above ("Immune Activation, Inflammation, and HIV Pathogenesis"), a subset of CD4+ T cells referred to as *T regulatory cells*, or T-regs, may be involved in damping aberrant immune activation that propagates HIV replication. The presence of these T-reg cells correlates with lower viral loads and higher CD4+/CD8+ T cell ratios. A loss of this T-reg capability with advanced disease may be detrimental to the control of virus replication.

It is difficult to explain completely the profound immunodeficiency noted in HIV-infected individuals solely on the basis of direct infection and quantitative depletion of CD4+ T cells. This is particularly apparent during the early stages of HIV disease, when CD4+ T cell numbers may be only marginally decreased. In this regard, it is likely that CD4+ T cell dysfunction results from a combination of depletion of cells due to direct infection of the cell and a number of virus-related but indirect effects on the cell (Table 226-5). Several of these effects have been demonstrated ex vivo and/or by the analysis of cells isolated from the peripheral blood. However, as explained above, many of the defects are related to specialized CD4+ T cells that reside in lymphoid tissues. Furthermore, since the main targets of HIV infection are immunocompetent cells, these responses may contribute to immune cell depletion and immunologic dysfunction by eliminating both infected cells and "innocent bystander" cells. Soluble viral proteins, particularly gp120, can bind with high affinity to the CD4 molecules on uninfected T cells and monocytes; in addition, virus and/or viral proteins can bind to DCs or FDCs. HIV-specific antibody can recognize these bound molecules and potentially collaborate in the elimination of the cells by ADCC. HIV envelope glycoproteins gp120 and gp160 manifest high-affinity binding to the CD4 molecule as well as to various chemokine receptors. Intracellular signals transduced by gp120 through both CD4 and CCR5/CXCR4 have been associated with a number of immunopathogenic processes including anergy, apoptosis, and abnormalities of cell trafficking. The molecular mechanisms responsible for these abnormalities include dysregulation of the T cell receptor–phosphoinositide pathway, p56lck activation, phosphorylation of focal adhesion kinase, activation of the MAP kinase and ras signaling pathways, and downregulation of the co-stimulatory molecules CD40 ligand and CD80.

The inexorable decline in CD4+ T cell counts that occurs in most HIV-infected individuals may result in part from the inability of the immune system to regenerate over an extended period of time the rapidly turning over CD4+ T cell pool efficiently enough to compensate for both HIV-mediated and naturally occurring attrition of cells. In this regard, the degree and duration of decline of CD4+ T cells at the time of initiation of therapy is an important predictor of the restoration of these cells. A person who maintains a very low CD4+ T cell count for a considerable period of time before the initiation of cART almost invariably has an incomplete reconstitution of such cells. At least two major mechanisms may contribute to the failure of the CD4+ T cell pool to reconstitute itself adequately over the course of HIV infection. The first is the destruction of lymphoid precursor cells, including thymic and bone marrow progenitor cells; the other is the gradual disruption of the lymphoid tissue microenvironment, which is essential for efficient regeneration of immunocompetent cells. Finally, during the advanced stages of CD4+ T lymphopenia, there are increased serum levels of the homeostatic cytokine IL-7. It was initially felt that this elevation was a homeostatic response to the lymphopenia; however, recent findings suggest that the increase in serum IL-7 was a result of reduced utilization of the cytokine related to the loss of cells expressing the IL-7 receptor, CD127, which serves as a normal physiologic regulator of IL-7 production.

CD8+ T Cells A relative CD8+ T lymphocytosis is generally associated with high levels of HIV plasma viremia and likely reflects an immune response to the virus as well as dysregulated homeostasis associated with generalized immune activation. During the late stages of HIV infection, there may be a significant reduction in the numbers of CD8+ T cells despite the presence of high levels of viremia. HIV-specific CD8+ CTLs have been demonstrated in HIV-infected individuals early in the course of disease, and their emergence often coincides with a decrease in plasma viremia—an observation that is a factor in the proposal that virus-specific CTLs can control HIV disease for a finite period of time in a certain percentage of infected individuals. However, emergence of HIV escape mutants that ultimately evade these HIV-specific CD8+ T cells has been described in the majority of HIV-infected individuals who are not receiving cART. In addition, as the disease progresses, the functional capability of these cells gradually decreases, at least in part due to the persistent nature of HIV infection that causes functional exhaustion via the upregulation of inhibitory receptors such as PD-1 on HIV-specific CD8+ T cells (see "Immune Activation, Inflammation, and HIV Pathogenesis," above). As chronic immune activation persists, there are also systemic effects on CD8+ T cells, such that as a population they assume an abnormal phenotype characterized by expression of activation markers such as HLA-DR and CD38 with an absence of expression of the IL-2 receptor (CD25) and a reduced expression of the IL-7 receptor (CD127). In addition, CD8+ T cells lacking CD28 expression are increased in HIV disease, reflecting a skewed expansion of a less differentiated CD8+ T cell subset. This skewing of subsets is also associated with diminished polyfunctionality, a qualitative difference that distinguishes nonprogressors from progressors. It has been reported that nonprogressors can also be distinguished from progressors by the maintenance in the former of a high proliferative capacity of their HIV-specific CD8+ T cells coupled to increases in perforin expression, characteristics that are markedly diminished in advanced HIV disease. It has been reported that the phenotype of CD8+ T cells in HIV-infected individuals may be of prognostic significance. Those individuals whose CD8+ T cells developed a phenotype of HLA-DR+/CD38– following seroconversion had stabilization of their CD4+ T cell counts, whereas those whose CD8+ T cells developed a phenotype of HLA-DR+/CD38+ had a more aggressive course and a poorer prognosis. In addition to the defects in HIV-specific CD8+ CTLs, functional defects in other MHC-restricted CTLs, such as those directed against influenza and CMV, have been demonstrated. CD8+ T cells secrete a variety of soluble factors that inhibit HIV replication, including the CC-chemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4) as well as potentially a number of unidentified factors. The presence of high levels of HIV viremia in vivo as well as exposure of CD8+ T cells in vitro to HIV envelope, both of which are associated with aberrant immune activation, have been shown to be associated with a variety of cellular functional abnormalities. Furthermore, since the integrity of CD8+ T cell function depends in part on adequate inductive signals from CD4+ T cells, the defect in CD8+ CTLs is likely compounded by the quantitative loss and qualitative dysfunction of CD4+ T cells.

B Cells The predominant defect in B cells from HIV-infected individuals is one of aberrant cellular activation, which is reflected by increased propensity to terminal differentiation and immunoglobulin secretion and increased expression of markers of activation and exhaustion. As a result of activation and differentiation in vivo, B cells from HIV viremic patients manifest a decreased capacity to mount a proliferative response to ligation of the B cell antigen receptor and other B cell stimuli in vitro. B cells from HIV-infected individuals manifest enhanced spontaneous secretion of immunoglobulins in vitro, a process that reflects their highly differentiated state in vivo. There is also an increased incidence of EBV-related B cell lymphomas in HIV-infected individuals that are likely due to combined effects of defective T cell immune surveillance and increased turnover that increases the risk of oncogenesis. Untransformed B cells cannot be infected with HIV, although HIV or its products can activate B cells directly. B cells from patients with high levels of viremia bind virions to their surface via the CD21 complement receptor. It is likely that in vivo activation of B cells by replication-competent or defective virus as well as viral products during the viremic state accounts at least in part for their activated phenotype. B cell subpopulations from HIV-infected individuals undergo a number of changes over the course of HIV disease, including the attrition of resting memory B cells and replacement with several aberrant memory and differentiated B cell subpopulations that collectively express reduced levels of CD21