drug abuse, and the potential for neurotoxicity of certain of the antiretroviral drugs. HIV has been demonstrated in the brain and CSF of infected individuals with and without neuropsychiatric abnormalities. As opposed to lymphoid tissues, there are no resident lymphocytes in the brain. The main cell types that are infected in the brain in vivo are the perivascular macrophages and the microglial cells; low-level viral replication is also seen in perivascular astrocytes. Monocytes that have already been infected in the blood can migrate into the brain, where they then reside as macrophages, or macrophages can be directly infected within the brain. The precise mechanisms whereby HIV enters the brain are unclear; however, they are thought to relate, at least in part, to the ability of virus-infected and immune-activated macrophages to induce adhesion molecules such as E-selectin and vascular cell adhesion molecule 1 (VCAM-1) on brain endothelium. Other studies have demonstrated that HIV gp120 enhances the expression of intercellular adhesion molecule 1 (ICAM-1) in glial cells; this effect may facilitate entry of HIV-infected cells into the CNS. Virus isolates from the brain are preferentially R5 strains as opposed to X4 strains; in this regard, HIV-infected individuals who are heterozygous for *CCR5-Δ32* appear to be relatively protected against the development of HIV encephalopathy. Once HIV enters the brain due to pressures of the local environment, it evolves to develop distinct sequences in the env, tat, and LTR genes. These unique sequences have been associated with neurocognitive dysfunction; however, it is unclear if they are causal (see below).

HIV-infected individuals may manifest white matter lesions as well as neuronal loss. The white matter lesions are due to axonal injury and a disruption of the blood-brain barrier and not due to demyelination. Given the absence of evidence of HIV infection of neurons either in vivo or in vitro, it is highly unlikely that direct infection of these cells accounts for their loss. Rather, the HIV-mediated effects on neurons are thought to involve indirect pathways whereby viral proteins, particularly gp120 and Tat, trigger the release of endogenous neurotoxins from macrophages and to a lesser extent from astrocytes. In addition, it has been demonstrated that both HIV-1 Nef and Tat can induce chemotaxis of leukocytes, including monocytes, into the CNS. Neurotoxins can be released from monocytes as a consequence of infection and/or immune activation. Monocyte-derived neurotoxic factors have been reported to kill neurons via the *N*-methyl-D-aspartate (NMDA) receptor. In addition, HIV gp120 shed by virus-infected monocytes could cause neurotoxicity by antagonizing the function of vasoactive intestinal peptide (VIP), by elevating intracellular calcium levels, and by decreasing nerve growth factor levels in the cerebral cortex. A variety of monocyte-derived cytokines can contribute directly or indirectly to the neurotoxic effects in HIV infection; these include TNF-α, IL-1, IL-6, TGF-β, IFN-γ, platelet-activating factor, and endothelin. Furthermore, among the CC-chemokines, elevated levels of monocyte chemotactic protein-1 (MCP-1 or CCL-2) in the brain and CSF have been shown to correlate best with the presence and degree of HIV encephalopathy. In addition, infection and/or activation of monocyte-lineage cells can result in increased production of eicosanoids, quinolinic acid, nitric oxide, excitatory amino acids such as L-cysteine and glutamate, arachidonic acid, platelet activating factor, free radicals, TNF-α, and TGF-β, which may contribute to neurotoxicity. Astrocytes may play diverse roles in HIV neuropathogenesis. Reactive gliosis or astrocytosis has been demonstrated in the brains of HIV-infected individuals, and TNF-α and IL-6 have been shown to induce astrocyte proliferation. In addition, astrocyte-derived IL-6 can induce HIV expression in infected cells in vitro. Furthermore, it has been suggested that astrocytes may downregulate macrophage-produced neurotoxins. Treatment with cART leads to improvement in neuropsychiatric manifestations and a decrease in these cytokine levels in CSF, suggesting that they are driven by the virus or by its products. However, even in patients on long-term cART, there may be evidence of persistently activated lymphocytes in the CSF. It is unclear if these lymphocytes may contribute to neuronal injury in the brain or are critical for controlling the CNS viral reservoir. The contribution of host genetic factors to development of neuropsychiatric manifestations of HIV infection has not been well studied. However, evidence supports the role of the E4 allele for apoE in an increased risk of HIV-associated neurocognitive disorders and peripheral neuropathy.

It has also been suggested that the CNS may serve as a relatively sequestered site for a reservoir of latently infected cells that might be a barrier for the eradication of virus by cART (see "Reservoirs of HIV-Infected Cells: Obstacles to the Eradication of Virus," above).

PATHOGENESIS OF KAPOSI'S SARCOMA

There are at least four distinct epidemiologic forms of KS: (1) the classic form that occurs in older men of predominantly Mediterranean or eastern European Jewish backgrounds with no recognized contributing factors; (2) the equatorial African form that occurs in all ages, also without any recognized precipitating factors; (3) the form associated with organ transplantation and its attendant iatrogenic immunosuppressed state; and (4) the form associated with HIV-1 infection. In the latter two forms, KS is an opportunistic disease; in HIV-infected individuals, unlike typical opportunistic infections, its occurrence is not strictly related to the level of depression of CD4+ T cell counts. The pathogenesis of KS is complex; fundamentally, it is an angioproliferative disease that is not a true neoplastic sarcoma, at least not in its early stages. It is a manifestation of excessive proliferation of spindle cells that are believed to be of vascular origin and have features in common with endothelial and smooth-muscle cells. In HIV disease the development of KS is dependent on the interplay of a variety of factors including HIV-1 itself, human herpes virus 8 (HHV-8), immune activation, and cytokine secretion. A number of epidemiologic and virologic studies have clearly linked HHV-8, which is also referred to as *Kaposi's sarcoma–associated herpesvirus* (KSHV), to KS not only in HIV-infected individuals but also in individuals with the other forms of KS. HHV-8 is a γ-herpesvirus related to EBV and *herpesvirus saimiri*. It encodes a homologue to human IL-6 and, in addition to KS, has been implicated in the pathogenesis of body cavity lymphoma, multiple myeloma, and monoclonal gammopathy of undetermined significance. Sequences of HHV-8 are found universally in the lesions of KS, and patients with KS are virtually all seropositive for HHV-8. HHV-8 DNA sequences can be found in the B cells of 30–50% of patients with KS and 7% of patients with AIDS without clinically apparent KS.

Between 1 and 2% of eligible blood donors are positive for antibodies to HHV-8, while the prevalence of HHV-8 seropositivity in HIV-infected men is 30–35%. The prevalence of HHV-8 seropositivity in HIV-infected women is ~4%. This finding is reflective of the lower incidence of KS in women. It has been debated whether HHV-8 is actually the transforming agent in KS; the bulk of the cells in the tumor lesions of KS are not neoplastic cells. However, it has been demonstrated that endothelial cells can be transformed in vitro by HHV-8. In this regard, HHV-8 possesses a number of genes, including homologues of the IL-8 receptor, Bcl-2, and cyclin D, that can potentially transform the host cell. Despite the complexity of the pathogenic events associated with the development of KS in HIV-infected individuals, HHV-8 is the etiologic agent of this disease. The initiation and/or propagation of KS requires an activated state and is mediated, at least in part, by cytokines. A number of factors, including TNF-α, IL-1β, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), basic fibroblast growth factor, and oncostatin M, function in an autocrine and paracrine manner to sustain the growth and chemotaxis of the KS spindle cells. In this regard, KSHV-derived IL-6 has been demonstrated to induce proliferation of lymphoma cells and to inhibit the cytostatic effects of IFN-α on KSHV-infected lymphoma cells.

IMMUNE RESPONSE TO HIV

As detailed above and below, following the initial burst of viremia during primary infection, HIV-infected individuals mount robust immune responses that in most cases substantially curtail the levels of plasma viremia and likely contribute to delaying the ultimate development of clinically apparent disease for a median of 10 years in untreated individuals. This immune response contains elements of both humoral and cell-mediated immunity involving both innate and adaptive immune responses **(Table 226-7; Fig. 226-26)**. It is directed against multiple antigenic determinants of the HIV virion as