as programmed death (PD) 1 molecule (of the B7-CD28 family of molecules), as well as loss of polyreactivity and proliferative capacity. Another mechanism contributing to the evasion by HIV of immune system control is the downregulation of HLA class I molecules on the surface of HIV-infected cells by the viral proteins Nef, Tat, and Vpu, resulting in the lack of ability of the CD8+ CTL to recognize and kill the infected target cell. Although this downregulation of HLA class I molecules would favor elimination of HIV-infected cells by natural killer (NK) cells, this latter mechanism does not seem to remove HIV-infected cells effectively (see below).

The principal targets of neutralizing antibodies against HIV are the envelope proteins gp120 and gp41. HIV employs at least three mechanisms to evade neutralizing responses: hypervariability in the primary sequence of the envelope, extensive glycosylation of the envelope, and conformational masking of neutralizing epitopes. Several studies that have followed the humoral immune response to HIV from the earliest points after primary infection indicate that the virus continually mutates to escape the emerging antibody response such that the sequential antibodies that are induced do not neutralize the autologous virus. *Broadly neutralizing antibodies* capable of neutralizing a wide range of primary HIV isolates in vitro occur in only about 20% of HIV-infected individuals, and, when they do occur, it generally requires 2 to 3 years of infection with continual virus replication to drive the affinity maturation of the antibodies. Unfortunately, by the time these broadly neutralizing antibodies are formed, they are ineffective in containing the virus replication in the patient. Persistent viremia also results in exhaustion of B cells similar to the exhaustion reported for CD4+ T cells, adding to the defects in the humoral response to HIV.

CD4+ T cell help is essential for the integrity of antigen-specific immune responses, both humoral and cell-mediated. HIV preferentially infects activated CD4+ T cells including HIV-specific CD4+ T cells, and so this loss of viral-specific helper T cell responses has profound negative consequences for the immunologic control of HIV replication. Furthermore, this loss occurs early in the course of infection, and animal studies indicate that 40–70% of all memory CD4+ T cells in the GALT are eliminated during acute infection. Another potential means of escape of HIV-infected cells from elimination by CD8+ CTLs is the sequestration of infected cells in immunologically privileged sites such as the central nervous system (CNS).

Finally, the escape of HIV from immune-mediated elimination during primary infection allows the formation of a pool of latently infected cells that may not be recognized or completely eliminated by virus-specific CTLs or by ART (see below). Thus, despite a potent immune response and the marked downregulation of virus replication following primary HIV infection, HIV succeeds in establishing a state of chronic infection with a variable degree of persistent virus replication. During this period most patients make the clinical transition from acute primary infection to variable periods of clinical latency or smoldering disease activity (see below).

The HIV Reservoir: Obstacles to the Eradication of Virus A pool of latently infected, resting CD4+ T cells that serves as at least one component of the persistent reservoir of virus exists in virtually all HIV-infected individuals, including those who are receiving cART. Such cells carry an integrated form of HIV DNA in the genome of the host and can remain in this state until an activation signal drives the expression of HIV transcripts and ultimately replication-competent virus. This form of latency is to be distinguished from preintegration latency, in which HIV enters a resting CD4+ T cell and, in the absence of an activation signal, reverse transcription of the HIV genome occurs to a certain extent but the resulting proviral DNA fails to integrate into the host genome. This period of preintegration latency may last hours to days, and if no activation signal is delivered to the cell, the proviral DNA loses its capacity to initiate a productive infection. If these cells do become activated prior to decay of the preintegration complex, reverse transcription proceeds to completion and the virus continues along its replication cycle (see above and Fig. 226-20). The pool of cells that are in the postintegration state of latency is established early during the

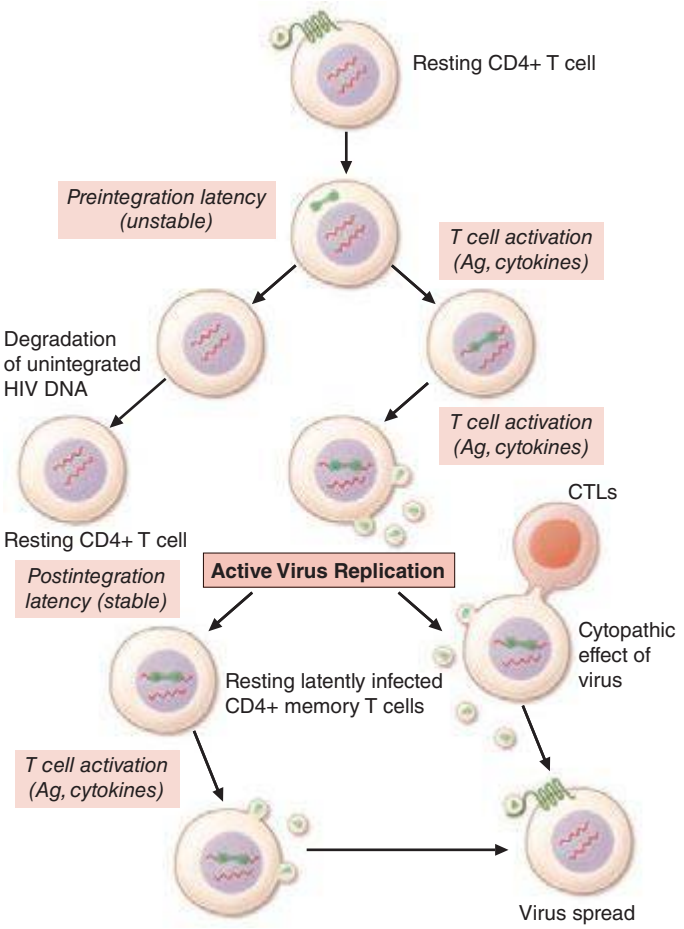

FIGURE 226-20 Generation of latently infected, resting CD4+ T cells in HIV-infected individuals. See text for details. Ag, antigen; CTLs, cytolytic T lymphocytes. *(Courtesy of TW Chun; with permission.)*

course of primary HIV infection. Despite the suppression of plasma viremia to <50 copies of HIV RNA per milliliter by potent regimens of cART administered over several years, this pool of latently infected cells persists and can give rise to replication-competent virus upon cellular activation. Modeling studies built on projections of decay curves have estimated that in such a setting of prolonged suppression, it would require a few to several years for the pool of latently infected cells to be completely eliminated. This has not been documented to occur spontaneously in any patients very likely because the latent viral reservoir is continually replenished by the low levels of persistent virus replication that may remain below the limits of detection of current assays (see below) (Fig. 226-20), even in patients who for the most part are treated successfully. Reservoirs of HIV-infected cells, latent or otherwise, can exist in a number of compartments including the lymphoid tissue, peripheral blood, and the CNS (likely in cells of the monocyte/macrophage lineage) as well as in other unidentified locations. Over the past several years attempts have been made to eliminate HIV in the latent viral reservoir using agents that stimulate resting CD4+ T cells during the course of cART; however, such attempts have been unsuccessful. Thus, this persistent reservoir of infected cells and/or low levels of persistent virus replication are major obstacles to the goal of eradication of virus from infected individuals and hence a "cure," despite the favorable clinical outcomes that have resulted from cART.

Viral Dynamics The dynamics of viral production and turnover have been quantified using mathematical modeling in the setting of the administration of reverse transcriptase and protease inhibitors to HIV-infected individuals in clinical studies. Treatment with these drugs resulted in a precipitous decline in the level of plasma viremia, which typically fell by well over 90% within 2 weeks. The number of CD4+ T cells in the blood increased concurrently, which suggested that the