most often are HLA-DR5. This syndrome appears to be less common with the increased use of effective cART. The term *diffuse infiltrative lymphocytosis syndrome* (DILS) is used to describe this entity and to distinguish it from Sjögren's syndrome.

Approximately one-third of HIV-infected individuals experience arthralgias; furthermore, 5–10% are diagnosed as having some form of reactive arthritis, such as Reiter's syndrome or psoriatic arthritis as well as undifferentiated spondyloarthropathy (Chap. 384). These syndromes occur with increasing frequency as the competency of the immune system declines. This association may be related to an increase in the number of infections with organisms that may trigger a reactive arthritis with progressive immunodeficiency or to a loss of important regulatory T cells. Reactive arthritides in HIV-infected individuals generally respond well to standard treatment; however, therapy with methotrexate has been associated with an increase in the incidence of opportunistic infections and should be used with caution and only in severe cases.

HIV-infected individuals also experience a variety of joint problems without obvious cause that are referred to generically as *HIV-* or *AIDS-associated arthropathy*. This syndrome is characterized by subacute oligoarticular arthritis developing over a period of 1–6 weeks and lasting 6 weeks to 6 months. It generally involves the large joints, predominantly the knees and ankles, and is nonerosive with only a mild inflammatory response. X-rays are nonrevealing. Nonsteroidal anti-inflammatory drugs are only marginally helpful; however, relief has been noted with the use of intraarticular glucocorticoids. A second form of arthritis also thought to be secondary to HIV infection is called *painful articular syndrome*. This condition, reported as occurring in as many as 10% of AIDS patients, presents as an acute, severe, sharp pain in the affected joint. It affects primarily the knees, elbows, and shoulders; lasts 2–24 h; and may be severe enough to require narcotic analgesics. The cause of this arthropathy is unclear; however, it is thought to result from a direct effect of HIV on the joint. This condition is reminiscent of the fact that other lentiviruses, in particular the caprine arthritis-encephalitis virus, are capable of directly causing arthritis.

A variety of other immunologic or rheumatologic diseases have been reported in HIV-infected individuals, either de novo or in association with opportunistic infections or drugs. Using the criteria of widespread musculoskeletal pain of at least 3 months' duration and the presence of at least 11 of 18 possible tender points by digital palpation, 11% of an HIV-infected cohort containing 55% IDUs were diagnosed as having *fibromyalgia* (Chap. 396). While the incidence of frank arthritis was less in this population than in other studied populations that consisted predominantly of men who have sex with men, these data support the concept that there are musculoskeletal problems that occur as a direct result of HIV infection. In addition there have been reports of leukocytoclastic vasculitis in the setting of zidovudine therapy. CNS angiitis and polymyositis also have been reported in HIV-infected individuals. Septic arthritis is surprisingly rare, especially given the increased incidence of staphylococcal bacteremias seen in this population. When septic arthritis has been reported, it has usually been due to *Staphylococcus aureus*, systemic fungal infection with *C. neoformans, Sporothrix schenckii*, or *H. capsulatum* or to systemic mycobacterial infection with *M. tuberculosis, M. haemophilum, M. avium*, or *M. kansasii*.

Patients with HIV infection treated with cART have been found to have an increased incidence of osteonecrosis or avascular necrosis of the hip and shoulders. In a study of asymptomatic patients, 4.4% were found to have evidence of osteonecrosis on MRI. While precise cause-and-effect relationships have been difficult to establish, this complication has been associated with the use of lipid-lowering agents, systemic glucocorticoids, and testosterone; bodybuilding exercise; alcohol consumption; and the presence of anticardiolipin antibodies. Osteoporosis has been reported in 7% of women with HIV infection, with 41% of women demonstrating some degree of osteopenia. Several studies have documented decreases in bone mineral density of 2–6% in the first 2 years following the initiation of cART. This may be particularly apparent with tenofovir-containing regimens.

**TABLE 226-12 CHARACTERISTICS OF IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)**

- Paradoxical worsening of an existing clinical condition or abrupt appearance of a new clinical finding (unmasking) is seen following the initiation of antiretroviral therapy
- Occurs weeks to months following the initiation of antiretroviral therapy
- Is most common in patients starting therapy with a CD4+ T cell count <50/μL who experience a precipitous drop in viral load
- Is frequently seen in the setting of tuberculosis; particularly when cART is starting soon after initiation of anti-TB therapy
- Can be fatal

### Immune Reconstitution Inflammatory Syndrome (IRIS)

Following the initiation of effective cART, a paradoxical worsening of preexisting, untreated, or partially treated opportunistic infections may be noted. One may also see exacerbations of pre-existing or the development of new autoimmune conditions following the initiation of antiretrovirals (Table 226-12). IRIS related to a known pre-existing infection or neoplasm is referred to as *paradoxical IRIS*, while IRIS associated with a previously undiagnosed condition is referred to as *unmasking IRIS*. The term *immune reconstitution disease (IRD)* is sometimes used to distinguish IRIS manifestations related to opportunistic diseases from IRIS manifestations related to autoimmune diseases. IRD is particularly common in patients with underlying untreated mycobacterial or fungal infections. IRIS is seen in 10–30% of patients, depending on the clinical setting, and is most common in patients starting therapy with CD4+ T cell counts <50 cells/μL who have a precipitous drop in HIV RNA levels following the initiation of cART. Signs and symptoms may appear anywhere from 2 weeks to 2 years after the initiation of cART and can include localized lymphadenitis, prolonged fever, pulmonary infiltrates, hepatitis, increased intracranial pressure, uveitis, sarcoidosis, and Graves' disease. The clinical course can be protracted, and severe cases can be fatal. The underlying mechanism appears to be related to a phenomenon similar to type IV hypersensitivity reactions and reflects the immediate improvements in immune function that occur as levels of HIV RNA drop and the immunosuppressive effects of HIV infection are controlled. In severe cases, the use of immunosuppressive drugs such as glucocorticoids may be required to blunt the inflammatory component of these reactions while specific antimicrobial therapy takes effect.

**Diseases of the Hematopoietic System** Disorders of the hematopoietic system including lymphadenopathy, anemia, leukopenia, and/or thrombocytopenia are common throughout the course of HIV infection and may be the direct result of HIV, manifestations of secondary infections and neoplasms, or side effects of therapy (Table 226-13). Direct histologic examination and culture of lymph node or bone marrow tissue are often diagnostic. A significant percentage of bone marrow aspirates from patients with HIV infection have been reported to contain lymphoid aggregates, the precise significance of which is unknown. Initiation of cART will lead to reversal of most hematologic complications that are the direct result of HIV infection.

**TABLE 226-13 CAUSES OF BONE MARROW SUPPRESSION IN PATIENTS WITH HIV INFECTION**

| HIV infection | Medications |
|---|---|
| Mycobacterial infections | Zidovudine |
| Fungal infections | Dapsone |
| B19 parvovirus infection | Trimethoprim/sulfamethoxazole |
| Lymphoma | Pyrimethamine |
| | 5-Flucytosine |
| | Ganciclovir |
| | Interferon α |
| | Trimetrexate |
| | Foscarnet |