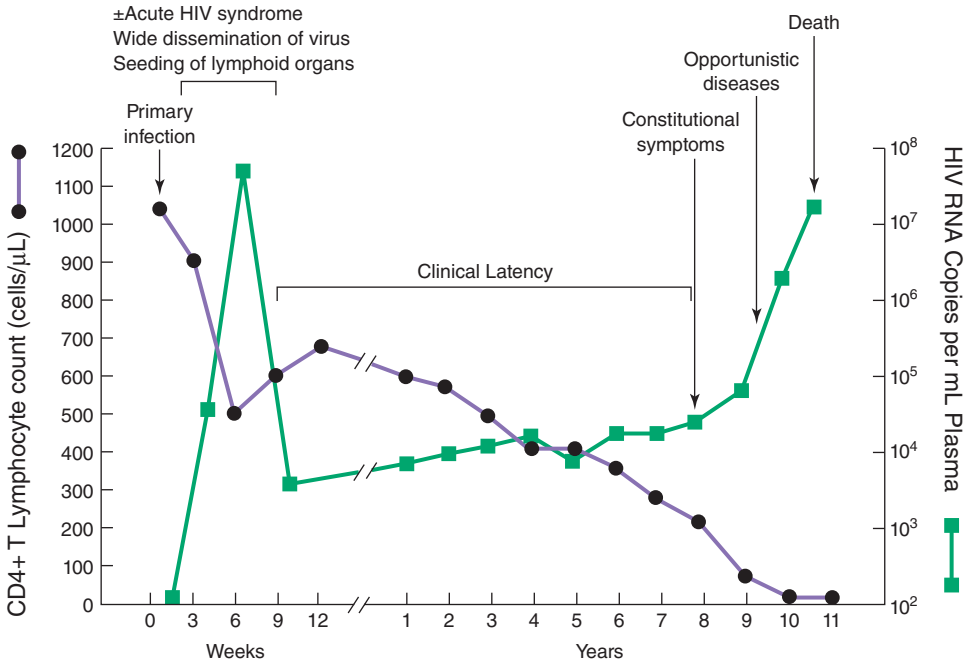

FIGURE 226-17 Typical course of an untreated HIV-infected individual. See text for detailed description. *(From G Pantaleo et al: N Engl J Med 328:327, 1993. Copyright 1993 Massachusetts Medical Society. All rights reserved.)*

with resulting cellular dysfunction. Patients with CD4+ T cell levels below certain thresholds are at high risk of developing a variety of opportunistic diseases, particularly the infections and neoplasms that are AIDS-defining illnesses. Some features of AIDS, such as Kaposi's sarcoma and certain neurologic abnormalities, cannot be explained completely by the immunodeficiency caused by HIV infection, since these complications may occur prior to the development of severe immunologic impairment.

The combination of viral pathogenic and immunopathogenic events that occurs during the course of HIV disease from the moment of initial (primary) infection through the development of advanced-stage disease is complex and varied. It is important to appreciate that the pathogenic mechanisms of HIV disease are multifactorial and multiphasic and are different at different stages of the disease. Therefore, it is essential to consider the typical clinical course of an untreated HIV-infected individual in order to more fully appreciate these pathogenic events (Fig. 226-17).

EARLY EVENTS IN HIV INFECTION: PRIMARY INFECTION AND INITIAL DISSEMINATION OF VIRUS

Using mucosal transmission as a model, the earliest events (within hours) that occur following exposure of HIV to the mucosal surface determine whether an infection will be established as well as the subsequent course of events following infection. Although the mucosal barrier is relatively effective in limiting access of HIV to susceptible targets in the lamina propria, the virus can cross the barrier by transport on Langerhans cells, an epidermal type of DC, just beneath the surface or through microscopic rents in the mucosa. Significant disruptions in the mucosal barrier as seen in ulcerative genital disease facilitate viral entry and increase the efficiency of infection. Virus then seeks susceptible targets, which are primarily CD4+ T cells that are spatially dispersed in the mucosa. This spatial dispersion of targets provides a significant obstacle to the establishment of infection. Such obstacles account for the low efficiency of sexual transmission of HIV (see "Sexual Transmission," above). Both "partially" resting CD4+ T cells and activated CD4+ T cells serve as early amplifiers of infection. Resting CD4+ T cells are more abundant; however, activated CD4+ T cells produce larger amounts of virus. In order for infection to become established, the basic reproductive rate (R_0) must become equal to or greater than 1, i.e., each infected cell would infect at least one other cell. Once infection is established, the virus replicates in lymphoid cells in the mucosa, the submucosa, and to some extent the lymphoreticular tissues that drain the gut tissues. For a variable period of time ranging from a few to several days, the virus cannot yet be detected in the plasma. This period is referred to as the "eclipse" phase of infection. As more virus is produced within several days to weeks, it is disseminated, first to the draining lymph nodes and then to other lymphoid compartments where it has easy access to dense concentrations of CD4+ T cell targets, allowing for a burst of high-level viremia that is readily detectable by currently available assays (Fig. 226-18). An important lymphoid organ, the gut-associated lymphoid tissue (GALT), is a major target of HIV infection and the location where large numbers of CD4+ T cells (usually memory cells) are infected and depleted, both by direct viral effects and by activation-associated apoptosis. Once virus replication reaches this threshold and virus is widely disseminated, infection is firmly established and the process is irreversible. It is important to point out that the initial infection of susceptible cells may vary somewhat with the route of infection. Virus that enters directly into the bloodstream via infected blood or blood products (i.e., transfusions, use of contaminated needles for injection drugs, sharp-object injuries, maternal-to-fetal transmission either intrapartum or perinatally, or sexual intercourse where there is enough trauma to cause bleeding) is likely first cleared from the circulation to the spleen and other lymphoid organs, where primary focal infections begin, followed by wider dissemination throughout other lymphoid tissues as described above.

It has been demonstrated that sexual transmission of HIV is the result of a single infectious event and that a viral genetic bottleneck exists for transmission. In this regard, certain characteristics of the HIV envelope glycoprotein have a major influence on transmission, at least in subtype A and C viruses. Transmitting viruses, often referred to as "founder viruses," are usually underrepresented in the circulating viremia of the transmitting partner and are less-diverged viruses with signature sequences including shorter V1–V2 loop sequences and fewer predicted N-linked glycosylation sites relative to the major circulating variants. These viruses are almost exclusively R5 strains and are usually sensitive to neutralization by antibody from the transmitting partner. Once replication proceeds in the newly infected partner, the founder virus diverges and accumulates glycosylation sites, becoming progressively more resistant to neutralization (Fig. 226-19).

The acute burst of viremia and wide dissemination of virus in primary HIV infection may be associated with an *acute HIV syndrome,* which occurs to varying degrees in ~50% of individuals with primary infection (see below). This syndrome is usually associated with high levels of viremia measured in millions of copies of HIV RNA per milliliter of plasma that last for several weeks. Acute mononucleosis-like symptoms are well correlated with the presence of viremia. Virtually all patients develop some degree of viremia during primary infection, which contributes to virus dissemination throughout the lymphoid tissue, even though they may remain asymptomatic or not recall experiencing symptoms. It appears that the initial level of plasma viremia in primary HIV infection does not necessarily determine the rate of disease progression; however, the set point of the level of steady-state plasma viremia after ~1 year does seem to correlate with the slope of disease progression in the untreated patient. The strikingly high levels of viremia observed in many patients with acute HIV infection is felt to be associated with a higher likelihood of transmission of the virus