HIV and autoimmunity
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Abstract

The association of immune dysfunction in patients with human immunodeficiency virus (HIV) infection and AIDS and the development of autoimmune diseases is intriguing. Yet, the spectrum of reported autoimmune phenomena in these patients is increasing. An infectious trigger for immune activation is one of the postulated mechanisms and derives from molecular mimicry. During frank loss of immunocompetence, autoimmune diseases that are predominantly T cell subtype CD8 driven predominate. There is evidence for B cell stimulation and many autoantibodies are reported in HIV patients. We propose a staging of autoimmune manifestations related to HIV/AIDS manifestations and the total CD4 count and viral load that may be beneficial in identifying the type of autoimmune disease and establishing the proper therapy. In stage I there is the acute HIV infection, and the immune system is intact. In this stage, autoimmune diseases may develop. Stage II describes the quiescent period without overt manifestations of AIDS. However, there is a declining CD4 count indicative of some immunosuppression. Autoimmune diseases are not found. During stage III there is immunosuppression with a low CD4 count and the development of AIDS, CD8 T cells predominant and diseases such as psoriasis and diffuse immune lymphocytic syndrome (similar to Sjogren’s syndrome) may present or even be the initial manifestation of AIDS. Also during this stage no autoimmune diseases are found. In stage IV there is restoration of immune competence following highly active anti-retroviral therapy (HAART). In this setting, there is a resurgence of autoimmune diseases. The frequency of reported rheumatological syndromes in HIV-infected patients ranges from 1 to 60%. The list of reported autoimmune diseases in HIV/AIDS include systemic lupus erythematosus, anti-phospholipid syndrome, vasculitis, primary biliary cirrhosis, polymyositis, Graves’ disease, and idiopathic thrombocytopenic purpura. Also, there is an array of autoantibodies reported in HIV/AIDS patients which include anti-cardiolipin, anti-β2 GPI, anti-DNA, anti-small nuclear ribonucleoproteins (snRNP), anti-thyroglobulin, anti-thyroid peroxidase, anti-myosin, and anti-erythropoietin antibodies. The association of autoantibodies in HIV-infected patients to clinical autoimmune disease is yet to be established. With the upsurge of HAART, the incidence of autoimmune diseases in HIV-infected patients is increasing. In this review, we describe the various autoimmune diseases that develop in HIV/AIDS patients through possible mechanisms related to immune activation.

Keywords: HIV; AIDS; Autoimmunity; Immune restoration; Autoantibodies

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Table 1
HIV and autoimmunity

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stage description</th>
<th>CD4 count</th>
<th>Viral load</th>
<th>AIDS</th>
<th>Autoimmunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Clinical latency</td>
<td>High (&gt;500)</td>
<td>High</td>
<td>No</td>
<td>Autoimmune disease</td>
</tr>
<tr>
<td>II</td>
<td>Cellular response</td>
<td>Normal/low (200–499)</td>
<td>High</td>
<td>No</td>
<td>Immune-complex, vasculitis</td>
</tr>
<tr>
<td>III</td>
<td>Immune deficiency</td>
<td>Low (&lt;200)</td>
<td>High</td>
<td>Yes</td>
<td>Spondylo-arthritis</td>
</tr>
<tr>
<td>IV</td>
<td>Immune restoration</td>
<td>High (&gt;500)</td>
<td>Low</td>
<td>Controlled</td>
<td>Autoimmune disease</td>
</tr>
</tbody>
</table>

Autoimmune disease can occur with a preserved immune system requiring B and T cell interactions (normal CD4 count). Therefore, autoimmunity is possible in Stages I, II and IV. With profound immunodeficiency (low CD4 count), autoimmune diseases are not found. Stage IV (high CD4 count) describes HIV-infected patients with immune restoration, but possibly altered immuno-regulation enabling the resurgence of autoimmune diseases.

1. Introduction

The combination of immune dysfunction in patients with human immunodeficiency virus (HIV) infection and AIDS and the development of autoimmune diseases is intriguing. Yet, the spectrum of reported autoimmune phenomena in these patients is increasing [1,2]. This wide range is due to different patient selection, and association with the development of AIDS.

An infectious trigger for immune activation is one of the postulated mechanisms in autoimmunity and derives from molecular mimicry [3,4]. During frank loss of immunocompetence, autoimmune diseases that are predominantly T cell subtype CD8 driven may predominate. Multiple anti-retroviral drug therapy for patients with AIDS provides prolonged survival and immune restoration, a setting where autoimmune diseases develop. We propose a staging of autoimmune manifestations related to HIV/AIDS manifestations and CD4 count that may be beneficial in identifying the type of autoimmune disease and establishing the proper therapy (Table 1). During Stage I there is the acute HIV infection, and the immune system is intact. In this stage, autoimmune diseases may present. While Stage II is a quiescent period without overt manifestations of AIDS, there is a declining CD4 count indicative of some immunosuppression. Autoimmune diseases are not found. During Stage III there is immunosuppression with a low CD4 count. However, diseases where T cell subtype CD8 predominant such as psoriasis and diffuse immune lymphocytic syndrome (Sjogren’s-like syndrome) may present or even be the initial manifestation of AIDS. Autoimmune diseases are not found. In Stage IV there is restoration of immune competence following anti-retroviral therapy. In this setting, there may be a resurgence of autoimmune diseases. In this review, we describe the various autoimmune diseases that develop in HIV/AIDS patients through possible mechanisms related to immune activation.

2. Autoimmune diseases in HIV infection

The frequency of rheumatological syndromes in HIV patients varies from less than 1 to 60% [2,5–7]. The reported autoimmune diseases in HIV/AIDS are reviewed.

2.1. Systemic lupus erythematosus

The unrestrained state of immune activation may contribute to chronic inflammatory and autoimmune sequelae in HIV-infected individuals. Several rheumatic entities, such as Reiter’s syndrome, psoriatic arthritis, Sjogren’s-like syndrome, myopathy and HIV-related vasculitis are often correlated with the severity of the HIV infection and improve with anti-retroviral therapy. However, other entities, such as systemic lupus erythematosus (SLE) and sarcoidosis [8,9], have a decreased incidence in the HIV-infected population than would be expected in the general population. This inconsistency suggests that the immunosuppressive effect of HIV may inhibit the development of autoimmune diathesis. On the other hand, in a setting of HIV infection that is controlled by protease inhibitors and other anti-retroviral agents, the immune system is no longer immunodeficient. There is immune restoration with normalization of
the CD4 count and functional T cell reconstitution [10], so that a genetically predisposed host can develop autoimmunity. This has been postulated in the coexistence of HIV with SLE [11]. SLE may be influenced by HIV type-1 infection. It has been suggested that the immunosuppression resulting from HIV infection can prevent the emergence of SLE. There appear to be fewer cases of SLE in the HIV-infected population than would be predicted, based on the overall incidence of SLE. To date, 29 cases of association between the two diseases have been reported, but the diagnosis was simultaneous in just two of these and only 18 fulfilled the ARA criteria for the diagnosis of SLE. Most patients experienced an improvement in their SLE after development of their HIV associated immunosuppression and a reactivation of lupus manifestations has also been noted after immunological recovery secondary to anti-retroviral therapy [12].

Fox and Isenberg [13] described a female patient with SLE who was infected with HIV. Using stored serum, the precise timing of HIV seroconversion was determined and the early effects of HIV infection on SLE examined. This infection resulted in clinical improvement and the disappearance of autoantibody production. On the other hand, Diri et al. [14] reported a patient with HIV infection who developed SLE after the initiation of highly active anti-retroviral therapy (HAART).

A number of clinical and laboratory features of HIV infection are found in SLE. Gonzalez et al. [15] analyzed the presence of circulating antibodies to small nuclear ribonucleoproteins (snRNP) in both diseases. Sera from 44 HIV-infected children, from 22 patients with childhood-onset SLE, and from 50 healthy children were studied. Results included the detection of anti-snRNP antibodies by ELISA in 30 HIV-infected patients (68.1%) and 19 SLE patients (86.3%). These antibodies were directed against U1-RNP (61.3 and 77.2%, respectively), Sm (29.5 and 54.5%, respectively), 60 kDa Ro/SS-A (47.7 and 50%, respectively), and La/SS-B proteins (18.1 and 9%, respectively). None of the HIV-infected children and 11 SLE patients (50%) showed anti-snRNP antibodies by counter immunoelectrophoresis. None of the HIV-infected patients showed anti-70 kDa U1-RNP or anti-D-Sm antibodies by immunoblotting. No differences between the two groups were noted on the presence of non-precipitating anti-snRNP antibodies. No such reactivities were observed among the normal sera tested. The authors concluded that non-precipitating anti-snRNP antibodies in HIV-infected children are as frequent as in childhood-onset SLE. The significance of these antibodies is not clear at present. Although polyreactive and low-affinity antibodies and a mechanism of molecular mimicry may explain these results, a specific stimulation of B cells by nuclear antigens could not be excluded. Review of the literature revealed that rheumatologic signs and symptoms were common in HIV and overlapped significantly with SLE. Autoantibodies also occurred frequently in both diseases.

2.2. Anti-phospholipid syndrome/anti-cardiolipin antibodies/anti-β2 GPI antibodies

In 1992, the association of anticardiolipin (aCL) antibodies with HIV infection in male homosexuals was reported [16]. Since then, many studies have alluded to this specific combination [17–20]. We described an unusual presentation of antiphospholipid syndrome (APS) associated with acute HIV infection. The APS in this patient was characterized by elevated titers of aCL antibodies and anti-β2 GPI, necrotic lesions in the lower extremities and testicular necrosis requiring orchidectomy. The patient had no history of AIDS, no previous opportunistic infections, and was not on any retroviral medications. The CD4 count was only minimally decreased (CD4-322) indicating that the patient had an acute infection and was not immunosuppressed [17].

The aCL antibodies described in HIV patients are of both the pathogenic type (β2 GPI cofactor dependent) and the infectious type (non-β2 GPI dependent). It seems that following infections, one may see both types of aCL as well as all isotypes and diversity of aCL including anti-PS [21]. Antiphospholipid antibodies have previously been detected in HIV patients. The presence of lupus anticoagulant (LA), aCL antibodies, anti-prothrombin antibodies, and anti-β2 GPI antibodies were investigated in 61 HIV patients and 45 patients with APS. LA was present in 72% of HIV
patients and 81% of APS patients. Anti-cardiolipin antibodies were detected in 67% of the HIV patients and 84% of APS patients. The detection of anti-prothrombin and anti-β2 GPI antibodies was significantly less in HIV patients compared to APS patients. Anti-cardiolipin antibodies were detected in 67% of the HIV patients and 84% of APS patients. The detection of anti-prothrombin and anti-β2 GPI antibodies was significantly less in HIV patients.

Petrovas et al. [19] investigated the phospholipid specificity, avidity, and reactivity with β2 GPI in 44 patients with HIV infection and compared to the results in 6 SLE patients with secondary APS, 30 SLE patients without APS, and 11 patients with primary APS. Interestingly, the prevalence of aCL, anti-phosphotidyl serine, anti-phosphotidyl inositol, and anti-phosphotidyl choline (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. Anti-β2 GPI antibodies occurred in only 5% of HIV-1 infected patients. A significant decrease of aPL binding after treatment with urea and NaCl was observed in the sera of HIV-1 infected patients when compared to APS patients, indicating that aCL antibodies from HIV patients have low resistance to dissociating agents. Guerin et al. [22] investigated anti-β2 GPI antibody isotype and IgG subclass in APS patients and a variety of other thrombotic and non-thrombotic disorders including infections. Elevated levels of IgM anti-β2 GPI antibodies were observed in 65% of patients with APS and 27% of patients with HIV infection.

In another study, Guglielmone et al. [23] investigated the distribution of aCL isotypes and requirement of protein cofactor in viral infections including HIV. The isotype distribution of aCLs in the sera from 40 patients with infection caused by HIV-1 was studied by ELISA in the presence and absence of protein cofactor (mainly β2-GPI). The prevalence of one or more aCL isotypes in serum of patients with HIV-1 infection was 47%. Most of these antibodies were mainly cofactor independent.

2.3. Autoimmune thrombocytopenia

Immune thrombocytopenic purpura (ITP) occurs in as many as 40% of patients infected with the HIV. Aboulafia et al. sought to evaluate the effect of HAART on platelet counts in 11 homosexual men with HIV-associated ITP patients. At initial evaluation, 7 patients were anti-retroviral naive, 2 were taking zidovudine alone, and 2 were receiving combination anti-retroviral therapy for known HIV infection. For 6 patients with \(<30 \times 10^9\) platelets, prednisone was initially coadministered with HAART. The primary outcome measure was the platelet count response to HAART, which was measured weekly until counts had normalized on 3 consecutive occasions, then every 3 months while on HAART. Secondary outcome measures were HIV-viral RNA levels and CD4+ cell counts. The results were that 1 month after the initiation of HAART, 10 patients had an increase in mean platelet count. This improvement was sustained at 6 and 12 months’ follow-up for 9 of 10 patients. Increases in mean platelet count at 6 and 12 months of the 9 responders were statistically significant. The range of follow-up in the 9 responders was 21–46 months (median, 30 months), with no thrombocytopenic relapses. The 9 long-term platelet responders were maintained on HAART and at 12 months had a mean reduction of >1.5 log 10 in HIV-viral RNA serum levels and a marked improvement in CD4+ T-lymphocyte cell count. HAART seems to be effective in improving platelet counts in the setting of HIV-associated ITP, enhancing CD4+ cell counts, and reducing HIV viral loads [24].

2.4. Vasculitis

Different types of vasculitis are associated with HIV infection. Co-infections inducing vasculitis have been reported, including hepatitis B and C. Systemic necrotizing vasculitis, leukocytoclastic vasculitis, cryoglobulinemia, and CNS vasculitis have been reported [2,25,26]. Panarteritis nodosum more frequently affects the neuromuscular system and skin. Antineutrophilic cytoplasmic antibodies are found less commonly. Vasculitis of the peripheral nerve may cause mononeuritis multiplex or polyneuropathy, sometimes the presenting symptom of HIV infection or after the development of AIDS [26]. HIV antigens and HIV-particles can be identified by electron microscope and positive in situ hybridization studies for HIV have been reported in perivascular cells [2].
Acute coronary vasculitis resulting in a fatal myocardial infarction in a 32-year-old HIV patient without coronary heart disease risk factors was reported. Histological analysis of two coronary arteries on autopsy showed a dense infiltration of lymphocytes with necrosis of the intima. In situ hybridization showed sparse intense staining indicating the presence of HIV-1 sequences within the arterial wall [27].

2.5. Polymyositis and dermatomyositis

HIV-associated polymyositis was first described in 1983, and many reports in the past several years confirm this association [2,28]. Dermatomyositis is also seen in HIV infection [29]. The clinical course, laboratory and electromyography findings are similar to the idiopathic form [2].

2.6. Thyroid disease/Graves’ disease/anti-thyro-globulin antibodies/anti-thyroid peroxidase antibodies

Jubault et al. [30] analyzed the kinetics of CD4 cells, HIV viral load, and autoantibodies in AIDS patients with Graves’ disease after immune restoration on (HAART). Five patients were diagnosed with Graves’ disease after 20 months on HAART, several months after the plasma HIV viral load was undetectable, and when the CD4 count had risen from 14 to 340×10⁶ cells/l Anti-thyroid peroxidase (anti-TPO) and anti-TSHR antibodies appeared 14 months after starting HAART and 12 months after the rise in the CD4 count. No other autoantibodies were detected. The autoantibodies were not detected in HIV-1 patients without hyperthyroidism.

2.7. Primary biliary cirrhosis

Mason et al. [31] used immunoblots as a surrogate test to find out whether retroviruses play a part in the development of primary biliary cirrhosis. Western blot tests were performed for HIV-1 and the human intracisternal A-type particle (HIAP), on serum samples from 77 patients with primary biliary cirrhosis, 126 patients with chronic liver disease, 48 patients with SLE, and 25 healthy volunteers. HIV-1 p24 gag seroreactivity was found in 27 (35%) of 77 patients with primary biliary cirrhosis, 14 (29%) of 48 patients with SLE, 14 (50%) of 28 patients with chronic viral hepatitis, and 9 (39%) of 23 patients with either primary sclerosing cholangitis or biliary atresia, compared with only one (4%) of 24 patients with alcohol-related liver disease or α1-antitrypsin-deficiency liver disease, and only 1 (4%) of 25 healthy volunteers (P=0.003). Western blot reactivity to more than two HIAP proteins was found in 37 (51%) of patients with primary biliary cirrhosis, in 28 (58%) of patients with SLE, in 15 (20%) of patients with chronic viral hepatitis, and in 4 (17%) of those with other biliary diseases. None of the 23 patients with either alcohol-related liver disease or α1-antitrypsin-deficiency, and only one of the healthy controls showed the same reactivity to HIAP proteins (P<0.0001). The results showed a strong association between HIAP seroreactivity and the detection of autoantibodies to double-stranded DNA. HIAP seroreactivity was also strongly associated with the detection of mitochondrial, nuclear, and extractable nuclear antigens. The HIV-1 and HIAP antibody reactivity found in patients with primary biliary cirrhosis and other biliary disorders may be attributable either to an autoimmune response to antigenically related cellular proteins or to an immune response to uncharacterized viral proteins that share antigenic determinants with these retroviruses.

2.8. Other autoimmune diseases

Other reported diseases include Raynaud’s phenomenon and Behcet’s disease. The prevalence of these disorders is not known [32,33].

3. Autoantibodies in HIV infection

The array of autoantibodies reported in HIV/AIDS patients is found in Table 2. In a prospective study of 100 sequentially selected HIV-infected patients, the frequency and specificity of autoantibodies in HIV-infected subjects and their association with rheumatic manifestations, immunodeficiency, total CD4⁺ cell count and prognosis was evaluated. Patients were followed for 2 years. HIV-infected patients presented high overall frequency of autoantibodies. No difference was observed between immunodeficient and asymptomatic HIV-infected patients. The most frequent specificities were antibodies to cardiolipin and to
Table 2
Autoantibodies in HIV

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Disease</th>
<th>Frequency</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-α myosin</td>
<td>Left ventricular dysfunction</td>
<td>43%</td>
<td>[35]</td>
</tr>
<tr>
<td>Anti-EPO</td>
<td>Anemia</td>
<td>23.5%</td>
<td>[36]</td>
</tr>
<tr>
<td>Anti-TPO</td>
<td>Grave’s disease</td>
<td>5 patients</td>
<td>[30]</td>
</tr>
<tr>
<td>Anti-TSHR</td>
<td>Grave’s disease</td>
<td>5 patients</td>
<td>[30]</td>
</tr>
<tr>
<td>Anti-cardiolipin</td>
<td>APS</td>
<td>1 patient</td>
<td>[17]</td>
</tr>
<tr>
<td>Anti-PS</td>
<td>APS</td>
<td>56%</td>
<td>[19]</td>
</tr>
<tr>
<td>Anti-PI</td>
<td>APS</td>
<td>34%</td>
<td>[19]</td>
</tr>
<tr>
<td>Anti-PC</td>
<td>APS</td>
<td>43%</td>
<td>[19]</td>
</tr>
<tr>
<td>Anti-β2 GPI</td>
<td>APS</td>
<td>5–27%</td>
<td>[19,22]</td>
</tr>
<tr>
<td>Anti-prothrombin</td>
<td></td>
<td></td>
<td>[22]</td>
</tr>
<tr>
<td>Anti-DNA</td>
<td></td>
<td></td>
<td>[34]</td>
</tr>
<tr>
<td>ANTI-snRNP</td>
<td></td>
<td>68.1%</td>
<td>[15]</td>
</tr>
</tbody>
</table>

APS, antiphospholipid syndrome; EPO, erythropoietin; NG, not given.

denatured DNA. Immunoglobulin serum levels did not correlate with the occurrence of autoantibodies. Rheumatic manifestations were observed in 35/100 HIV-infected patients and were not associated with the occurrence of autoantibodies or the presence of immunodeficiency. The presence of autoantibodies was significantly associated with lower CD4 lymphocyte counts and increased mortality, which implies prognostic significance to this phenomenon in the context of HIV infection [34].

3.1. Cardiac autoimmunity/anti-myosin autoantibodies

Currie et al. [35] investigated the frequency of circulating specific autoantibodies in 74 HIV positive patients with and without echocardiographic evidence of left ventricular failure. Abnormal anti-α myosin autoantibody concentrations were found more often in HIV patients with heart disease (43%) than in HIV positive patients without heart disease (19%) or in HIV negative controls (3%). The data support a role for cardiac autoimmunity in the pathogenesis of HIV related heart muscle disease.

3.2. Anemia/anti-erythropoietin antibodies/autoimmune hemolytic anemia

In a cohort of 204 unselected consecutive HIV-1 infected patients, the association of circulating autoantibodies to endogenous erythropoietin (EPO) with HIV-1 related anemia was studied. Circulating autoantibodies to EPO were present in 48/204 (23.5%) of the patients. The circulating autoantibodies were an independent predictor of anemia. Autoimmunity may contribute to the pathogenesis of HIV-1 related anemia [36].

In addition, autoimmune hemolytic anemia (HIV-AIHA) was described in 4 men diagnosed with HIV infection (AIDS). All patients presented with the acute onset of severe hemolytic anemia, fever, and splenomegaly. The direct and indirect antiglobulin tests were positive in all, and 3 patients had mixed warm and cold autoantibody hemolytic anemia. Two patients responded to prednisone therapy and remained in remission from AIHA for 15 and 30 months, respectively [37].

3.3. Mechanisms

The possible mechanisms for autoimmune manifestations of HIV infection include the direct effect of HIV on endothelial, synovial, and other hematopoietic cells resulting in destruction of CD4 cells, increased cytotoxic cell activity, and increased expression of autoantigens. Molecular mimicry is one of the proposed mechanisms in the development of autoimmune disease. The exogenous infectious agent may have molecular similarity to a self-antigen and may therefore induce an autoimmune response. The basis for this mechanism has been substantiated in several studies. Deas et al. [38] previously demonstrated that about one-third of patients with either Sjogren’s
syndrome (SS) or SLE react to HIV p24 core protein antigen without any evidence of exposure to, or infection with, HIV itself. They further characterized the specificity of this reaction using enzyme-linked immunosorbent assay to peptides representing fragments of p24. Characteristic epitope-specific profiles were seen for SS and SLE patients. SS patients had significantly increased responses to peptides F (p24 amino acids 69–86) and H (amino acids 101–111) and diminished reactivity to peptides A (amino acids 1–16) and P (amino acids 214–228). SLE patients had increased reactivity to peptides E (amino acids 61–76), H, and P. Utilization of peptide P hyporeactivity as the criterion to select for SS patients results in a screen that is moderately sensitive (64%) and specific (79.3%). Adding hyperreactivity to one other peptide (F or H) as an additional criterion yields an expected decrease in sensitivity (to 41%) while increasing specificity (to 93.1%). All sera-reactive peptides from regions of known structure of HIV p24 were located in the apex of the p24 molecule. Thus, the specificity of the peptide reactivities described indicates a specific pattern of a nonrandom cross-reactivity between HIV type 1 p24 and autoimmune sera, which may be partially syndrome specific.

Autoimmunity during HIV-1 infection may contribute to the immunopathogenesis of AIDS. Titers of autoantibodies to HLA molecules and other surface markers of CD4+ T cells appear to increase with the progression of disease and may correlate with lymphopenia. Other autoantibodies are directed at a number of regulatory molecules of the immune system. Genesis of autoreactivity may be related to structural homologies of HIV-1 env-products, to such functional molecules involved in the control of self-tolerance. The most impressive similarities include the HLA-DR4 and -DR2, the variable regions of TCR α-, β- and γ-chain, the Fas protein, and several functional domains of IgG and IgA. Thus, HIV-1 infection may induce dysregulation leading to autoimmune response, through a number of molecular mimicry mechanisms. Pathogenicity of antibodies to T cells could also include the activation of membrane-to-nucleus signal transducers resulting in increased apoptosis. The evolution of autoimmune mechanisms during HIV-1 infection cannot exclude, however, progression to immunoproliferative malignancy, since
aspects of oligoclonal immune response to HIV-1 components may occur in several autoimmune diseases, which in some instances evolve to lymphoma [39].

In summary, autoimmune diseases and autoantibodies are present in HIV infection. Autoimmune diseases may develop during acute viral infection (Stage I), with normal to low CD4 counts (Stage II). However, past a threshold where the CD4 count is profoundly low, autoimmune disease cannot develop (Stage III). Following HAART, immune restoration (normal CD4 count) with possible altered immune regulation may lead to the emergence of autoimmune diseases (Stage IV) (Fig. 1). More studies are necessary to identify the subgroups of HIV-infected patients that may be prone to develop autoimmune diseases and autoantibodies.

**Take-home messages**

- Autoimmune diseases may occur in patients with HIV infection.
- We propose a staging of HIV/AIDS by clinical manifestations, and CD4 count to assess the concurrence with autoimmune diseases.
- Autoimmune diseases occur when there is no immunosuppression such as during acute infection (Stage I), when the CD4 count > 200 (Stage II), or following highly active antiretroviral therapy (Stage IV). Autoimmune disease is not reported in patients with profound immunosuppression (Stage III).
- Reported autoimmune diseases in the setting of HIV infection include SLE, anti-phospholipid syndrome, autoimmune thrombocytopenia, vasculitis, polymyositis, Graves’ disease, and primary biliary cirrhosis.
- Autoantibodies in HIV infected patients are diverse.
- Molecular mimicry may be a possible mechanism.

**References**


