because of their ability to induce immune activation that leads to enhanced viral production and an increase in readily available target cells for HIV (activated CD4+ T cells). The induction of IFN-α, one of the first cytokines induced during primary HIV infection, is thought to play a particularly important role in HIV pathogenesis by inducing a large number of IFN-associated genes that activate the immune system and alter the homeostasis of CD4+ T cells. Other cytokines that are elevated during the chronic phase of HIV infection and linked to immune activation include IFN-γ, the *CC-chemokine* RANTES (CCL5), macrophage inflammatory protein (MIP)-1β (CCL4), and IL-18.

Several specific cytokines and soluble factors have been associated with HIV pathogenesis at various stages of disease, in various tissues or organs, and in the regulation of HIV replication. Plasma levels of IP-10 are predictive of disease progression, whereas the proinflammatory cytokine IL-6, soluble CD14 (sCD14), and coagulation marker D-dimer are associated with increased risk of all-cause mortality in HIV-infected individuals. In particular, IL-6, sCD14, and D-dimer are associated with increased risk of cardiovascular disease and other causes of death, even in individuals receiving cART. IL-18 has also been shown to play a role in the development of the HIV-associated lipodystrophy syndrome, whereas increased levels of transforming growth factor (TGF)-β are associated with the induction of collagen deposition in lymph nodes (see above). Elevated levels of TNF-α and IL-6 have been demonstrated in plasma and cerebrospinal fluid (CSF), and increased expression of TNF-α, IL-1β, IFN-γ, and IL-6 has been demonstrated in the lymph nodes of HIV-infected individuals. RANTES, MIP-1α (CCL3), and MIP-1β (CCL4) **(Chap. 372e)** inhibit infection by and spread of R5 HIV-1 strains, while *stromal cell–derived factor* (SDF) 1 inhibits infection by and spread of X4 strains. The mechanisms whereby the CC-chemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4) inhibit infection of R5 strains of HIV, or SDF-1 blocks X4 strains of HIV, involve blocking of the binding of the virus to its co-receptors, the CC-chemokine receptor CCR5 and the CXC-chemokine receptor CXCR4, respectively. Other soluble factors that have not yet been fully characterized have also been shown to suppress HIV replication, independent of co-receptor usage.

LYMPHOCYTE TURNOVER IN HIV INFECTION

The immune systems of patients with HIV infection are characterized by a profound increase in lymphocyte turnover that is immediately reduced with effective cART. Studies utilizing in vivo or in vitro labeling of lymphocytes in the S-phase of the cell cycle have demonstrated a tight correlation between the degree of lymphocyte turnover and plasma levels of HIV RNA. This increase in turnover is seen in CD4+ and CD8+ T lymphocytes as well as B lymphocytes and can be observed in peripheral blood and lymphoid tissue. Mathematical models derived from these data suggest that one can view the lymphoid pool as consisting of dynamically distinct subpopulations of cells that are differentially affected by HIV infection. A major consequence of HIV infection appears to be a shift in cells from a more quiescent pool to a pool with a higher turnover rate. It is likely that a consequence of a higher rate of turnover is a higher rate of cell death. The role of the thymus in adult human T cell homeostasis and HIV pathogenesis is an area of controversy. While some data point to an important role for the thymus in maintaining T cell numbers and suggest that impairment of thymic function may be responsible for the declines in CD4+ T cells seen in the setting of HIV infection, other studies have concluded that the thymus plays a minor role in HIV pathogenesis. More recently, it has been suggested that the more rapid decline in CD4+ compared to CD8+ T cells may be linked to alterations in inflammatory and homeostatic cytokines that caused increased activation-induced death of CD4+ but not CD8+ T cells (see **Table 226-5** for additional mechanisms of depletion).

THE ROLE OF VIRAL RECEPTORS AND CO-RECEPTORS IN HIV PATHOGENESIS

As mentioned above, HIV-1 utilizes two major co-receptors along with CD4 to bind to, fuse with, and enter target cells; these co-receptors are CCR5 and CXCR4, which are also receptors for certain endogenous chemokines. Strains of HIV that utilize CCR5 as a co-receptor are referred to as *R5 viruses*. Strains of HIV that utilize CXCR4 are referred to as *X4 viruses*. Many virus strains are *dual tropic* in that they utilize both CCR5 and CXCR4; these are referred to as *R5X4 viruses*.

TABLE 226-5 PROPOSED MECHANISMS OF CD4+ T CELL DYSFUNCTION AND DEPLETION

Direct Mechanisms	Indirect Mechanisms
Loss of plasma membrane integrity due to viral budding	Aberrant intracellular signaling events
Accumulation of unintegrated viral DNA	Autoimmunity
Activation of DNA-dependent protein kinase during viral integration into host genome	
Interference with cellular RNA processing	Innocent bystander killing of viral antigen–coated cells
Intracellular gp120-CD4 autofusion events	Apoptosis, pyroptosis (caspase-1 associated inflammation), autophagy
Syncytia formation	Inhibition of lymphopoiesis from reduced survival cytokines and lymphoid tissue integrity
	Activation-induced cell death
	Elimination of HIV-infected cells by virus-specific immune responses

The natural chemokine ligands for the major HIV co-receptors can readily block entry of HIV. For example, the CC-chemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4), which are the natural ligands for CCR5, block entry of R5 viruses, whereas SDF-1, the natural ligand for CXCR4, blocks entry of X4 viruses. The mechanism of inhibition of viral entry is a steric inhibition of binding that is not dependent on signal transduction **(Fig. 226-25)**.

The transmitting virus is almost invariably an R5 virus that predominates during the early stages of HIV disease. In ~40% of HIV-infected individuals, there is a transition to a predominantly X4 virus that is associated with a relatively rapid progression of disease. However, at least 60% of infected individuals progress in their disease while maintaining predominance of an R5 virus. It should be pointed out that clade C viruses, unlike other subgroups, almost never switch from CCR5 tropism to CXCR4 tropism; the reason for this difference is unclear.

The basis for the tropism of different envelope glycoproteins for either CCR5 or CXCR4 relates to the ability of the HIV envelope, including the third variable region (V3 loop) of gp120, to interact with these co-receptors. In this regard, binding of gp120 to CD4 induces a conformational change in gp120 that increases its affinity for CCR5 (see above). Finally, R5 viruses are more efficient in infecting monocytes/macrophages and microglial cells of the brain (see "Neuropathogenesis in HIV Disease," below).

THE INTEGRIN α4β7 AND MUCOSAL TRANSMISSION OF HIV Several "accessory receptors" for HIV have been reported over the years, although only a few have withstood the test of time. These receptors are not necessary for virus binding and fusion to its target CD4+ T cell or for virus replication. However, the integrin *α4β7* is an accessory receptor for HIV and it likely plays an important role in the transmission of HIV at mucosal surfaces such as the genital tract and gut. The integrin α4β7, which is the gut homing receptor for peripheral T cells, binds in its activated form to a specific tripeptide in the V2 loop of gp120, resulting in rapid activation of leukocyte function–associated antigen 1 (LFA-1), the central integrin in the establishment of virologic synapses, which facilitate efficient cell-to-cell spread of HIV. It has been demonstrated that $\alpha4\beta7^{high}$ CD4+ T cells are more susceptible to productive infection than are $\alpha4\beta7^{low-neg}$ CD4+ T cells because this cellular subset is enriched with metabolically active CD4+ T cells that are $CCR5^{high}$. These cells are present at the gut and genital tract mucosal surfaces. Importantly, it has been demonstrated that the virus that is transmitted during sexual exposure binds much more efficiently to α4β7 than does the virus that diversifies from the transmitting virus over time by mutation,