proteins, in addition to the viral proteins, may be important for viral replication. Viral particles are assembled at the cell membrane, each containing two copies of unspliced mRNA within the core as the viral genome, and virions then are released from the cell by budding. Productive viral replication is lytic to infected T cells. A number of other host cells, including macrophages and certain dendritic cells, are also infected by HIV, but viral replication does not appear to be lytic to these cells.

Following acute infection, high-level viral multiplication occurs in mucosal lymphoid tissues of the gut and in other lymphatic sites, and plasma HIV RNA levels (i.e., the plasma viral load [PVL]) often exceed 1 million copies per milliliter during the second to fourth weeks after infection. Almost all instances of acute HIV infection are caused by R5 tropic viruses, viruses that use the chemokine receptor CCR5 for cellular entry. During subsequent weeks, the PVL decreases, often rapidly. This decrease in viremia results largely from a partially effective immune response. After 6 to 12 months, the PVL typically stabilizes at a level denoted the viral *set point*, and it may remain at approximately that level for several years (Fig. 101-3). The set point, assessed as the PVL at 6 to 12 months after infection, is a significant predictor of the subsequent rate of progression of HIV disease but accounts for only half of the population variability in disease progression rates.

After recovery from the acute retroviral syndrome, the patient may feel entirely well for several years, but even in the asymptomatic infected individual, more than 100 billion new virions may be produced daily. Rapid production and turnover of circulating CD4 cells also occurs throughout the course of HIV infection, and a progressive decline in circulating CD4 cells occurs in most individuals. As disease progresses, a more dramatic CD4 cell decline is observed, following a sharp rise in the PVL (see Fig. 101-3). Cell lysis associated with HIV replication accounts only partially for this progressive loss of CD4 cells. During the years of clinical latency, virions are present in large numbers in the follicular dendritic processes of the germinal centers of the lymph nodes, which undergo both hyperplasia and progressive fibrosis. As HIV disease progresses over several years, the lymphatic tissue atrophies and plasma viremia intensifies. In later-stage HIV disease, there is often persistent high-level viremia.

The decline in the number of CD4 cells is accompanied by profound functional impairment of the remaining lymphocyte populations. Anergy may develop early in HIV infection and eventually occurs in almost all persons with AIDS. T-helper lymphocyte proliferation in response to antigenic stimuli is dramatically impaired, T-cell cytotoxic responses are diminished, and natural killer cell activity against virus-infected cells is greatly impaired. Decrease in function as well as number of CD4 cells is central to the immune dysfunction, and this impairment partly underlies the failure of B-lymphocyte function, as measured by impaired capacity to synthesize antibody in response to new antigens.

For a deeper discussion of these topics, please see Chapter 385, "Immunopathogenesis of Human Immunodeficiency Virus Infection," in Goldman-Cecil Medicine, *25th Edition.*

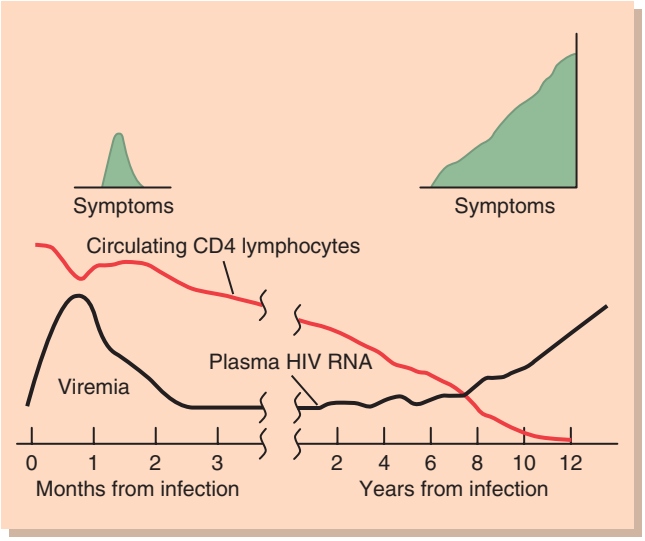

FIGURE 101-3 Natural history of HIV without antiretroviral therapy. Following acute infection, an initial burst of viral replication causes an immediate drop in the CD4 count. Partially effective cell-mediated immunity suppresses viral replication to a nadir level and allows for a rise in the CD4 count to a plateau that is less than a normal CD4 count. Left without treatment, the CD4 count declines somewhat proportionally to the nadir viral level until the patient begins to experience significant immune deficiency. At that time, the viral count may rise and the patient typically becomes symptomatic. Though this usually occurs within 8 to 10 years, considerable variability exists, with some patients progressing to AIDS within a few years and others without a significant decline in CD4 count after 20 years.

CLINICAL PRESENTATION

Acute HIV Infection and the Acute Retroviral Syndrome

Up to 50% of HIV-infected persons report a mononucleosis-like syndrome *(acute retroviral syndrome)* occurring 2 to 6 weeks after initial infection. The symptoms may include fever, sore throat, lymph node enlargement, rash, arthralgias, and headache, and they usually persist for several days to 3 weeks (Table 101-1). The rash is typically maculopapular and short-lived and usually affects the trunk or face. Ten percent of infected individuals experience an acute, self-limited aseptic meningitis, which on lumbar puncture is characterized by cerebrospinal fluid (CSF) pleocytosis with detectable HIV in the CSF. The acute retroviral syndrome is often sufficiently severe that the patient seeks medical attention. It is critical to maintain a high index of suspicion for acute HIV retroviral syndrome because a very high plasma HIV RNA level during this period indicates a high likelihood of HIV transmission to sexual or needle-sharing partners, or from mother to infant.

TABLE 101-1 SIGNS AND SYMPTOMS ASSOCIATED WITH HIV ACUTE RETROVIRAL SYNDROME

SIGN OR SYMPTOM	FREQUENCY (%)
Fever	98
Lymph node enlargement	75
Sore throat	70
Myalgia or arthralgia	60
Rash	50
Headache	35