For this reason, CD4+ cell counts and not viral load are the primary clinical measurements used to determine when to start antiretroviral therapy.

Chronic Infection: Phase of Clinical Latency

In the next, chronic phase of the disease, lymph nodes and the spleen are sites of continuous HIV replication and cell destruction (Fig. 6-41). During this period of the disease, few or no clinical manifestations of the HIV infection are present. Therefore, this phase of HIV disease is called the clinical latency period. Although the majority of peripheral blood T cells do not harbor the virus, destruction of CD4+ T cells within lymphoid tissues continues during this phase, and the number of circulating blood CD4+ T cells steadily declines. More than 90% of the body's approximately 10^{12} T cells are normally found in lymphoid tissues, and it is estimated that HIV destroys up to 1×10^9 to 2×10^9 CD4+ T cells every day. Early in the course of the disease, the body may continue to make new CD4+ T cells, and therefore CD4+ T cells can be replaced almost as quickly as they are destroyed. At this stage, up to 10% of CD4+ T cells in lymphoid organs may be infected, but the frequency of circulating CD4+ T cells that are infected at any one time may be less than 0.1% of the total CD4+ T cells. Eventually, over a period of years, the continuous cycle of virus infection, T-cell death, and new infection leads to a steady decline in the number of CD4+ T cells in the lymphoid tissues and the circulation.

Concomitant with this loss of CD4+ T cells, host defenses begin to wane, and the proportion of the surviving CD4+ cells infected with HIV increases, as does the viral burden per CD4+ cell. Not unexpectedly, HIV RNA levels increase as the host begins to lose the battle with the virus. How HIV escapes immune control is not entirely clear, but several mechanisms have been proposed. These include destruction of the CD4+ T cells that are critical for effective immunity, antigenic variation, and down-modulation of class I MHC molecules on infected cells so that viral antigens are not recognized by CD8+ CTLs. During this period the virus may evolve and switch from relying solely on CCR5 to enter its target cells to relying on either CXCR4 or both CCR5 and CXCR4. This coreceptor switch is associated with more rapid decline in CD4+ T-cell counts, presumably because of greater infection of T cells.

In this chronic phase of infection, patients are either asymptomatic or develop minor opportunistic infections, such as oral candidiasis (thrush), vaginal candidiasis, herpes zoster, and perhaps mycobacterial tuberculosis (the latter being particularly common in resource-poor regions such as sub-Saharan Africa). Autoimmune thrombocytopenia may also be noted (Chapter 14).

AIDS

The final phase is progression to AIDS, characterized by a breakdown of host defense, a dramatic increase in plasma virus, and severe, life-threatening clinical disease. Typically the patient presents with long-lasting fever (>1 month), fatigue, weight loss, and diarrhea. After a variable period, serious opportunistic infections, secondary neoplasms, or clinical neurologic disease (grouped under the rubric *AIDS indicator diseases*, discussed later) emerge, and the patient is said to have developed AIDS.

In the absence of treatment, most patients with HIV infection progress to AIDS after a chronic phase lasting from 7 to 10 years. Exceptions to this typical course are exemplified by rapid progressors and long-term nonprogressors. In *rapid progressors* the middle, chronic phase is telescoped to 2 to 3 years after primary infection. About 5% to 15% of infected individuals are *long-term nonprogressors*, defined as untreated HIV-1–infected individuals who remain asymptomatic for 10 years or more, with stable CD4+ T-cell counts and low levels of plasma viremia (usually less than 500 viral RNA copies per milliliter). Remarkably, about 1% of infected individuals have undetectable plasma virus (<50-75 RNA copies/mL); these have been called *elite controllers*. Individuals with such an uncommon clinical course have attracted great attention in the hope that studying them may shed light on host and viral factors that influence disease progression. Studies thus far indicate that this group is heterogeneous with respect to the variables that influence the course of the disease. In most cases, the viral isolates do not show qualitative abnormalities, suggesting that the course of the disease cannot be attributed to a "wimpy" virus. In all cases there is evidence of a vigorous anti-HIV immune response, but the immune correlates of protection are still unknown. Some of these individuals have high levels of HIV-specific CD4+ and CD8+ T-cell responses, and these levels are maintained over the course of infection. The inheritance of particular HLA alleles seems to correlate with resistance to disease progression, perhaps reflecting the ability to mount antiviral T cell responses. Further studies, it is hoped, will provide the answers to this and other questions critical to understanding disease progression.

Clinical Features of AIDS

The clinical manifestations of HIV infection can be readily surmised from the foregoing discussion. They range from a mild acute illness to severe disease. Because the salient clinical features of the acute early and chronic middle phases of HIV infection were described earlier, here we summarize the clinical manifestations of the terminal phase, AIDS. At the outset it should be pointed out that the clinical manifestations and opportunistic infections associated with HIV infection may differ in different parts of the world. Also, the course of the disease has been greatly modified by new antiretroviral therapies, and many complications that were once devastating are now infrequent.

In the United States, the typical adult patient with AIDS presents with fever, weight loss, diarrhea, generalized lymphadenopathy, multiple opportunistic infections, neurologic disease, and, in many cases, secondary neoplasms. The infections and neoplasms listed in Table 6-16 are included in the surveillance definition of AIDS.

Opportunistic Infections. **Opportunistic infections account for the majority of deaths in untreated patients with AIDS**. Many of these infections represent reactivation of latent infections, which are normally kept in check by a robust immune system but are not completely eradicated because the infectious agents have evolved to coexist with their hosts. The actual frequency of infections varies in different regions of the world, and has been markedly reduced by the advent of highly active antiretroviral therapy (HAART), which relies on a combination of three