neoplasm in patients with AIDS. The morphology of KS and its occurrence in patients not infected with HIV are discussed in Chapter 11. At the onset of the AIDS epidemic, up to 30% of infected homosexual or bisexual men had KS, but in recent years, with use of HAART there has been a dramatic decline in its incidence. In contrast, in areas of sub-Saharan Africa where HIV infection is both frequent and largely untreated, Kaposi sarcoma is one of the most common tumors.

The lesions of KS are characterized by the proliferation of spindle-shaped cells that express markers of both endothelial cells (vascular or lymphatic) and smooth muscle cells. There is also a profusion of slitlike vascular spaces, suggesting that the lesions may arise from primitive mesenchymal precursors of vascular channels. In addition, KS lesions display chronic inflammatory cell infiltrates. Many of the features of KS suggest that it is not a malignant tumor (despite its ominous name). For instance, spindle cells in many KS lesions are polyclonal or oligoclonal, although more advanced lesions occasionally show monoclonality. The current model of KS pathogenesis is that the spindle cells produce proinflammatory and angiogenic factors, which recruit the inflammatory and neovascular components of the lesion, and the latter components supply signals that aid in spindle cell survival and growth.

There is compelling evidence that KS is caused by the *KS herpesvirus* (KSHV), also called *human herpesvirus 8* (HHV8). Exactly how KSHV infection leads to KS is still unclear. Like other herpesviruses, KSHV establishes latent infection, during which several proteins are produced with potential roles in stimulating spindle cell proliferation and preventing apoptosis. These include a viral homologue of cyclin D and several inhibitors of p53. However, KSHV infection, while necessary for KS development, is not sufficient, and additional cofactors are needed. In the AIDS-related form, that cofactor is clearly HIV. (The relevant cofactors for HIV-negative KS remain unknown.) HIV-mediated immune suppression may aid in widespread dissemination of KSHV in the host.

KSHV infection is not restricted to endothelial cells. The virus is related phylogenetically to the lymphotropic subfamily of herpesviruses (γ-herpesvirus); in keeping with this, its genome is found in B cells of infected subjects. In fact, KSHV infection is also linked to rare B-cell lymphomas in AIDS patients (called *primary effusion lymphoma*) and to multicentric Castleman disease, a B-cell lymphoproliferative disorder.

Clinically, AIDS-associated KS is quite different from the sporadic form (Chapter 11). In HIV-infected individuals the tumor is usually widespread, affecting the skin, mucous membranes, gastrointestinal tract, lymph nodes, and lungs. These tumors also tend to be more aggressive than classic KS.

Lymphomas. Lymphoma occurs at a markedly increased rate in individuals with AIDS, making it one of several AIDS-defining conditions. Roughly 5% of AIDS patients present with lymphoma, and approximately another 5% develop lymphoma during their subsequent course. With the advent of effective antiretroviral therapy, the incidence of lymphoma has fallen substantially in some HIV-infected populations. However, even in the era of retroviral therapy, lymphoma continues to occur in HIV-infected people at an incidence that is at least 10-fold greater than the population average. These epidemiologic findings suggest that the association of lymphoma and HIV infection is only partially explained by T-cell immunodeficiency. Indeed, based on molecular characterization of HIV-associated lymphomas and the epidemiologic considerations above, at least two mechanisms appear to underlie the increased risk of B-cell tumors in HIV infected individuals (Fig. 6-43).

- **Unchecked proliferation of B cells infected with oncogenic herpesviruses in the setting of profound T cell depletion (AIDS).** T-cell immunity is required to restrain the proliferation of B cells infected with oncogenic viruses such as EBV and KSHV. With the appearance of severe T-cell depletion late in the course of HIV infection, this control is lost. As a result AIDS patients are at high risk of developing aggressive B cell lymphomas composed of tumor cells infected by oncogenic viruses, particularly EBV.

  By adulthood, most normal individuals are infected by EBV. Once immunity is established, EBV persists in such individuals as a latent infection in approximately 1 in 100,000 B cells, most of which have a memory B-cell

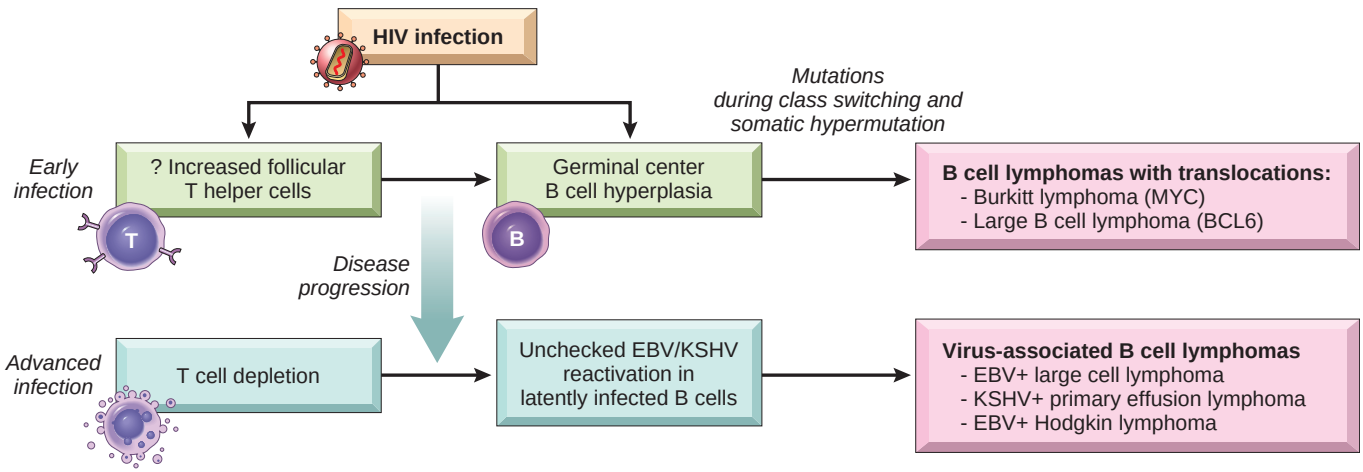

Figure 6-43 A model for the pathogenesis of B-cell lymphomas in HIV infection. HIV infection results in several changes that may cooperate to produce B-cell lymphomas.