Human Immunodeficiency Virus Infection: Spectrum of Rheumatic Manifestations

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Introduction

Despite extraordinary advances in diagnostics, therapeutics, and vaccine development, emerging and reemerging viral diseases have occurred during the past several decades [1, 2]. Several factors that contributed to the emergence of recent epidemics have been identified including those related to the microbial agent, the human host, and the human environment. Also among the most important factors are genetic adaptations of the microbial agent, international travel, human susceptibility to infection, population growth, an aging population, climate and weather changes, and expanding vector habitats [2–5]. Three recent examples of disease emergence are the Middle East Respiratory syndrome coronavirus (MERS-CoV), Chikungunya, and the Zika viruses, which represent new viral entities or viruses emergent in new geographic locales and characterized by novel complications [6, 7]. However, the most important newest example of an emergent infectious disease is human immunodeficiency virus (HIV) infection, which emerged a century ago in a primate host(s), and subsequently spread within the human population. HIV-related acquired immune deficiency syndrome (AIDS), the most dreadful complication, was first recognized in 1981 in men who have sex with men, injection drug users, and recipients of blood transfusions [8–10]. Subsequently, in the year 1983, Francois Barré-Sinoussi, Luc Montagnier, and others from the Institute Pasteur in Paris identified the etiologic agent of this disease and called it the human immunodeficiency virus (HIV). Both French virologists were awarded the Nobel Prize in 2008 for this discovery. At present, however, HIV infection has become a global disease affecting heterosexual individuals, especially within the developing world [11].

Table 15.1 Differences between HIV 1 and HIV 2

Species	Virulence	Infectivity	Prevalence	Inferred origin
HIV-1	High	High	Global	Chimpanzee
HIV-2	Low	Low	West Africa	Sooty Mangabey

The virus HIV belongs to the Retroviridae family and genus lentivirus. There are two serotypes: HIV 1 and HIV 2. HIV1 is the etiologic agent of epidemic AIDS. See some differences between both serotypes (Table 15.1).

Structure

HIV has a lipid envelope, in which two glycoproteins (gp), the gp41 and gp120, are inserted. These two viral glycoproteins are responsible for attachment to the host cell. Beneath the envelope, is the matrix p17, the core proteins p24 and p6 and the nucleocapsid protein p7. Within the viral core lie two copies of the viral ribonucleic acid (RNA) genome, together with the protease, integrase, and reverse transcriptase enzymes (Fig. 15.1). All of these structures are codified by different viral genes.

Life Cycle

Once the human immunodeficiency virus enters in the body of a human being, it binds to its specific receptor. The HIV virus attaches to the CD4 receptor which is present on the surface of the CD4+ T cell and then either a CCR5 or CXCR4 co-receptor, to replicate itself and infect other cells. After binding to the CD4+ receptor the virus uses the machinery of the CD4+ T cell, to replicate and spread throughout the body. The process of replication is carried out in several stages: binding, fusion, reverse transcription, integration, replication, assembly, and budding.

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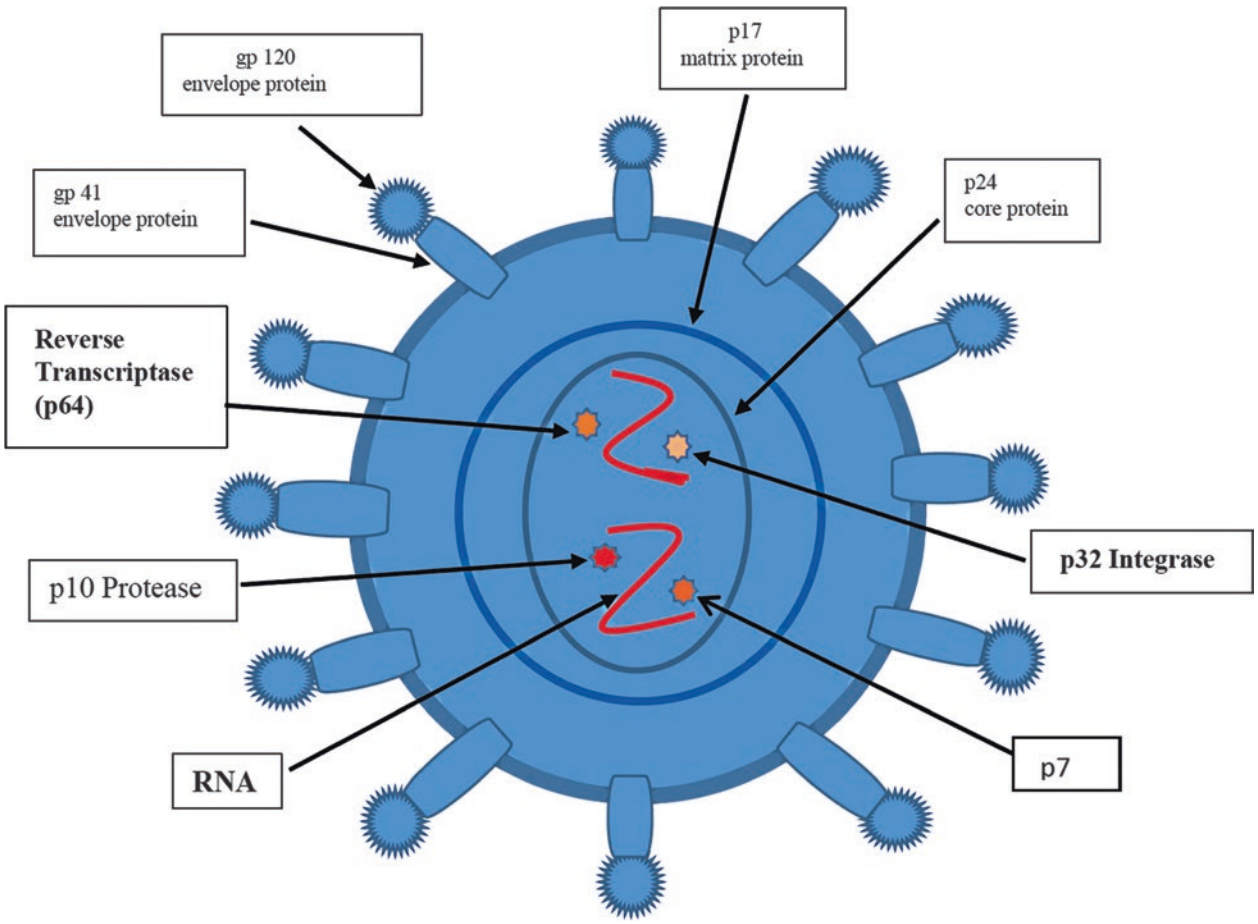


Fig. 15.1 Structure of HIV

Pathogenesis

Pathogenesis of HIV infection is complex, multifactorial, and incompletely understood. HIV infection's main target is the resting memory CD4 + T cell and selective depletion of CD4 + T cells is accompanied by aberrant activation of all the components of the immune system [12]. Immune activation is the major force that drives the HIV process and is associated with viremia and has a negative correlation with the CD4+ T cell count during chronic infection [13]. Cellular and soluble factors play an important role in acute and chronic immune activation and progression to AIDS [12–14] (Table 15.2 and Fig. 15.2).

Autoimmunity and HIV

The combination of immune dysfunction in patients with HIV infection and the development of autoimmune diseases is still incompletely understood. Autoantibodies are found with high prevalence in sera from HIV patients and may be fostered by a polyclonal stimulation of B cells.

Autoantibodies in HIV

- Anti-α-myosin
- Anti-EPO
- Anti-TPO
- Anti TSHR
- Anti-cardiolipin
- Anti-PS
- Anti-PI
- Anti-PC
- Anti-β2GPI
- Anti-prothrombin
- Anti-DNA
- Anti-RNP
- Anti-GBM
- ANCA

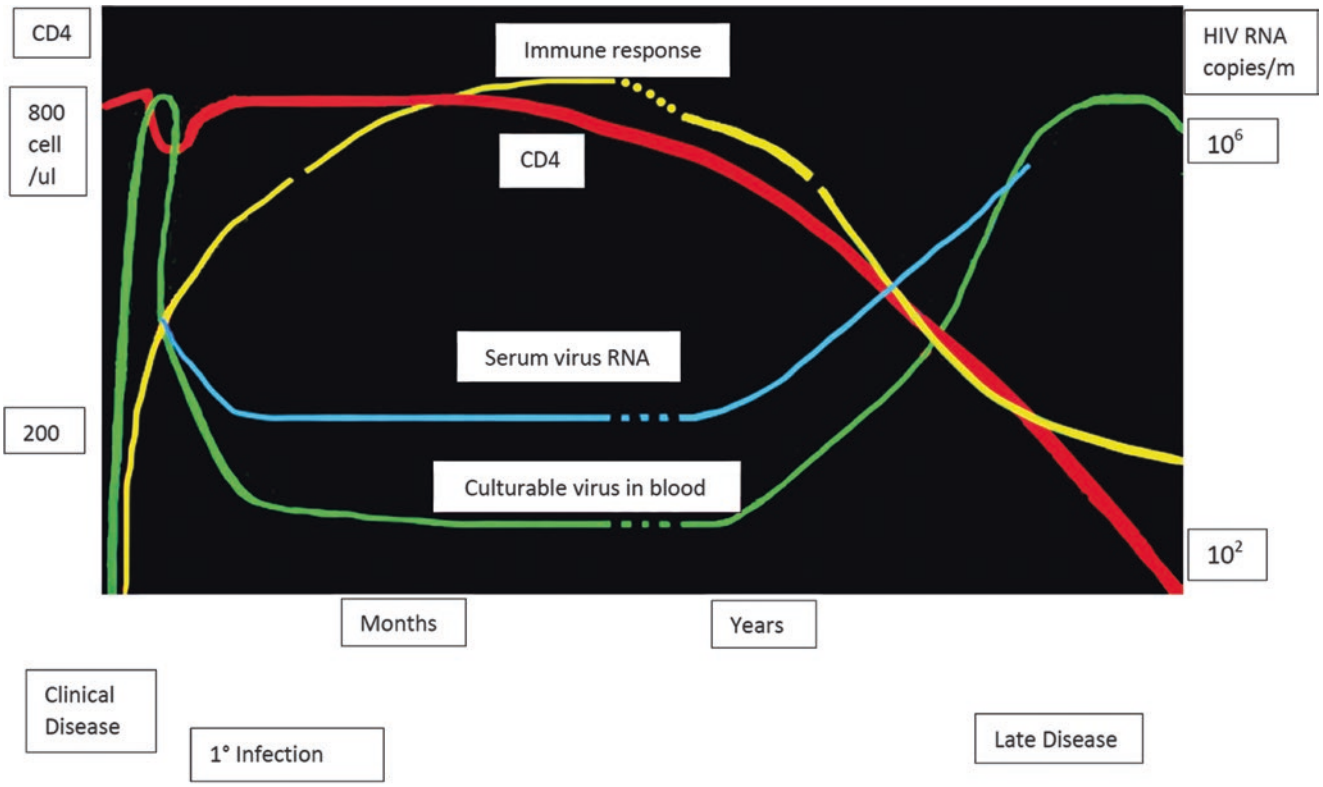
EPO erythropoietin, *TPO* thyroid peroxidase, *TSHR* thyroid stimulating hormone receptor, *PS* phosphatidylserine, *PI* phosphatidylinositol, *PC* phosphatidylcholine, *β2GPI* Beta 2 glicoproteína, *GBM* glomerular basal membrane.

Table 15.2 Cellular and soluble factors in immune activation

Innate	
Cells	Activation of macrophages and dendritic cells
Cytokines, chemokines	TNFα, IL-1, IL-6, IL-8, IL-12, IL-15, CXCL10, INFα
Acute phase proteins	Serum amyloide A, C reactive protein
Coagulation	D-dimers, tissue factor
Fibrosis	Activation of matrix metalloprotease, collagen deposition
Microbial sensors	Lipopolysaccharide binding protein, soluble CD14
Adaptive	
T cells	Increased turnover CD4+ and CD8+, CD4+ decrease, CD8+ increase and then decreases, formation of autoreactive CD8+, depletion Treg cell
B cells	Hyperactivation, hypergammaglobulinemia and immune complexes, autoantibodies

The presence of autoantibodies is associated with lower CD4+ T cell counts and increased mortality, which implies prognostic significance to this phenomenon in the context of HIV infection [15]. HIV immune dysregulation involving T or B cells or both may lead to autoimmune phenomena unique to HIV disease or to more classic autoimmune clinical syndromes.

Several possible mechanisms for autoimmune manifestations of HIV infection have been described, but molecular mimicry appears to be one of the most relevant. HIV virus has molecular similarity to self-antigens and may, therefore, induce antibody cross-reactions and lead to the development of autoimmune disease [16–18]. Whether autoimmunity is a component of natural immunity to HIV, its clinical significance and the role of neutralizing antibodies remain to be defined [16, 18].



Immune activation markers

TNFα	+++	+	+	+	++	+++
IL-6	+++	-/+	-/+	+	++	+++
sIL-2R	+++	-/+	-/+	+	++	+++
CD8-HLA-DR	+++	+	+	+	++	+++
CD8-CD38	+++	+	+	+	++	+++

Fig. 15.2 Natural course and immune activation markers of HIV

Autoimmune Mechanisms HIV

1. Direct effect of HIV: endothelial, synovial, hematopoietic cells
2. Increase cytotoxic cell activity
3. Increased expression of autoantigens
4. Molecular mimicry

Close to 40 years have elapsed since the onset of the HIV/AIDS pandemic and a total of 36.7 million individuals are living with the infection in 2016, including 1.8 million newly infected individuals, 1.0 million deaths, which includes 890,000 adults and 120,000 children under the age of 15 years, and 20.9 million living with HIV on antiretroviral therapy in 2017 [19]. Extraordinary progress in our understanding of pathogenesis, natural course, diagnostics, and combination antiretroviral therapy (cART) has occurred, which has led to a significant improvement in morbidity and mortality [20]. To date, the status of a considerable proportion of HIV/AIDS patients has changed from a near-fatal disorder secondary to opportunistic infections to a chronic disease in which cardiovascular, renal, diabetes, malignancy, and autoimmune co-morbid disorders have become prevalent and relevant [21–23]. The latter makes this topic of great relevance and importance to clinicians including rheumatologists and other practitioners dealing with this condition.

There are only a few longitudinal, descriptive, and comparative studies that allow with certainty define the impact of HIV infection during the pre-cART and post-cART eras, however, we will review and discuss available data on HIV infection and rheumatic manifestations.

Prevalence of Rheumatic Manifestations Before the Advent of cART Therapy

Winchester et al. first reported the association between HIV and rheumatic disease in 1987, when they described a series of patients with AIDS and Reiter's disease. Since that time, several reports have been published [24], and the prevalence of rheumatic manifestations among HIV infected patients ranges from 3% to 71% [25–29].

Arthralgia is the most common complaint, usually intermittent and polyarticular, with a reported prevalence between 1% and 79% [30]. **Myalgia** has also been frequently reported and difficult to separate from myopathy, so that the estimated prevalence rates may be misleading. Results of case-control studies revealed that myalgia is more common in HIV infected than in uninfected controls, with a frequency of 1.7–11% in the pre-cART while it increased between 0% and 77% in the post-cART. There are, however, other studies that showed the opposite; therefore, it is not clear whether therapy improves or exacerbates myalgia [31].

Painful Articular Syndrome

This syndrome is characterized by an acute onset and severe intensity of arthralgia presenting typically in one (usually large) joint in HIV-positive patients. It is of short duration (2–24 hours) and not associated with synovitis. It has an estimated prevalence of 10% among US patients in the late stages of the infection [26, 32] and a similar rate was observed among patients in Argentina [27]. This syndrome has not been reported in other case series from Africa and Asia continents [33–36]. The effect of cART on this syndrome is currently not well-defined.

HIV Arthritis

This syndrome is characterized by an acute onset of arthritis of large joints, non-erosive, lasting less than 6 weeks, absence of HLA B27 positivity and radiological changes, distinct from any other known rheumatic disease, with no known infective triggers, or other classical features. The prevalence rate ranges from 0.4% to 13.8% and most of these studies were performed in the USA. Most reports demonstrate that most cases occur in men, most commonly in the CDC stage IV of HIV infection [26, 27, 33, 37–42]. There is a cohort study from Africa where the reported prevalence was 82% [43]. Other African studies have not reported such high prevalence rates [44, 45].

Spondyloarthritis

Reactive Arthritis (ReA)

Most cases of ReA are associated with the late stages of immunosuppression seen in HIV-infected patients. The estimated prevalence of ReA in the pre-cART was as low as 0.02% to a high of 11%, variability depending on the sample studied. In the USA, two cohort studies performed through questionnaires, San Francisco Men's Health Study and the Johns Hopkins Multicenter AIDS Cohort Study, did not find an increase in ReA. However, most patients studied were in the early phase of HIV-infection [30, 31, 46].

In Latin American countries such as Mexico and Argentina, the frequency of ReA was found increased, while in Spain it was low. Mode of transmission appeared to explain the difference, with sexually-transmitted in Mexico and Argentina, and intravenous drug use in Spain [27, 38, 39, 47]. The low frequency of ReA has been reported in other cohorts in whom the mode of transmission was IV drug use [48].

Of great interest is the situation in Africa in which prior to the HIV pandemic ReA was rarely seen, which might be explained on the basis of the rarity of HLA-B27 [49, 50]. Following the advent of HIV, however, ReA became a com-

mon occurrence among HIV infected individuals with the majority being HLA-B27 negative [44]. Epidemiological studies in Zambia revealed that the presence of the allele HLA-B*57:03 confers a protective effect against the rapid progression of HIV [51].

Studies from Asian countries point out that ReA in HIV patients rarely occurs [36]. In this regard, mode of transmission of HIV appears to be similar in Asia and Africa, heterosexual, with a high prevalence of arthritogenic pathogens, which might suggest that other factors including genetics might play a role.

It can be concluded that ReA was relatively common in the western world pre-cART and its prevalence greatly diminished in the post-cART.

Psoriatic Arthritis (PsA)

A similar situation as in ReA occurs with PsA in which several studies on the pre-cART era revealed an increase in afflicted HIV infected patients. Rates of prevalence for PsA in HIV patients pre-cART was higher than in the general population, 0.4–5.7% vs. 0.25%, respectively [40, 52] and rates of incidence similar in both populations, 0.07%/annum vs. 0.05% [30, 46]. The populations studied, however, were in different stages of HIV infection. It should also be noted that patients with HIV and psoriasis had more severe and persistent lesions, and when compared with patients with classic psoriasis in HIV several morphological types can coexist in the same patient and that PsA was severe, deforming, erosive, and refractory to conventional therapy [53, 54].

The incidence and prevalence of both psoriasis and PsA in Africa are low even though black Africans have one of the risk alleles for psoriasis, HLA-CW6. This, however, drastically changed following the advent of HIV in which both disorders were increasingly recognized in African populations [55, 56]. Asian populations have a low prevalence rate of psoriasis and PsA, but this also changed following the HIV pandemic. Post-cART, both disorders have greatly diminished in Africa and Asia.

Ankylosing Spondylitis (AS)

AS, the prototype of the spondyloarthritides, is more common in the western world [57] and much less common among sub-Saharan Africans where the frequency of HLA-B27 is very low (<1%). The frequency, however, of HLA-B27 in West Africa is higher 7.8–9.7% [58, 59], but despite this higher prevalence AS is rarely seen in this region. This, however, changed following the onset of HIV in which several reports describing the association were reported from African populations.

In general, there have been few reports of AS in HIV infected patients and reported data might suggest that AS is uncommon in HIV. But it is probable that most patients with HIV or AIDS are classified as having undifferentiated spondyloarthritis in the absence of radiographic or HLA-B27 testing or the paucity of long-term follow-up studies.

Rheumatoid Arthritis (RA)

The immune dysregulation inherent to HIV infection and its clinical manifestations may mimic or interfere with a diagnosis of rheumatoid arthritis. HIV patients may exhibit symmetrical polyarthritis, which tends to be seronegative for the most part. However, erosive forms and seropositive for rheumatoid factor (RF) have also been described [60]. On the other hand, the presence of low titer RF and CCP antibodies in patients with HIV may lead to an erroneous diagnosis of RA. HIV patients may also exhibit a high proportion of RF and CCP antibodies, which decrease after initiation of cART suggesting that HIV is capable of inducing autoantibodies. Follow-up studies, however, of this HIV population does not reveal the development of RA [61–64]. In addition, it is well recognized the presence of false-positive HIV serology in patients with RA suggesting a cross-reactivity between HIV diagnostic tests in patients with RA [65]. Another important issue was the impact of de novo HIV infection in established RA [66, 67]. An early observation in the pandemic was that most RA patients might go into remission after the development of AIDS. However, the presence of active RA disease including radiological progression can be seen despite a profound state of immunosuppression [68, 69]. Also, development of de novo RF and CCP antibodies positive RA can be seen in well control HIV infection (normal CD4 cell count and negative HIV viral load), and RA disease activity behaves in identical fashion as in RA seen in HIV negative individuals.

Therapy for HIV patients affected with RA as well as for most connective tissue disorders is not well defined, but most can be safely treated in identical manner as in the non-HIV afflicted population. Caution, however, and prophylaxis for opportunistic infections, should be exerted when immunosuppressive or biologic therapy is used.

Systemic Lupus Erythematosus (SLE)

SLE has been rarely reported in association with HIV infection, but it represents a diagnostic and therapeutic challenge, especially when they co-exist in the same patient. HIV impacts on SLE in diagnosis and assessment of disease activity. HIV infection and SLE shares several clinical features and laboratory findings, which can make the diagnosis extremely difficult. A variety of constitutional manifestations such as fever, arthralgia, arthritis, myalgia, skin rash, lymph node enlargement, cytopenias, pulmonary, cardiovascular, renal, and CNS involvement can be observed in both active

SLE and HIV infection. A variety of autoantibodies including ANA, anti-dsDNA, anti-Sm, and anti-cardiolipin antibodies can be seen in both disorders. But hypocomplementemia secondary to HIV has not been described, and this finding may be used to distinguish lupus activity from HIV infection [70, 71]. Diagnostic tests for HIV have been reported as false-positive results in SLE patients and multiple studies have reported autoantibodies reactivity to HIV p18 and p24 antigens. These findings make necessary the need to perform confirmatory tests, such as viral RNA PCR or HIV-Western Blot assays [72].

HIV infection, as described in RA, may have an important effect on the natural course of SLE. The decrease in CD4 lymphocytes might ameliorate SLE disease activity and induce remission. However, SLE disease activity may persist during HIV infection and not related to the use of cART [73–75].

Lupus may also impact on HIV infection. Homology between self-antigens in lupus patients and viral proteins has been identified. Antibody production including neutralizing antibodies might develop during SLE may confer protection against HIV infection by molecular mimicry mechanisms [76]. In addition, antimalarial drugs such as chloroquine and its derivatives, which are used in SLE therapy, may have anti-HIV activity. A potential role for interleukin-16 in the observed low incidence of HIV infection in patients with SLE has been described [77].

Treatment of SLE with glucocorticoids and immunosuppressive drugs is challenging because they may trigger viral replication and rapid progression of the disease. On the other hand, the use of cyclophosphamide in lupus flares may also result in an increase in the viral load. Viral load becomes undetectable when cyclophosphamide is discontinued. Therefore, treatment of active lupus should be individualized and should be aimed at reaching a balance between HIV infection and lupus activity.

The association of HIV-related discoid lupus and HIV has rarely been reported and the few cases described have occurred after the onset of cART and in association with undetectable HIV viral load and normal CD4 T-cell count [78].

Anti-Phospholipid Antibody Syndrome (APS)

Presence of anti-phospholipid antibodies including anti-cardiolipin and lupus anticoagulant antibodies is seen in most HIV patients, 60–70%. However, the development of clinical manifestations characteristic of APS is uncommon, and only a handful of cases have been reported in the literature. Other anti-phospholipid antibodies such as anti-B2 Glycoprotein I appear to have a lower frequency [31, 79].

Systemic Sclerosis (SSc)

The association between HIV infection and SSc is rare. There are only a few reported cases. Two male patients developed localized scleroderma after several years of cART. Two other patients developed symptoms of diffuse systemic sclerosis. One of the two cases in the background of immunosuppression and responded well to therapy with steroids and cART. The other patient developed symptoms of SSc 7 years after HIV infection and cART and with good virologic suppression and normal CD4 cell count [80–82].

Polymyositis and Dermatomyositis

These diseases have rarely been reported. The prevalence of polymyositis is reported as 0.22% and dermatomyositis occurs less frequently, and when present can occur at any stage of HIV infection. HIV-associated polymyositis usually has mild disease activity, which is often difficult to recognize, especially in a population that frequently manifests generalized weakness and a debilitating course. Both polymyositis and dermatomyositis carry a relatively good prognosis, responds well to glucocorticoids and immunosuppressive therapy [83, 84].

Diffuse Infiltrative Lymphocytosis Syndrome (DILS)

DILS was initially identified in 1985 as lymph node hyperplasia and parotid gland enlargement in HIV-positive patients. Later, in 1989, this complex was named “diffuse infiltrative lymphocytosis syndrome”. Early criteria proposed by Itescu et al. for the diagnosis of DILS required salivary gland enlargement or xerostomia for >6 months and lymphocytic infiltration of the affected gland confirmed by biopsy [85].

Diagnostic Criteria for DILS (Itescu et al. [85])
Requires All Criteria

1. HIV infection (positive serology)
2. Bilateral salivary gland enlargement or xerostomia
3. Persistence of signs/symptoms for 6 months or more
4. Histologic confirmation of salivary or lacrimal gland lymphocytic infiltration without granulomatosis or neoplastic involvement

Table 15.3 Features of DILS

Feature	
Lymphocytic infiltration	CD8+ T cells
Sicca symptoms	Present
Glandular manifestations	Moderate to severe parotid enlargement
Extra-glandular manifestations	Present
Autoantibodies	Rarely present, exceptional low frequency of RF, ANA, anti-Ro
HLA association	DR5(DR11), DR6(DR13), B45, B49, B50

HIV-related DILS is characterized by salivary and lacrimal glandular swelling and sicca symptoms of varying intensity. Prevalence of this complication is highest among African Americans (up to 48% of infected individuals) and is associated with HLA class II alleles (DRB1) that are not seen in other racial groups with DILS, and it occurs in patients whose disease is at less advanced stages [86, 87]. The syndrome usually presents as a Sjögren-like illness that generally associates with sicca signs with bilateral parotid gland swelling, lymphadenopathy, and extra-glandular organ involvement. DILS is also characterized by CD8+ T cell infiltration, lack of autoantibodies (anti-Ro and anti-La), although they may be present in some exceptions, and extra-glandular visceral infiltration. The lung, being the most common extra-glandular organ involved and when affected it presents as a lymphocytic interstitial pneumonitis (LIP)[86, 88]. Its natural history has also changed since the introduction of cART, and it is less frequently seen including the extra-glandular manifestations such as LIP [87, 89].

Chen et al. conducted a nationwide population-based study in the Taiwanese population and showed that the incident rate of DILS was 0.56/1000 person-years higher compared with the general population, and the incidence was higher in patients without cART than in patients with cART, supporting the notion that HIV intervenes in the pathogenesis of DILS and that cART reduces the risk of acquiring DILS [90, 91]. Other clinical and laboratory features of DILS are shown in Table 15.3.

DILS patients with mild symptoms may not require specific treatment, but glucocorticoids or immunosuppressive drugs should be considered for patients with progressive glandular involvement.

Vasculitis

The entire clinical spectrum and size of involved blood vessels can be seen in HIV-associated vasculitides. The incidence of vasculitis in HIV infection is relatively low at 1%. Its presence, however, varies according to ethnic origin and it appears to have a higher prevalence in Orientals. Vasculitis has been reported in patients infected with HIV more commonly in those with a profound stage of immunosuppression (CD4+ < 200/μl), in some associated with hepatitis B infection, but has also been reported in early HIV stages (>500 μl) [92, 93].

Table 15.4 Features of HIV-PAN

Feature	
Virus-associated	No associated HBV
Involvement	Rare multisystem
Common symptoms	Peripheral neuropathy, rash
Clinical course	Usually not progressive or fulminant, nonlife-threatening

As it has been described with other rheumatic manifestations, factors such as ethnic origin and route of transmission might be implicated in its prevalence. Zhang et al. have reported a high prevalence of vasculitis when compared to other rheumatic syndromes. They reported 20 cases of vasculitis in a cohort of 98 Chinese patients and the main route of transmission in their population was blood transfusion. A variety of syndromes were reported including Behçet-like disease, Henoch-Schonlein purpura, digital gangrene, and central nervous system vasculitis [36].

Polyarteritis nodosa (PAN) is the most prevalent form of vasculitis coexistent with HIV infection, and it is not related to hepatitis B infection like the classic form, and can occur at any stage of HIV disease. The clinical course of HIV-related PAN exhibits major differences in comparison with classic HBV-related and it is clinically less aggressive, and peripheral neuropathy is the most common clinical manifestation [94, 95] (Table 15.4).

Presence of anti-neutrophil cytoplasmic antibodies, especially pANCA, is high (13–42%), but its clinical significance is not well defined. cART plays a beneficial role in its treatment due to a direct role of HIV in the pathogenesis of PAN. On the other hand, the impact of other viruses including hepatitis B, hepatitis C, cytomegalovirus (CMV), Epstein-Barr (EBV), and varicella-zoster virus (VZV), which often coexist in HIV positive individuals is not fully characterized [23, 94, 96].

Glucocorticoids have been successfully used in many cases of HIV-associated vasculitis and immunosuppressive drugs should be reserved for resistant patients.

Other forms of vasculitis such as Henoch-Schonlein purpura might occur secondary to various infectious triggers. ANCA-associated vasculitis is extremely rare in HIV infected patients [23].

Cryoglobulinemia may coexist with HIV infection. Its presence is usually asymptomatic and responds well to cART regimen [86]. In the cART era, HIV-infected patients have been shown to have decreased levels of serum cryoglobulins [95, 97, 98].

Septic Arthritis

Osteoarticular infection due to pyogenic bacterial does not occur more frequently in patients with HIV infection as compared with the general population. The incidence of musculoskeletal infections in patients with HIV appears to be low (0.3–3.5%). Case series reported from the USA, Europe (Italy), and Africa have shown that septic arthritis occurs less frequently in HIV patients [99–101]. There are retrospective HIV cohort studies that show a relatively low risk of septic arthritis [102, 103]. Marquez et al. studied prospectively 75 patients with HIV infection referred to a rheumatology clinic in New Orleans and reported prevalence of septic arthritis and osteomyelitis in 8% and 20%, respectively. Atypical mycobacterial (mycobacterium haemophilum and Kansasii) and fungal (candida and sporotrichosis schenckii) infections rarely occur except in advanced HIV infection (CD4 count less than 100/mL).

Rheumatic Disorders in the Combination Antiretroviral Therapy (cART): Future Trends

Introduction of cART in the management of patients infected with HIV marks a milestone in the history of medicine because it led to a significant change of the natural history, long-term outcome, occurrence of comorbidities, and as importantly a drastic reduction in mortality.

A significant decline in inflammatory rheumatic complications has been observed following the introduction of cART [90, 99]. And of great interest and importance, a new group of rheumatic disorders has emerged covering the spectrum of systemic autoimmune and autoinflammatory diseases, posing new clinical challenges [90, 99] (Table 15.5). Currently, three diseases deserve special attention: avascular necrosis, osteoporosis, and immune reconstitution inflammatory syndrome.

Table 15.5 HIV and autoimmune/non-autoimmune diseases

Pre-cART	Post-cART
Connective tissue diseases	Avascular necrosis
DILS	Osteopenia/osteoporosis
Myositis	IRIS
Vasculitis	Sarcoidosis
	Graves' disease
Arthritis	Autoimmune hemolytic anemia
Reactive arthritis/psoriasis	Autoimmune thrombocytopenia
HIV related	Uveítis
	Inflammatory bowel disease
	Psoriasis

Changes in the Prevalence of Inflammatory Rheumatic Diseases

Prior to the introduction of cART, reactive arthritis, psoriatic arthritis, and the painful articular syndrome were the most common rheumatic disorders observed in HIV-infected patients. However, after the introduction of cART, the incidence of these diseases decreased dramatically and new forms of rheumatic diseases appeared [99].

Calabrese et al. conducted a longitudinal cohort study and demonstrated post-cART a decline in ReA, PsA, and myositis [104]. Marquez et al. reported a rise in septic disorders and malignancies and a decline in spondyloarthritis [41]. DILS was also affected by cART. Basu et al. reported a decline in the incidence of DILS [86], but Mastroianni et al. reported opposite results [105]. As previously mentioned, Chen et al. reported that cART reduced the risk of acquiring DILS [91].

In contrast, Parperis et al. did not observe a higher risk of rheumatic diseases except avascular necrosis (AVN) and psoriasis [106]. Similar findings were reported by Yang et al. who showed that the prevalence of autoimmune arthritis among HIV infected patients was similar to that of the general population [107].

A recent study performed in the UK assessed 364 HIV-positive patients with musculoskeletal symptoms between January 2005 and December 2012. Majority of patients (85%) referred had no evidence of an inflammatory rheumatic disease but instead were diagnosed with regional musculoskeletal pain, specific soft tissue disorders, chronic widespread pain or osteoarthritis. Among the remaining 15%, most inflammatory diagnoses were not made more often than would be expected for the general population, except for spondyloarthritis [108].

There are few studies dealing with the incidence, prevalence, and chronology between rheumatic disorders associated with HIV infection and AIDS. Two large studies, one from Taiwan and the second from France, merit discussion [90, 109]. In the first study, Yen et al. reported on the incidence of AIDS in a nationwide HIV/AIDS patient (PLWHA) cohort in Taiwan and compared it with the general population; standardized incidence rates (SIRs) were higher for incident Sjögren's syndrome, psoriasis, SLE, autoimmune hemolytic anemia (AHA), and uveitis. An interesting observation was the lower risk for development of AS despite a high prevalence of HLA-B27 in Taiwanese people (5%). In contrast, PLWHA who received cART had higher SIRs for psoriasis, AHA, and uveitis, while those that did not receive cART had higher SIRs for Sjögren's syndrome, psoriasis, RA, SLE, and other autoimmune disorders. Lebrun et al. also conducted an epidemiologic study in a French nation-wide HIV cohort to estimate the prevalence of 26 inflammatory and autoimmune diseases

(IADs) among patients living with HIV (PLHIV) in the cART era (from January 2000 to July 2013), and to describe their occurrence according to cART onset, the immune-virological status and hepatitis C virus (HCV) and/or hepatitis B virus coinfection. Results showed that several IADs including psoriasis, sarcoidosis, RA, AS, Grave's disease, AHA, immune thrombocytopenia, and chronic inflammatory bowel disease were the most prevalent diseases. Majority of patients (59%) developed IAD after HIV infection with a mean delay of 10.6 + −6.4 years. In addition, patients developing IAD after the diagnosis of HIV infection, 572 (70%) were on cART and 419 of them (73%) had undetectable HIV viral load. Comparing data from Taiwan and French studies, some geographical variability in terms of IADs is observed, but both studies confirmed previous reports in the literature concerning the relationship between HIV/AIDS and rheumatic disorders.

Immune Reconstitution Inflammatory Syndrome (IRIS)

A resurgence of autoimmune disorders may occur following the introduction of cART due to the restoration of immune competence. This phenomenon known as IRIS is linked to a rapidly recovering immune system, and it appears directly related to an increase in CD4+ T cells, CD8+ T cells, CD4+:CD8+ T cell ratio, and an increased cytokine levels [110] (Fig. 15.3). IRIS may develop in the following manners:

A. "Paradoxical IRIS"
   In this subset, affected individuals develop symptoms and signs associated with a known opportunistic infection (OI) for which treatment is underway and exacerbate despite an earlier clinical response to therapy prior to ART.
B. "Unmasking IRIS"
   Patients on this subset experience a new OI with a marked inflammatory component following initiation of ART. Recent reports, however, have defined all-new OI in the first 6 months of ART as cases of unmasking IRIS.

Several classification criteria for IRIS have been proposed, but none has been validated. The reported incidence of IRIS varies widely from 6.4% to 37.7% depending on the offending microorganism involved [111, 112].

IRIS is not only associated with a new infection or exacerbation of quiescent infections but also may occur as either new appearance or an exacerbation of a previously quiescent or occult autoimmune syndrome [41, 104]. Calabrese

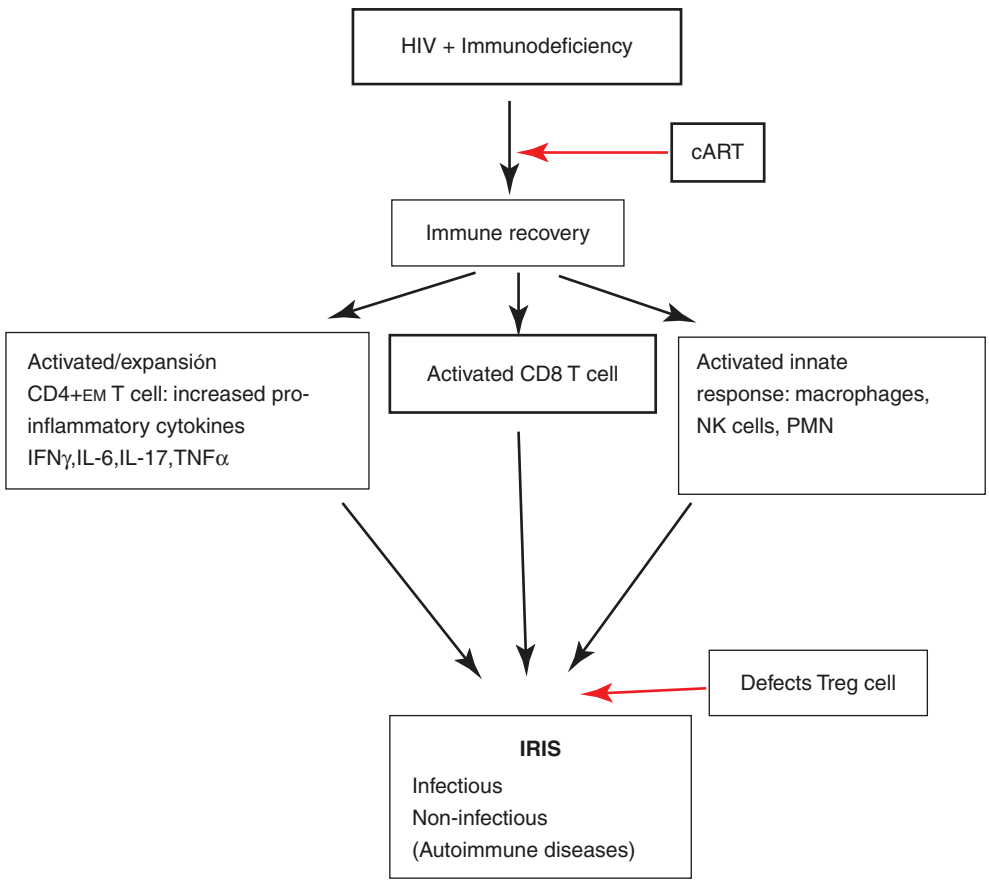


Fig. 15.3 Pathogenesis IRIS

et al. conducted a prospective, longitudinal cohort study and described 32 cases associated with IRIS including sarcoidosis, RA, and SLE [104].

IRIS symptomatology may ensue days to months after ART begins, and most cases resolve spontaneously, but at times they can become life-threatening in severity, necessitating other therapeutic interventions. It is, however, usually not necessary to discontinue cART during this time. IRIS is generally self-limiting and should not require lifelong therapy [41, 104, 111, 112].

Osteoporosis

As the life span in HIV-infected individuals increases, new comorbid conditions develop, including osteopenia and osteoporosis, with an increase in the risk of bone fractures. It is estimated that 2 out of 3 HIV infected individuals have osteopenia, and they also have 3.7 times more risk of developing osteoporosis than non-HIV infected individuals [113]. The estimated prevalence of osteoporosis in the HIV population is 15% and of osteopenia 52% [114]. This decrease in bone density is between 2% and 6% during the first 2 years of cART [115, 116]. The rate of fracture in the HIV population is between 30% and 70% compared with control non-HIV population [117–120].

In addition to the classic osteoporosis risk factors, other HIV-specific risk factors such as the same defined AIDS history, low CD4+ cell count, coinfection with hepatitis C, and antiretroviral therapy may all contribute to the increased risk in osteoporosis [118, 119].

There is no specific guide for the management of HIV patients with decreased bone density, and HIV patients are not included in the list of patients at risk in the osteoporosis management guidelines [121]. However, there are two instruments, BMD or the application of FRAX, that can be used for the assessment of HIV patients with this problem, especially when treatment is considered in the presence of osteopenia. It should be kept in mind, however, that the FRAX has not been validated for the HIV-positive population [122].

Regarding therapy, in addition to adequate nutrition including calcium and vitamin D and modification of lifestyles, pharmacological therapy with bisphosphonates, alendronate, and zoledronic acid, have been shown to have a positive effect on BMD and tolerability similar to those found in the general population [123–126]. Other therapies have not been evaluated.

Avascular Bone Necrosis (AVN)

Osteonecrosis (AVN) is another complication associated with HIV infection, and when it affects hips or any other major joint might lead to severe disability. Its incidence has been estimated to be 10 times compared to the general population [127, 128]. Prevalence also increases by almost 5% and is similar to the prevalence reported in patients at high risk for osteonecrosis in the context of a variety of underlying diseases [129].

Etiology of this complication is poorly understood, and little is known about potential risk factors in HIV patients. Use of glucocorticoids and hyperlipidemia contribute to osteonecrosis seen in HIV patients, but further studies are needed to fully characterize other potential risk factors for this complication [130, 131].

Approach to Therapy of Rheumatic Disorders in HIV-Infected Patients

The introduction of cART has had a profound effect on morbidity and survival in HIV-infected patients and the converse is also correct, HIV infection has also impacted a great deal on the natural history and therapeutic intervention of autoimmune diseases due to the presence of the underlying immunosuppression state and that complications can occur when immunosuppressive drugs or biologic agents are administered because they may lead to serious complications including infections [132].

Treatment of autoimmune diseases (AIDs) is similar in HIV-positive and HIV-negative patients. A significant proportion of HIV-associated AIDs including inflammatory musculoskeletal involvement respond well to conventional therapy such as NSAIDs, narcotic drugs and DMARDs, but refractory cases may need the use of biological agents, especially TNF inhibitors [133]. The use of these agents may represent a challenge, especially in patients with co-existent hepatitis infection, but published reports indicate that in the presence of stable CD4+ T cell counts and low viral loads their use can be both safe and efficacious. When considering immune suppressive therapy, it is important to keep in mind that CD4+ T cells are necessary in the control of intracellular and extracellular bacteria, parasites, and viruses, and the presence of TNF is needed and useful for controlling infection, and its increase favors replication of viral particles.

Rates of serious infections in HIV-infected patients treated with TNF-α inhibitors for concomitant AIDs are comparable to those observed in RA patients receiving TNF-α inhibitors [134].

At present, biologic agents and other DMARDs (including methotrexate, leflunomide, mycophenolate mofetil, azathioprine, cyclophosphamide, and cyclosporine) are recommended when patients have CD4+ T cell counts above 200 cells/mm3 and HIV viral activity completely suppressed [108, 135, 136]. Glucocorticoids, hydroxychloroquine, and sulfasalazine have been shown to be safe and well-tolerated [96]. Currently, however, there are no studies of good quality on the use of biologic therapy to treat inflammatory disorders in HIV-infected individuals; therefore, we cannot conclude on efficacy and safety of biologic therapies in HIV-infected populations [137].

Prophylaxis of Opportunistic Infections While on Immunosuppressive Therapy

HIV patients on immunosuppressive therapy have an increased risk of infection reactivation. Close attention to the association between tuberculosis, varicella zoster, and opportunistic infections such as *Pneumocystis jirovecii* (PJ) should be kept in mind [135, 138]. Patients should be screened for HIV viral load, HBV, HCV, TB, and other infections according to endemic geography [139].

There are no guidelines with regard to the use of synthetic disease-modifying anti-rheumatic drugs (sDMARDs) and biologics in patients with a history of hepatitis B and hepatitis C infections. With regard to PJ, there are no consensus guidelines for the prophylaxis of PCP in connective tissue diseases [140].

Prophylaxis for TB is recommended and it should follow the CDC guidelines. It is recommended to screen for latent TB prior to initiating chronic therapy with glucocorticoids, and chemoprophylaxis with either isoniazid (INH) for 9 months or rifampicin combined with INH for 3 months should be initiated in the presence of latent TB infection (LTBI) [141, 142].

Conclusion

Autoimmune and other inflammatory rheumatic disorders can occur in patients with HIV infection in the presence of poor or good immune-virological control under cART. Some AIDs are more prevalent according to cART and the cohort studied. In general, AIDs appear following diagnosis of HIV infection and also under cART, and clinical manifestations observed in the HIV population are similar to those seen in the general population. Glucocorticoids and other immunosuppressive agents seem to be effective and well-tolerated, but prophylaxis of infection is very important. Comorbidities such as osteoporosis and AVN appear as a consequence of the aging of the HIV-infected population and appropriate preventive measures should be taken. While the pathophysiology of HIV-related autoimmune rheumatic diseases is not well understood, the intricate enigma of this association merits further investigation.

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