phenotype. Activation of such cells, by antigen or by cytokines, reawakens an EBV-encoded program of gene expression that drives B-cell proliferation. Patients with AIDS have high levels of several cytokines, some of which, including IL-6, are growth factors for B cells. These patients are also chronically infected with pathogens that may lead to B-cell stimulation. In the absence of T-cell immunity, these activated, EBV infected clones proliferate and eventually acquire additional somatic mutations, leading to their outgrowth as full-blown EBV-positive B-cell lymphomas. The tumors often occur in extranodal sites, such as the central nervous system, but also the gut, the orbit, and the lungs, and elsewhere. AIDS patients are also prone to rare lymphomas that present as malignant effusions (so-called primary effusion lymphoma), which are remarkable in that the tumor cells are usually coinfected by both EBV and KSHV, a highly unusual example of cooperativity between two oncogenic viruses.

- **Germinal center B-cell hyperplasia in the setting of early HIV infection.** As mentioned, even in the face of effective antiretroviral therapy, the overall rate of lymphoma in the HIV-infected population remains elevated, even in those with normal CD4+ T-cell counts. As might be anticipated, the majority of the lymphomas that arise in patients with preserved CD4 T-cell counts are not associated with EBV or KSHV. What then explains the continued increased risk of lymphoma? The answer is not known, but it may be related to the profound germinal center B-cell hyperplasia that occurs early in HIV infection. Recall that in germinal centers, B cells diversify their immunoglobulin genes via lesions introduced into their DNA by the enzyme activation-induced deaminase (AID). This process is imperfect, and there is experimental evidence showing that AID can cause mutations in oncogenes implicated in B-cell lymphomagenesis. Of note, the aggressive B cell tumors that arise outside of the setting of full-blown AIDS in HIV-infected individuals, such as Burkitt lymphoma and diffuse large B-cell lymphoma, are often associated with mutations in oncogenes such as *MYC* and *BCL6* that bear the molecular hallmarks of "mistakes" made during attempted immunoglobulin class-switching and somatic hypermutations, two AID-dependent events that occur in germinal center B cells. Thus, the striking germinal center B-cell hyperplasia that occurs early in HIV infection may contribute to lymphomagenesis by simply increasing the number of B cells that are "at-risk" for acquiring potential lymphoma-initiating events.

Several other EBV-related proliferations also merit mention. Hodgkin lymphoma, an unusual B cell tumor associated with a pronounced tissue inflammatory response (Chapter 13), also occurs at increased frequency in HIV-infected individuals. In virtually all instances of HIV-associated Hodgkin lymphoma, the characteristic tumor cells (Reed-Sternberg cells) are infected with EBV. Many (but not all) HIV patients with Hodgkin lymphoma have low CD4 counts at the time of disease presentation. EBV infection also is responsible for oral hairy leukoplakia (white projections on the tongue), which results from EBV-driven squamous cell proliferation of the oral mucosa (Chapter 16).

Other Tumors. In addition to KS and lymphomas, patients with AIDS also have an increased occurrence of carcinoma of the uterine cervix and of anal cancer. This is most likely due to reactivation of latent human papillomavirus (HPV) infection in the setting of immunosuppression. This virus is intimately associated with squamous cell carcinoma of the cervix and its precursor lesions, cervical dysplasia and carcinoma in situ (Chapters 7 and 22). HPV-associated cervical dysplasia is 10 times more common in HIV-infected women as compared with uninfected women attending family planning clinics. Hence it is recommended that gynecologic examination be part of a routine work-up of HIV-infected women.

Central Nervous System Disease. Involvement of the central nervous system is a common and important manifestation of AIDS. Ninety percent of patients demonstrate some form of neurologic involvement at autopsy, and 40% to 60% have clinically apparent neurologic dysfunction. Importantly, in some patients, neurologic manifestations may be the sole or earliest presenting feature of HIV infection. In addition to opportunistic infections and neoplasms, several virally determined neuropathologic changes occur. These include a self-limited meningoencephalitis occurring at the time of seroconversion, aseptic meningitis, vacuolar myelopathy, peripheral neuropathies, and, most commonly, a progressive encephalopathy designated clinically as HIV-associated neurocognitive disorder (Chapter 28).

Effect of Antiretroviral Drug Therapy on the Clinical Course of HIV Infection. The advent of new antiretroviral drugs that target the viral reverse transcriptase, protease, and integrase has changed the clinical face of AIDS. These drugs are given in combination to reduce the emergence of mutants that develop resistance to any one; treatment regimens are commonly called *highly active antiretroviral therapy (HAART)* or *combination antiretroviral therapy.* Over 25 antiretroviral drugs from six distinct drug classes have been developed for the management of HIV infection. When a combination of at least three effective drugs is used in a motivated, compliant patient, HIV replication is reduced to below the level of detection (<50 copies RNA per milliliter) and remains there indefinitely (as long as the patient adheres to therapy). Even when a drug-resistant virus breaks through, there are several second- and third-line options to combat the virus. Once the virus is suppressed, the progressive loss of CD4+ T cells is halted. Over a period of several years the peripheral CD4+ T-cell count slowly increases and often returns to a normal level. With the use of these drugs, in the United States the annual death rate from AIDS has decreased from its peak of 16 to 18 per 100,000 people in 1995-1996 to less than 4 per 100,000. Many AIDS-associated disorders, such as opportunistic infections with *P. jiroveci* and Kaposi sarcoma, are very uncommon now. Effective antiretroviral therapy has reduced the transmission of the virus, especially from infected mothers to newborns. However, because of the reduced mortality, more people are living with HIV, and since they are not virus-free, there is a fear that the risk of spreading the infection may increase if vigilance is relaxed. Indeed, there is compelling evidence that even treated patients who remain asymptomatic, with virtually