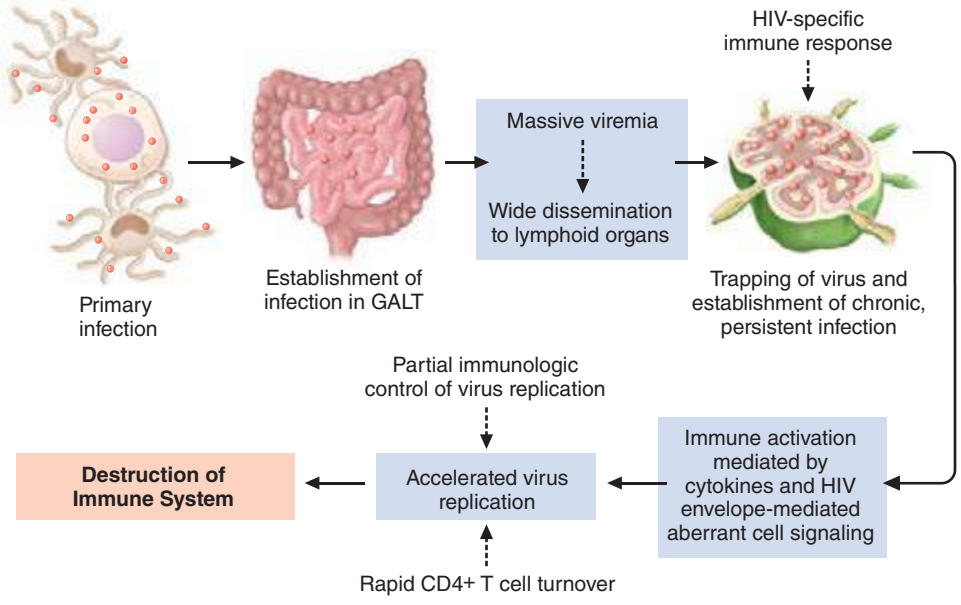

FIGURE 226-24 **Events that transpire from primary HIV infection** through the establishment of chronic persistent infection to the ultimate destruction of the immune system. See text for details. CTLs, cytolytic T lymphocytes; GALT, gut-associated lymphoid tissue.

this early damage to GALT, which constitutes a major component of lymphoid tissue in the body, may play a role in determining the potential for immunologic recovery of the memory cell subset.

IMMUNE ACTIVATION, INFLAMMATION, AND HIV PATHOGENESIS

Activation of the immune system and variable degrees of inflammation are essential components of any appropriate immune response to a foreign antigen. However, immune activation and inflammation, which can be considered aberrant in HIV-infected individuals, play a critical role in the pathogenesis of HIV disease and other chronic conditions associated with HIV disease. Immune activation and inflammation in the HIV-infected individual contribute substantially to (1) the replication of HIV, (2) the induction of immune dysfunction, and (3) the increased incidence of chronic conditions associated with persistent immune activation and inflammation (Table 226-4).

INDUCTION OF HIV REPLICATION BY ABERRANT IMMUNE ACTIVATION The immune system is normally in a state of homeostasis, awaiting perturbation by foreign antigenic stimuli. Once the immune response deals with and clears the antigen, the system returns to relative quiescence (Chap. 372e). This is generally not the case in HIV infection where, in the untreated patient, virus replication is invariably persistent with very few exceptions and immune activation is persistent. HIV replicates most efficiently in activated CD4+ T cells; in HIV infection, chronic activation provides the cell substrates necessary for persistent virus replication throughout the course of HIV disease, particularly in the untreated patient and to variable degrees even in certain patients receiving cART whose levels of plasma viremia are suppressed to below the level of detection by standard assays. From a virologic standpoint, although quiescent CD4+ T cells can be infected with HIV, reverse transcription, integration, and virus spread are much more efficient in activated cells. Furthermore, cellular activation induces expression of virus in cells latently infected with HIV. In essence, immune activation and inflammation provide the engine that drives HIV replication. In addition to endogenous factors such as cytokines, a number of exogenous factors such as other microbes that are associated with heightened cellular activation can enhance HIV replication and thus may have important effects on HIV pathogenesis. Co-infection in vivo or in vitro with a range of viruses, such as HSV types 1 and 2, cytomegalovirus (CMV), human herpesvirus (HHV) 6, Epstein-Barr virus (EBV), HBV, adenovirus, and HTLV-1 have been shown to upregulate HIV expression. In addition, infestation with nematodes has been shown to be associated with a heightened state of immune activation that facilitates HIV replication; in certain studies deworming of the infected host has resulted in a decrease in plasma viremia. Two diseases of extraordinary global health significance, malaria and tuberculosis (TB), have been shown to increase HIV viral load in dually infected individuals. Globally, *Mycobacterium tuberculosis* is the most common opportunistic infection in HIV-infected individuals (Chap. 202). In addition to the fact that HIV-infected individuals are more likely to develop active TB after exposure, it has been demonstrated that active TB can accelerate the course of HIV infection. It has also been shown that levels of plasma viremia are greatly elevated in HIV-infected individuals with active TB who are not on cART, compared with pre-TB levels and levels of viremia after successful treatment of the active TB. The situation is similar in the interaction between HIV and malaria parasites (Chap. 248). Acute infection of HIV-infected individuals with *Plasmodium falciparum* increases HIV viral load, and the increased viral load is reversed by effective malaria treatment.

TABLE 226-4 CONDITIONS ASSOCIATED WITH PERSISTENT IMMUNE ACTIVATION AND INFLAMMATION IN PATIENTS WITH HIV INFECTION

- Accelerated aging syndrome
- Bone fragility
- Cancers
- Cardiovascular disease
- Diabetes
- Kidney disease
- Liver disease
- Neurocognitive dysfunction

MICROBIAL TRANSLOCATION AND PERSISTENT IMMUNE ACTIVATION One proposed mechanism of persistent immune activation involves the disruption of the mucosal barrier in the gut due to HIV replication in and disruption of submucosal lymphoid tissue. As a result of this disruption, there is an increase in the products, particularly lipopolysaccharide (LPS), of bacteria that translocate from the bowel lumen through the damaged mucosa to the circulation, leading to persistent systemic immune activation and inflammation. This effect can persist even after the HIV viral load is brought to <50 copies/mL by cART. Depletion in the GALT of IL-17–producing T cells, which are responsible for defense against extracellular bacteria and fungi, also is thought to contribute to HIV pathogenesis.

PERSISTENT IMMUNE ACTIVATION AND INFLAMMATION INDUCE IMMUNE DYSFUNCTION The activated state in HIV infection is reflected by hyperactivation of B cells leading to hypergammaglobulinemia; increased lymphocyte turnover; activation of monocytes; expression of activation markers on CD4+ and CD8+ T cells; increased activation-associated cellular apoptosis; lymph node hyperplasia, particularly early in the course of disease; increased secretion of proinflammatory cytokines, particularly IL-6; elevated levels of high-sensitivity C-reactive protein, fibrinogen, D-dimer, neopterin, β_2-microglobulin, acid-labile interferon, soluble (s) IL-2 receptors (R), sTNFR, sCD27, and sCD40L; and autoimmune phenomena (see "Autoimmune Phenomena," below). Even in the absence of direct infection of a target cell, HIV envelope proteins can interact