Table 6-14 Major Abnormalities of Immune Function in AIDS

Lymphopenia
Predominantly caused by selective loss of the CD4+ helper T-cell subset
Decreased T-Cell Function In Vivo
Preferential loss of activated and memory T cells Decreased delayed-type hypersensitivity Susceptibility to opportunistic infections Susceptibility to neoplasms
Altered T-Cell Function In Vitro
Decreased proliferative response to mitogens, alloantigens, and soluble antigens Decreased cytotoxicity Decreased helper function for B-cell antibody production Decreased IL-2 and IFN-γ production
Polyclonal B-Cell Activation
Hypergammaglobulinemia and circulating immune complexes Inability to mount de novo antibody response to new antigens Poor responses to normal B-cell activation signals in vitro
Altered Monocyte or Macrophage Functions
Decreased chemotaxis and phagocytosis Decreased class II HLA expression Diminished capacity to present antigen to T cells

HLA, Human leukocyte antigen; IFN-γ, interferon-γ; IL-2, interleukin-2; TNF, tumor necrosis factor.

Low-level chronic or latent infection of T cells is an important feature of HIV infection. It is widely believed that integrated provirus, without viral gene expression (latent infection), can remain in the cells for months to years. Even with potent antiviral therapy, which practically sterilizes the peripheral blood, latent virus lurks within the CD4+ cells (both T cells and macrophages) in the lymph nodes. According to some estimates, 0.05% of CD4+ T cells in the lymph nodes are latently infected. Because most of these CD4+ T cells are memory cells, they are long-lived, with a life span of months to years, and thus provide a persistent reservoir of virus.

CD4+ T cells play a pivotal role in regulating both cellular and humoral immune responses. Therefore, loss of this "master regulator" has ripple effects on virtually every other component of the immune system, as summarized in Table 6-14.

HIV Infection of Non–T Cells

In addition to infection and loss of CD4+ T cells, **infection of macrophages and dendritic cells is also important in the pathogenesis of HIV infection**. Similar to T cells, the majority of the macrophages that are infected by HIV are found in the tissues and the number of blood monocytes infected by the virus may be low. In certain tissues, such as the lungs and brain, as many as 10% to 50% of macrophages are infected. Several aspects of HIV infection of macrophages should be emphasized:

- Although cell division is required for nuclear entry and replication of most retroviruses, HIV-1 can infect and multiply in terminally differentiated nondividing macrophages. This property of HIV-1 is dependent on the viral *vpr* gene. The Vpr protein allows nuclear targeting of the HIV preintegration complex through the nuclear pore.
- Infected macrophages bud relatively small amounts of virus from the cell surface, but these cells contain large numbers of virus particles often located in intracellular vacuoles. Even though macrophages allow viral replication, they are quite resistant to the cytopathic effects of HIV, in contrast to CD4+ T cells. Thus, macrophages may be reservoirs of infection whose output remains largely protected from host defenses. In late stages of HIV infection, when CD4+ T-cell numbers decline greatly, macrophages may be an important site of continued viral replication.
- Macrophages may act as portals of infection. Recall that in more than 90% of cases acute HIV infection is characterized by predominantly circulating M-tropic strains. This finding suggests that the initial infection of macrophages or dendritic cells may be important in the pathogenesis of HIV disease.
- Even uninfected monocytes are reported to have unexplained functional defects that may have important consequences for host defense. These defects include impaired microbicidal activity, decreased chemotaxis, decreased secretion of IL-1, inappropriate secretion of TNF, and poor capacity to present antigens to T cells. Also, even the low number of infected blood monocytes may be vehicles for HIV to be transported to various parts of the body, including the nervous system.

Studies have documented that, in addition to macrophages, two types of dendritic cells are also important targets for the initiation and maintenance of HIV infection: mucosal and follicular dendritic cells. It is thought that **mucosal dendritic cells are infected by the virus and may transport it to regional lymph nodes**, where the virus is transmitted to CD4+ T cells. Dendritic cells also express a lectin-like receptor that specifically binds HIV and displays it in an intact, infectious form to T cells, thus promoting infection of the T cells.

Follicular dendritic cells in the germinal centers of lymph nodes are potential reservoirs of HIV. Although some follicular dendritic cells may be susceptible to HIV infection, most virus particles are found on the surface of their dendritic processes. Follicular dendritic cells have receptors for the Fc portion of immunoglobulins, and hence they trap HIV virions coated with anti-HIV antibodies. The antibody-coated virions localized to follicular dendritic cells retain the ability to infect CD4+ T cells as they traverse the intricate meshwork formed by the dendritic processes of the follicular dendritic cells.

B Cell Function in HIV Infection. Although much attention has been focused on T cells, macrophages, and dendritic cells because they can be infected by HIV, individuals with AIDS also display profound abnormalities of B-cell function. Paradoxically, there is polyclonal activation of B cells, resulting in germinal center B-cell hyperplasia (particularly early in the disease course), bone marrow plasmacytosis, hypergammaglobulinemia, and formation of circulating immune complexes. This activation may result from multiple interacting factors: reactivation of or reinfection with cytomegalovirus and EBV, both of which are polyclonal B-cell activators, can occur; gp41 itself can promote B-cell growth and differentiation; and HIV-infected macrophages produce increased amounts of IL-6,