cells (including E-selectin and sICAM-1). HDL also improves endothelial function via stimulation of nitric oxide synthase activity, increases prostacyclin production by endothelial cells and inhibits endothelial TF expression, all of which enhance endothelium-dependent vasodilation and down-regulate thrombotic pathways. In this way, HDL possesses anti-inflammatory and antithrombotic properties. A cross-sectional study [14] was designed to assess large and small high density lipoprotein particle (HDLp) concentrations in persons with untreated HIV infection. Lower small HDLp (primarily responsible for HDL's anti-inflammatory properties and inhibition of

endothelial activation) concentrations and higher IL-6, sICAM-1 and D-dimer levels were found. The relationship of these markers to HIV-mediated atherosclerotic risk requires further study. The Strategies for Management of AntiRetroviral Therapy (SMART) trial demonstrated a 60% increased relative risk for cardiovascular disease (CVD) with a strategy of CD4+ cell count–guided interruption of ART, and adverse changes in HDL after stopping ART may explain some of the excess CVD risk. IL-6 and D-dimer levels increased after discontinuation of ART, and this was associated with increases in HIV RNA levels. In addition, baseline HDLp, but not low density lipoprotein particle (LDLp), predicted CVD risk in SMART.

2.2. HIV disease state

2.2.1. CD4 cell count

CD4 cell count at the time of the thrombotic event, is the strongest predictor in some multivariate models. Protein C and protein S deficiencies [5] and increased von Willebrand factor and fibrinogen concentrations [4], have been correlated with immunossuppresion, evidenced by reduced CD4 cell counts. Although the frequency of thrombosis is higher in the presence of lower CD4, there are reports of thrombosis occurring with higher CD4 [15].

2.2.2. Viral load

High HIV RNA level is predictive of progression of HIV infection and higher risk of thrombosis.

The frequencies of thrombophilic abnormalities (described above), increases with the progression to AIDS [2].

2.3. Comorbidities - Secondary prothrombotic abnormalities

2.3.1. Infections

A link between infection and thrombosis via endothelial activation [2] has been suggested, through up-regulation of some cytokines (the same ones that activate the coagulation system and appear during HIV infection), such as TNF α, IL-1, IL-6, factor VIII and fibrinogen, as well as down-regulation of fibrinolytic proteins, protein C (consumption as an antiinflammatory mediator) and free protein S concentrations. Deficiency of free protein S appears during an acute inflammatory process, such as opportunistic infections: C4b binding protein is increased up to 400% of its typical concentration [4] and binds free protein S, which is the active component as anticoagulant [5].

HIV-associated infections, including syphilis, *Pneumocystis jiroveci*, *Mycobacterium tuberculosis and avium intracellulare* [3] and hepatitis C [5], have been related to the induction of antiphospholipid antibodies (molecular mimicry between infectious agent

and beta2-glycoprotein I). Furthermore, cytomegalovirus induces thrombotic events via endo- thelial damage [**5**]. In a cross-sectional study [**16**] of 104 consecutive HIV- infected patients, active cytomegalovirus infection (defined as patients who had anti - cytomegalovirus antibody levels above the 75th percentile, > 209IU/ml), was associated with hypercoagulability independently of stage of HIV disease. It was observed higher levels of anticoagulant factors (antithrombin and total protein S levels) and higher procoagulant factors (factor VIII and fibrinogen levels), with a balance shifted to a procoagu- lant state. The majority of thrombosis have been associated with gastroin-testinal-related disease [**3**].

2.3.2. HIV-associated malignancy

Kaposi´s sarcoma and non-Hodgkin lymphoma (B cell), via abnormalities of lymphatic flow and stasis; and anal and cervical carcinoma, via production of procoagulants, invasion of vascular space or secretion of vascular permeability factors from tumor cells [**5**].

2.4. Hospitalization

Hospitalization in the past 3 months, was the risk factor more strongly associated with thrombosis in patients with HIV/AIDS, in a case-control study by Ahonkhai et al. [**1**].

2.5. Therapy

- Protease Inhibitors (PI), in highly active ART (HAART), above all indinavir and saquinavir, are thought to interfere with hepatic metabolism, specifically cytochrome P450, and regulation of thrombotic proteins: increasing of the expression of CD36, receptor for oxidized LDL, inducing, in addition, increased absorption of cholesterol [**2**].
- HIV-positive individuals with lipodistrophy and fat redistribution induced by ART, may be at increased risk for developing an abnormal coagulation profile, such as increased fibrinogen, D-dimer, plasminogen activator inhibitor-1 or protein S deficiency.
- Some authors recommend that clinicians must remain aware about the possibility of the occurrence of a thromboembolic event, especially during [**17**] the first few months after introduction of the ART.
- However, other authors [18] have observed that ART or PI therapy does not appear to play a significant role in the occurrence of thrombotic events; advanced HIV disease is the most relevant risk factor for development of thromboses, possibly due to an increased inflammatory state or the presence of concurrent comorbidities such as infections.

  The Nederland cohort of 109 patients with HIV, previously referred above [**4**], showed that ART may improve thrombophilic abnormalities and lead to a decreased risk of venous and arterial thrombosis.

In other study [19], the incidence of VTE in patients with HIV in the post - protease inhibitor era (after 1996) was higher than in HIV patients before 1996. However, the higher incidence since 1996 is small, probably not clinically significant, and not necessarily because of protease inhibitors.

Moreover, another study [20] analyzed levels of von Willebrand factor, D-dimer and factor VIII, in 160 HIV-infected and homosexual patients with a median age of 46 years, of whom 92% were male, 70% using ART, 74% Caucasian, 11% African American, 9% Hispanic, and 6% Asian. Significant lower levels of these parameters were observed in HIV-infected patients on ART compared to patients not on ART. Significant lower levels of protein C and free protein S, and increased activated protein C sensitivity ratio (APCsr) were found in the HIV-infected patients not on ART. However, *although the prevalence of coagulation abnormalities was lower in HIV- infected patients using ART, a considerable proportion of HIV - infected patients on ART showed endothelial cell activation and increased APCsr, suggestive of a persistent procoagulant state.*

Immune depletion contributes to HIV – related inflammation, and ADMA concentrations decrease in patients with HIV infection under ART, slowing down endothelial activation. However, ADMA levels (or changes) did not consistently correlate with HIV RNA levels (or changes) [21].

Otherwise, some drugs from ART show more favourable profile related to decrease immune activation. Switching from ritonavir - boosted protease inhibitors to raltegravir (integrase inhibitor), appeared to de- crease biomarkers of inflammation (high sensitivity C reactive protein, osteoprotegerin, IL-6, TNFα, insulin and D-dimer) [22].

- Megestrol acetate (progestational agent), used widely to stimulate appetite and weight gain in patients with AIDS-related anorexia and/or cachexia, could increase risk of VTE [3].

The data referred above, support the hypothesis that HIV-infected individuals are more likely to have clinically detected thromboembolic disease as opposed to non-HIV-infected individuals. One study performed by Malek et al. [23] revealed up to a 43% increase in developing a pulmonary embolism (PE), 10% increase in developing a deep venous thrombosis (DVT), and 40% increase in developing PE or DVT, in an HIV-infected individual over the 9-year study period. This increase differed by age group, with age group 21 to 50 years having the highest odds for PE among HIV+ individuals (OR, 1.58; 95% CI, 1.54-1.63).

Also, other study by Kiser et al. [24], showed patients with HIV had higher rate of VTE, being younger than 50 years (3.31% vs 0.53% in age-matched healthy controls, $p < 0.0001$), had a CD4(+) cell count less than 200 cells/mm³, or a diagnosis of acquired immunodeficiency syndrome.

Anyway, many authors propose the need to perform long-term, prospective studies assessing the factors associated with thrombotic events in patients with HIV.

3. Case reports

[25] In a previous published letter, we described 9 patients with HIV infection and thrombotic event, defined as thrombosis involving an artery or a deep or splanchnic vein. Here, we included 2 patients more as follows.

All of them were heterosexual patients, and one of them was an intravenous drug user. Median age was 38 years (range, 35-58 years). Seven of them were male. Only one patient had a family history of thrombosis (stroke). Four patients were coinfected with hepatitis C virus. The most frequent Centers for Disease Control and Prevention (CDC) HIV stage was 3 [**26**]. There were neither AIDS-related malignancies or autoimmune disorders nor concurrent opportunistic infections at the time of the thrombotic event. Six patients were on ART, and only two patients were undergoing protease inhibitor therapy. Basic coagulation assays were unremarkable and only one patient was evaluated for hypercoagulate state and was found to have low protein C and S values.

- Misdiagnosis of thromboembolism as a *Pneumocystis jiroveci* pneumonia (diagnosed by computed tomographic pulmonary angiogram) delayed anticoagulant treatment in a patient. Several months after this event, the same patient developed yugular vein thrombosis associated with a catheter placement.
- Four patients had a diagnosis of lower extremity DVT, as confirmed by venous duplex ultrasonography. One of them had recurrent DVT, in the setting of progressive multifocal leukoencephalopathy. Another one, a young woman, developed a DVT in the setting of malabsorption syndrome by *Giardia lamblia*; she had been diagnosed with non-B HIV infection a few months before, and she showed high CD4 cell counts, high viral load, as well as increasing aCL antibodies and probably decreasing C protein and antithrombin-III (enteral loss); she was not receiving ART.
- One male patient felt pain in the lower back since several weeks before admission, and his condition was diagnosed by abdominal computed tomography (CT), as inferior vena cava thrombosis (the patient had a congenital double inferior vena cava system). He was receiving interferon and ribavirin for the treatment of chronic hepatitis C.
- A man was admitted to the hospital complaining of pain in the epigastric area. His condition was diagnosed by CT as alcoholic chronic pancreatitis and mesenteric vein thrombosis.
- A woman was attended in the emergency unit because of massive hematemesis, and a portal vein thrombosis was documented by splanchnic angiography. A portocaval shunt was performed and the patient survived and went well.
- Two patients died, and a suspicious diagnosis of pulmonary embolism was made on the basis of a clinical approach (pleuritic chest pain, cough and shortness of breath) in the setting of septic shock (an autopsy was not available) in one case, and by high-probability ventilation/perfusion lung scanning, in another one.
- A young man developed severe pulmonary hypertension secondary to recurrent pulmonary embolism, in the presence of aCL antibodies and high CD4 cells count, but high viral load, without ART.

4. Specific settings for thrombotic events

4.1. Autoimmune background

Autoimmune disturbances have emerged in the setting of immunological reconstitution and constant antigenic viral stimulation in HIV-infected patients. Different types of autoantibodies have been observed, including aCL, anti-Beta2-glycoprotein I and antiprothrombin antibodies [27]. Clinical challenges can arise when the two conditions coexist.

Lupus anticoagulants were first described in AIDS and asymptomatic HIV-infected individuals (in whom they could be transient), by Bloom et al. in 1986. The association between aCL and HIV infection in men who have sex with men was reported in 1991. Falco et al., in 1993, found that, on the contrary to systemic lupus erythematosus (SLE), in the HIV-positive serum samples, reduced aCL binding capacity was evident if the cofactor (beta2-glycoprotein I) was added. Canoso et al. reported in 1997, aCL positivity in association with human T cell lymphotropic virus type 3 infection.

The presence of SLE and HIV infection in the same individual is being increasingly reported, particularly in Africa and Asia. This coexistence has been associated with remissions or amelioration of SLE symptoms, with advancing HIV infection during pre-Highly Active ART (HAART) era (before 1996 and introduction of protease inhibitors); or with flares in immune reconstitution, during effective HAART, through a cross-reactive mechanism between inflammatory factors and common nuclear antibodies.

Overlapping features between SLE and HIV infection can include: arthralgias and arthritis, polyclonal B cell activation, antibodies against double-stranded DNA, anti-Smith antibodies, antiphospholipid antibodies and autoimmune haemolytic anemia with positive Coombs test; however, low complement has not been detected in HIV infection. In addition, patients with SLE without previous exposure to retroviral infection may express antibodies against retroviral proteins, including gag, env, nef and p24 of HIV-1, with false-positive results of ELISA and Western blot for detection of HIV. Some authors have suggested that these antibodies directed against HIV proteins may protect SLE subjects from exogenous infection.

4.2. Immune reconstitution inflammatory syndrome (IRIS)

When ART is started, a striking immune restoration inflammatory response can appear. In this setting, there could be a predisposition to thrombotic events, as in the case reported as follows [28]. A 26-year-old HIV-infected man who had started HAART a few months earlier, developed multiple linear nodules following the superficial veins in both legs. Histopathologic examination demonstrated a mostly septal panniculitis with features of superficial thrombophlebitis. Authors propose that superficial thrombophlebitis should be added to the list of clinical manifestations of this newly observed immune reconstitution disease.

4.3. Acute coronary artery disease and non-bacterial thrombotic endocarditis

In addition to the issues referred above, protease inhibitors [**29**] have also been implicated in direct endothelial damage, which may be mediated by reduced nitric oxide production or release. The development of CVD risk factors such as insulin resistance, hyperlipidemia and fat redistribution syndrome, may exacerbate already existing underlying atherosclerotic risk in patients using these medications. However, necropsy studies de- monstrated *premature CVD in HIV-infected patients even before the advent of protease inhibitors*, indicating that other mechanisms might be involved independent of these drugs.

Other authors could not demonstrate relation between a patient's human immunodeficiency virus status and valve thrombosis [**30**] or non-bacterial thrombotic endocarditis [**31**].

4.4. Non cirrhotic portal hypertension

A multifactorial mechanism has been proposed to explain the pathogenesis of non-cirrhotic portal hypertension (NCPH) in HIV-infected patients, and we have reviewed it and described two cases, in a previous published paper [**32**]: prothrombotic state, by HIV as a direct cause or through anti-protein S antibodies, leading to protein S deficiency; as well as didanosine, an ARTdrug, adenosine analogue, which has been postulated as an independent predictor of developing NCPH through cumulative dosing or idiosyncratic mechanisms. It results in an obliteration of the small portal venules and liver regenerative hyperplasia. Considering the data regarding prothrombotic abnormalities in HIV-infected patients, we wondered if patients with HIV and NCPH should be evaluated for hypercoagulate state.

4.5. Pregnancy-puerperium

Annual incidence of VTE within 3 months postpartum in a cohort of 41 consecutive HIV-infected pregnant women [33], was 313 per 1000 person-years (95% CI, 65- 915). This risk is 120-fold higher than in HIV-positive controls, whereas the risk is 157-fold higher compared to HIV-negative pregnant women.

4.6. Other settings

Thrombophilia might have a limited role in the development of osteonecrosis in HIV-positive, according a case - control study [34], being only significantly associated with osteonecrosis: nadir of CD4(+) < 60 cells/microL and steroid use.

5. Management

Notably, the 2008 American College of Chest Physicians (ACCP) guidelines on antithrombotic and thrombolytic therapy, are silent regarding HIV-infected patients [**35**]. Anyway, the management of proven VTE should be the same as for the non HIV-patients [**3**].

Some special issues must be considered:

5.1. Antiretroviral therapy and warfarin drug interaction

Interactions between warfarin and ART (non-nucleoside reverse transcriptase inhibitors-NNRTIs and protease inhibitors-PIs), are through influence of ART on CYP2C9, the enzyme responsible for the metabolism of the more active S-enantiomer of warfarin [3]. Among the NNRTIs, induction of warfarin metabolism is likely with nevirapine. Inhibition of warfarin metabolism may occur with efavirenz o etravirine. Interactions involving ritonavir-boosted PIs are most frequent when warfarin is initiated in patients receiving concurrent efavirenz therapy [36]. International Normalized Ratio (INR) response should be used to guide warfarin dosage requirements; otherwise, low-molecular-weight heparin (LMWH) could be considered as a safer choice, although always keeping in mind that HIV infection may be an independent risk factor for the development of heparin-induced thrombocytopenia (HIT).

5.2. Warfarin-induced skin necrosis (WISN)

The presentation of WISN, a condition due to decrease protein C levels by warfarin, in HIV-1 infected patients, is a novel clinical entity, reported recently [37]. Six cases of WISN occurred in 973 patients receiving warfarin therapy for venous thrombosis (0.62%, 95% CI 0.25 - 1.37%) at a referral hospital in Cape Town, South Africa. All 6 cases occurred in HIV-1-infected women (median age 30 years, range 27 - 42) with microbiologically confirmed tuberculosis (TB) and venous thrombosis. All were profoundly immunosuppressed (median CD4+ count at TB diagnosis 49 cells/microl, interquartile range 23 - 170). Of the 3 patients receiving combination ART, 2 had TB-IRIS. The occurrence of 6 WISN cases in a 40-month period may be attributed to: hypercoagulability secondary to HIV-1(above all if associated to decreased protein C levels) and TB, short concurrent heparin and warfarin therapy and high loading doses of warfarin. Active prevention and appropriate management of WISN are likely to improve the morbidity and mortality of this unusual condition.

6. Questions and remarks arised from clinical practice [3, 25]

- Should young patients (especially men) who develop thromboembolic events, in the absence of classic thrombophilic risk factors, be evaluated for HIV infection?
- Given the overlapping features between SLE and HIV-infection, should be mandatory to rule out HIV infection in black South African patients with SLE (above all if they are not females of childbearing age), who present an unsatisfactory course?.
- Should patients with HIV with severe immunosuppression be screened for prothrombotic abnormalities?
- Venous thromboembolism can mimic opportunistic lung infection in patients with HIV; so, the former should be considered in differential diagnosis of lung diseases in this setting, above all when patients have unexplained dyspnea or hypoxemia.

- Should patients with HIV with low CD4 cell count receive prophylactic anticoagulation?
- Appropriate prophylactic measures should be instituted, including low-molecular weight heparin on hospitalization and for high-risk HIV-infected outpatients.
- HIV infection may be an independent risk factor for the development of heparin-induced thrombocytopenia (HIT). Should be considered any special caution regarding it?
- Finally, considering the absence of specific recommendations or guidelines on antithrombotic and thrombolytic therapy directed to VIH-infected patients, are traditional screening methods and management strategies applicable in HIV?

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