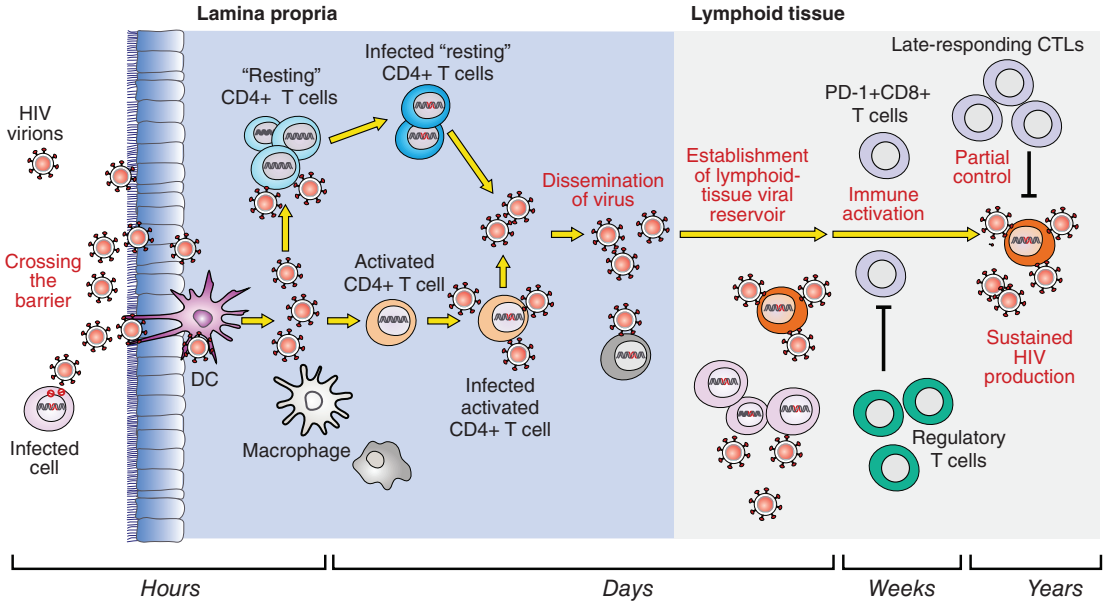

FIGURE 226-18 Summary of early events in HIV infection. See text for detailed description. CTLs, cytolytic T lymphocytes; HIV, human immunodeficiency virus. *(Adapted from AT Haase: Nat Rev Immunol 5:783, 2005.)*

to others by a variety of routes including sexual transmission, shared needles and syringes, and mother-to-child transmission intrapartum, perinatally, or via breast milk.

ESTABLISHMENT OF CHRONIC AND PERSISTENT INFECTION

Persistence of Virus Replication HIV infection is unique among human viral infections. Despite the robust cellular and humoral immune responses that are mounted following primary infection (see "Immune Response to HIV," below), once infection has been established the virus succeeds in escaping complete immune-mediated clearance, paradoxically seems to thrive on immune activation, and is never eliminated completely from the body. Rather, a chronic infection develops and persists with varying degrees of continual virus replication in the untreated patient for a median of ~10 years before the patient becomes clinically ill (see "Advanced HIV Disease," below). It is this establishment of a chronic, persistent infection that is the hallmark of HIV disease. Throughout the often protracted course of chronic infection, virus replication can invariably be detected in untreated patients by widely available assays that measure copies of HIV RNA per milliliter of plasma. Levels of virus vary greatly in most untreated patients, ranging from several thousand to a few million copies of HIV RNA per milliliter of plasma. Studies using highly sensitive molecular techniques have demonstrated that even in certain patients in whom plasma viremia is suppressed to below detection (lower limit, 20–50 copies of HIV RNA/mL depending on manufacturer) by cART, there is a continual low level of virus replication. In other human viral infections, with very few exceptions, if the host survives, the virus is completely cleared from the body and a state of immunity against subsequent infection develops. HIV infection very rarely kills the host during primary infection. Certain viruses, such as HSV (Chap. 216), are not completely cleared from the body after infection, but instead enter a latent state; in these cases, clinical latency is accompanied by microbiologic latency. This is not the case with HIV infection as described above. Chronicity associated with persistent virus replication can also be seen in certain cases of HBV and HCV infections (Chap. 362); however, in these infections the immune system is not a target of the virus.

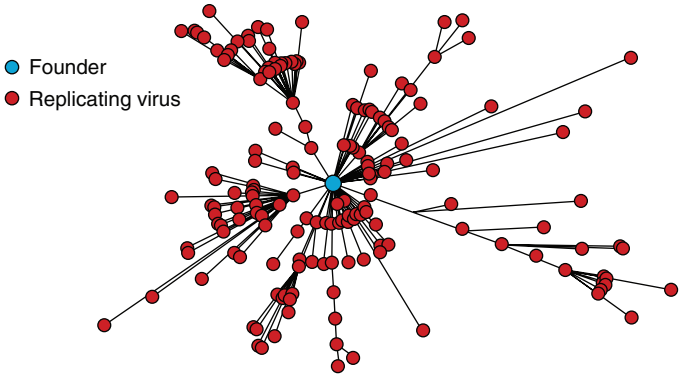

FIGURE 226-19 As HIV diverges from founder to chronically replicating virus, it accumulates N-linked glycosylation sites. See text for detailed description. *(Adapted from CA Derdeyn et al: Science 303:2019, 2004; B Chohan et al: J Virol 79:6528, 2005; and BF Keele et al: Proc Natl Acad Sci USA 105:7552, 2008.)*

Escape of HIV from Effective Immune System Control Inherent to the establishment of chronicity of HIV infection is the ability of the virus to evade adequate control and elimination by both the cellular and humoral limbs of the immune system. There are a number of mechanisms whereby the virus accomplishes this evasion. Paramount among these is the establishment of a sustained level of replication associated with the generation of viral diversity via mutation and recombination. The selection of mutants that escape control by CD8+ cytolytic T lymphocytes (CTLs) is critical to the propagation and progression of HIV infection. The high rate of virus replication associated with inevitable mutations also contributes to the inability of antibody to neutralize the autologous virus and thus to contain the virus quasispecies present in an individual at any given time. Extensive analyses of sequential HIV isolates and host responses have demonstrated that viral escape from B cell and CD8+ T cell epitopes occurs early after infection and allows the virus to stay one step ahead of effective immune responses. Virus-specific CD8+ CTLs expand greatly during primary HIV infection, and likely represent the high-affinity responses that would be expected to be most efficient in eliminating virus-infected cells; however, the restriction is generally incomplete as viral replication persists at relatively high levels in the majority of individuals. In addition to viral escape from CTLs through high rates of mutation, it is thought that the initially strong response becomes qualitatively dysfunctional owing to the overwhelming immune activation resulting from persistent viral replication, similar to the exhaustion of CD8+ CTLs that has been reported in the murine model of lymphocytic choriomeningitis virus (LCMV) infection. Several studies have indicated that exhaustion of HIV-specific CD8+ T cells during prolonged immune activation is associated with expression of inhibitory receptors, such