Over recent years it has become evident that the spectrum of autoimmune and rheumatic diseases in patients with human immunodeficiency virus (HIV) infection is increasing and includes conditions such as polymyositis/myopathies, Sjogren’s syndrome, Raynaud’s phenomenon, psoriatic arthritis, as well as primary biliary cirrhosis, HIV-related vasculitis, and Behcet’s syndrome.

Systemic lupus erythematosus (SLE) and sarcoidosis, however, in the HIV-infected population, seem to have a lower incidence than would be expected in the general population, although several cases of sarcoidosis, which is associated with depressed cellular immunity, have been documented in patients with AIDS. It is possible that the development of an autoimmune diathesis is suppressed by HIV infection and could be restored with therapy and normalization of CD4 counts with functional T cells. Indeed this hypothesis has been verified by the documentation of several such cases. Erdal, et al reported a patient with HIV who developed SLE after the initiation of highly effective retroviral treatment. Fox, et al documented a female patient with SLE who developed HIV infection followed by clinical improvement and disappearance of autoantibodies. Thyrotoxicosis and thyroid autoantibodies have also been reported in a patient with HIV after restoration of immune function as has sarcoidosis, which has been reported in 2 patients following potent anti-HIV therapy.

Antiphospholipid antibodies (aPL) may be demonstrated during the course of many infections in addition to occurring in conditions such as SLE, primary antiphospholipid syndrome (APS), and a wide variety of other rheumatic diseases. Syphilis was the first infection to be linked with aPL: one of the components of the VDRL reagent (cardiolipin) being responsible for the original finding that antibodies thought initially to be directed against cardiolipin, were, in fact, pivotal in the pathogenesis and for the diagnosis of the APS. It was subsequently found, however, that these antibodies were directed against a number of serum proteins, primarily β2-glycoprotein I (β2-GPI) and prothrombin, the phospholipids modifying the protein molecules to create a “cryptic epitope” neoantigen on the protein molecules that were revealed or formed only when these proteins were bound to certain anionic surfaces, e.g., gamma-irradiated polystyrene or anionic phospholipid membranes. Recent work by Roubey, et al has shed some light and offers another explanation of the relationship between anticardiolipin (aCL) and β2-GPI. Certain IgG aCL recognize β2-GPI. Binding occurs when β2-GPI is immobilized on gamma irradiated polystyrene, on cardiolipin-coated polystyrene (as in the standard aCL ELISA) or on cardiolipin-containing liposomes, but not when the antigen is immobilized on untreated polystyrene. Antibody binding to β2-GPI coated on gamma-irradiated polystyrene seems to be dependent upon high antigen density and antibody valency. Autoantibodies to β2-GPI are of relatively low intrinsic affinity and there are other examples of this phenomenon (e.g., binding of IgM rheumatoid factors to aggregated IgG).

The major infection worldwide over the past 20 years has been HIV-induced infection and it is not surprising that this condition has been so extensively studied by immunologists and rheumatologists in view of its eventual destruction of the patient’s immune system with resultant major “autoimmune” complications.

ANTIBODIES TO PHOSPHOLIPIDS IN HIV INFECTION

HIV infection is associated with many abnormalities in B cell function resulting in the production of a large variety of autoantibodies that include anti-alpha myosin, antibodies to endogenous erythropoetin, denatured DNA, thyroid peroxidase, and TSHR. However the antibodies most frequently found are those directed towards cardiolipin and those responsible for lupus anticoagulant (LAC) positivity. LAC were first described in 44% of patients with acquired immunodeficiency syndrome (AIDS) and in 43% of asymptomatic HIV positive individuals (they were found to be transient by Bloom, et al in 1986). In 1997, Canoso, et al reported on aCL positivity with HTLV -1 infection. In 1992, the association of aCL with HIV infection in male homosexuals was reported and several studies since then have confirmed these original findings. Daroca, et al tested 84 HIV-infected patients in the same year and found that 59.5% of the 84 patients were IgG aCL positive. None had any thromboembolic phenomena. No significant differ-
ences were found with respect to sex, risk factors, and stage of the disease. They stated that the aCL did not appear to be a prognostic marker in HIV-infected subjects but were indicative of impaired humoral immunity found in these patients. Falco, et al. in 1993 examined 39 HIV positive and 20 aCL positive SLE sera and found that, in the HIV sera, reduced binding was evident if the co-factor (β₂-GPI) was added. In the SLE sera, however, addition of the co-factor improved the binding. These authors concluded that the aCL in HIV infection appeared to have a different specificity to those found in SLE. LOIZOU, et al., in 1995 found aCL in 47% of HIV positive individuals, and other authors have also confirmed this association.

The aCL described in HIV patients are of both the pathogenic (β₂-GPI cofactor dependent) and the infectious type (β₂-GPI independent). Both types of aCL may be detected following several different types of infections. The isotypes and diversity of the aPL may also vary and may include antibodies to phosphatidylserine. The frequency of antibodies to prothrombin and β₂-GPI is significantly less in HIV patients according to Guerin, et al. These investigators found LAC positivity in 72% and aCL positivity in 67% of their patients. A previous paper by the same authors demonstrated significantly elevated antibodies to β₂-GPI in patients with definite APS but only in 10% of those with HIV infection. The detection of anti-prothrombin antibodies was significantly less in their HIV patients, but recent work by Loizou, et al. demonstrated a high frequency of antibodies to prothrombin in a group of 100 HIV positive black patients in South Africa. These variations in aPL (particularly antiprothrombin antibodies) in the study population may be due to the different strain of HIV encountered and predominating in infected African patients. The antigen used in the ELISA performed in these patients was prothrombin alone. The findings regarding β₂-GPI were subsequently confirmed by Petrovas, et al., who investigated the phospholipid specificity, avidity, and reactivity with β₂-GPI in 44 patients with HIV infection compared with 6 patients with SLE with secondary APS, 30 SLE patients without APS, and 11 patients with primary APS. The prevalence of aCL, antiphosphatidylserine, antiphosphatidylinositol, and antiphosphatidylcholine (36%, 56%, 34%, and 43%, respectively) was similar to that found in the SLE/APS and primary APS patients. The prevalence of these antibodies was significantly higher than that observed in SLE/non-APS patients. However, anti-β₂-GPI antibodies were detected in only 5% of the HIV-1 infected patients in this series. A significant decrease of aPL binding after treatment with urea and NaCl was observed in the sera of HIV-1 infected patients compared with APS patients, indicating that aPL from HIV patients have a low resistance to dissociating agents indicating low avidity of the antigen. GONZALEZ, et al. were also unable to detect anti-β₂-GPI in their HIV positive sera despite the presence of high concentrations of aCL.

In 1996, Silvesteris, et al. studied antibodies to phosphatidylserine in HIV patients among a panel of phospholipid antigens. They found that in vitro apoptosis of T cells was increased in patients with high serum anti-phosphatidyl serine IgG. Together with other studies they concluded that, because phosphatidyl serine is exteriorized by apoptotic lymphocytes, its persistence may cooperate with macrophages in the clearance of dead cells by an enhanced antibody-dependent cellular cytotoxicity mechanism and they postulated that this might explain the absence of thrombophilia in HIV positive patients with elevations of the aPL.

THROMBOEMBOLIC DISEASE AND HIV INFECTION

There are many reports of thrombosis occurring in patients with HIV/AIDS and these include peripheral vein, pulmonary embolism, retinal vein occlusion, cerebral vein, portal vein, and mesenteric occlusions. Both arterial and venous thromboembolic disease have been reported in one patient by Bosson, et al. There are many reasons for the existence of the hypercoagulable state in some HIV patients and these have recently been very ably reviewed in the HIV literature by Saif and Greenberg. These authors also reported a retrospective study of 131 patients. Not only may aPL (antibodies to cardiolipin and other negatively charged autoantibodies, LAC) be found, but increased levels of von Willebrand factor, and deficiencies of protein C, protein S, antithrombin III and heparin cofactor II have also been detected in HIV sera.

Opportunistic infections with cytomegalovirus (CMV) or, on occasion, Pneumocystis carinii have, in several reported cases, also been associated with thrombosis. CMV has been demonstrated locally within affected tissues (digital infarcts) by Smith, et al., as well as in blood. This is not unique to HIV infected individuals, as CMV infection has also been associated with thrombosis following liver transplantation. Masala, et al. demonstrated cross-reactions between P. carinii infections and cardiolipin similar to that previously reported by Misra, et al. in patients with infectious mononucleosis and aCL. They observed that in patients with AIDS, aCL occurred almost exclusively among those who had active P. carinii pneumonia.

Treatment with protease-inhibitor therapy, which causes major lipid disturbances such as hypercholesterolemia, hypertriglyceridemia, and insulin resistance has also been documented as causing deep vein thrombosis and pulmonary emboli in otherwise healthy, HIV-infected patients, as reported by George, et al. Carr reported portal vein thrombosis in a patient receiving indinavir therapy and the use of megestrol acetate has also been associated with a tendency to thrombosis.

reported that many occurrences of thrombosis may have been asymptomatic and that dehydration and debilitation or an advanced stage of the disease itself may have been contributing factors to the development of thrombosis.

Protein C, a vitamin K dependent protein that functions as a natural anticoagulant inactivates the procoagulant factors Va and VIIa. Decreased levels of functional protein C as well as antigenic protein C have been found in HIV-infected patients and these levels correlate with the degree of immunosuppression as determined by reduced CD4 cell counts, as reported by Feffer, et al54 and by Sarif, et al in one of their series50.

Heparin cofactor II (HCII) is a specific thrombin inhibitor, the inhibitory activity of which is enhanced by heparin. Zon and Groopman55 found a higher prevalence of inhibitor, the inhibitory activity of which is enhanced by lowering of the free protein S levels. Hassel, et al directed against protein S might be responsible for the (the pathogenic, ß2-GPI dependent as well as the nonpathogenic, non-ß2-GPI dependent) antibodies may be detected with the development of AIDS. Normal levels of C4b-binding protein have been found, suggesting that the mechanism for this reduction in protein S is different from that which occurs with inflammation. It seems that disturbances of endothelial cell function may be responsible. However, Sorice, et al56 suggested that specific autoantibodies directed against protein S might be responsible for the lowering of the free protein S levels. Hassel, et al51 and Ordi, et al52 also studied this association and drew attention to anti-protein S in HIV infected patients.

**HIV AND MANIFESTATIONS OF THE ANTIPHOSPHOLIPID SYNDROME**

It has become clear that in HIV infection, both types of aPL (the pathogenic, ß2-GPI dependent as well as the nonpathogenic, non-ß2-GPI dependent) antibodies may be detected and that there is diversity, not only of the isotypes, but also of the aPL including anti-protein S antibodies.

In addition, there is a low frequency of antibodies directed towards ß2-GPI in HIV-infected patients. It is therefore not surprising that the APS and its manifestations are infrequent in HIV. Certainly thrombotic and other manifestations are much more frequently encountered than with other viral infections, again pointing to a major immunological disturbance in HIV in contrast to other viral conditions63,64. However, CMV infections have also been reported as being associated with the APS65,66.

aCL and stroke in an HIV positive patient was reported by Thirumalai and Kirshner in 199467 and by Keeling, et al68. Deep vein thrombosis of the extremities by Orbea-Rios, et al69, and skin necrosis by Soweid, et al70. Skin necrosis was also recently reported by Leder, et al70 in a male patient with HIV who suffered from testicular infarction requiring orchidectomy. A 42-year-old woman with a 12 year history of HIV infection and who developed gangrene of both forefeet was reported by Cailleux, et al71. A skin biopsy revealed intracapillary thrombi and severe necrosis of the hypodermis with no evidence of vasculitis. IgG aCL concentrations were elevated.

A 33-year-old woman with AIDS who had had a cerebrovascular accident and who developed a splenic infarction was documented by Cappell, et al in 199372. A recent report has also drawn attention to aPL associated complications and APS in HIV infection. Turhal, et al73 reported 4 cases. The first developed livedo reticularis acutely; the second, probable avascular necrosis of the femoral head associated with demonstrable decreased blood flow; the third, thrombosis of the inferior vena cava and pulmonary emboli; and the fourth, a major pulmonary embolus. Avascular necrosis of bone (AVN) has been previously documented with HIV infection. Belmonte, et al reported 3 cases of AVN associated with aPL in 199374. No risk factors other than the presence of aPL were present in these patients. However, other subsequent reviews of the association failed to detect aPL as a risk factor in this condition75-80. It is likely that hyperlipidemia (associated with antiretroviral therapy)79, corticosteroid use, and alcohol abuse represent some of the risk factors in the pathogenesis of the condition, with aCL being present in a minority only. Pulmonary hypertension seen with APS may also be an aPL-related complication.

The incidence of HIV-associated pulmonary hypertension (PHT) is estimated to be 1/200, which is much higher than the 1/200,000 found in the general population81. The common reasons for PHT encountered in HIV-infected patients are pulmonary infections, venous thromboembolism, and left ventricular dysfunction. However, “primary” PHT has been reported in some patients without a history of thromboembolic disease, intravenous drug usage, or pulmonary infections. Its pathogenesis remains poorly understood and it has been hypothesized that HIV causes endothelial cell damage and mediator-related vasoconstriction through stimulation by the envelope gp 120, including direct release and effects of endothelin-1, the most potent vasoconstrictor, and by the effects of interleukin 6.
and tumor necrosis factor-α, on the pulmonary arteries themselves. It is well established that the frequency of aCL is elevated in patients with “primary” PHT, but the frequency of aCL elevations in the HIV group remains to be elucidated.

Thrombotic thrombocytopenic purpura (TTP) is a rare but well described complication of HIV infection, occurring equally frequently during the early asymptomatic phase of HIV infection as well as with clinical AIDS, the clinical spectrum varying from a low grade asymptomatic thrombocytopenia with mild renal insufficiency to a severe illness with major neurological manifestations and renal failure that may require dialysis82-85. Indeed the presence of von Willebrand factor-cleaving protease inhibitor, which may be involved in the pathogenesis of TTP, has been described in the plasma of a patient with both AIDS and TTP86. Thrombotic microangiopathy (TMA) encompassing microangiopathic hemolytic anemia, thrombocytopenia, and renal failure is another renal complication that may develop in patients with HIV87. This type of vascular lesion is more common in HIV patients than in the normal population, may be one of the first manifestations of HIV infection, and may be severe88. TTP has been infrequently associated with aPL, but TMA is relatively common in patients with APS. The association of both these conditions in HIV/AIDS patients, as yet, has also not been investigated and reported.

Questions of paramount importance and interest include the pathogenicity of the various types of aPL and why thrombosis is seen in selected patients with SLE only and very infrequently with infections. The recent work of Sheng, et al89, which measured the effects of test antibody or plasma samples on in vitro thrombin formation, will clearly be extended and may provide some clear information concerning this problem. These investigators found that plasma and affinity purified antibodies from patients with APS inhibited thrombin generation significantly more so than from patients with aPL from other causes; moreover, APS patient samples showed thrombin inhibition in the presence of anti-ß2-GPI or antiprothrombin antibodies.

In summary, it seems that the pathogenesis of thrombotic complications in patients with HIV infection and AIDS is multifactorial, with the aPL playing a role in selected patients only. The frequency of thrombotic complications encountered with aPL positivity, while several cases have been published from various centers, remains low at this time. Lipid disturbances after antiretroviral therapy (now increasingly available from drug companies at reduced cost) and their attendant vascular complications will no doubt overtake hematological and immunological disturbances seen in these patients, as a cause of these complications. However, discovery of new classes of antiretroviral compounds (e.g., fusion inhibitors, integrase inhibitors) will diminish usage of the protease inhibitor class of drugs, which seem to be mostly linked with these complications, thereby overcoming these iatrogenic problems.

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Supported by the Carole and Geoffrey Lawson Trust, United Kingdom.

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REFERENCES
55. Culpepper RM, Carr AE. Case report: a novel form of free protein...
84. Viale P, Pagani L. Thrombotic thrombocytopenic purpura (TTP) during the course of HIV infection. AIDS Patient Care STDS 1997;4:302-3.