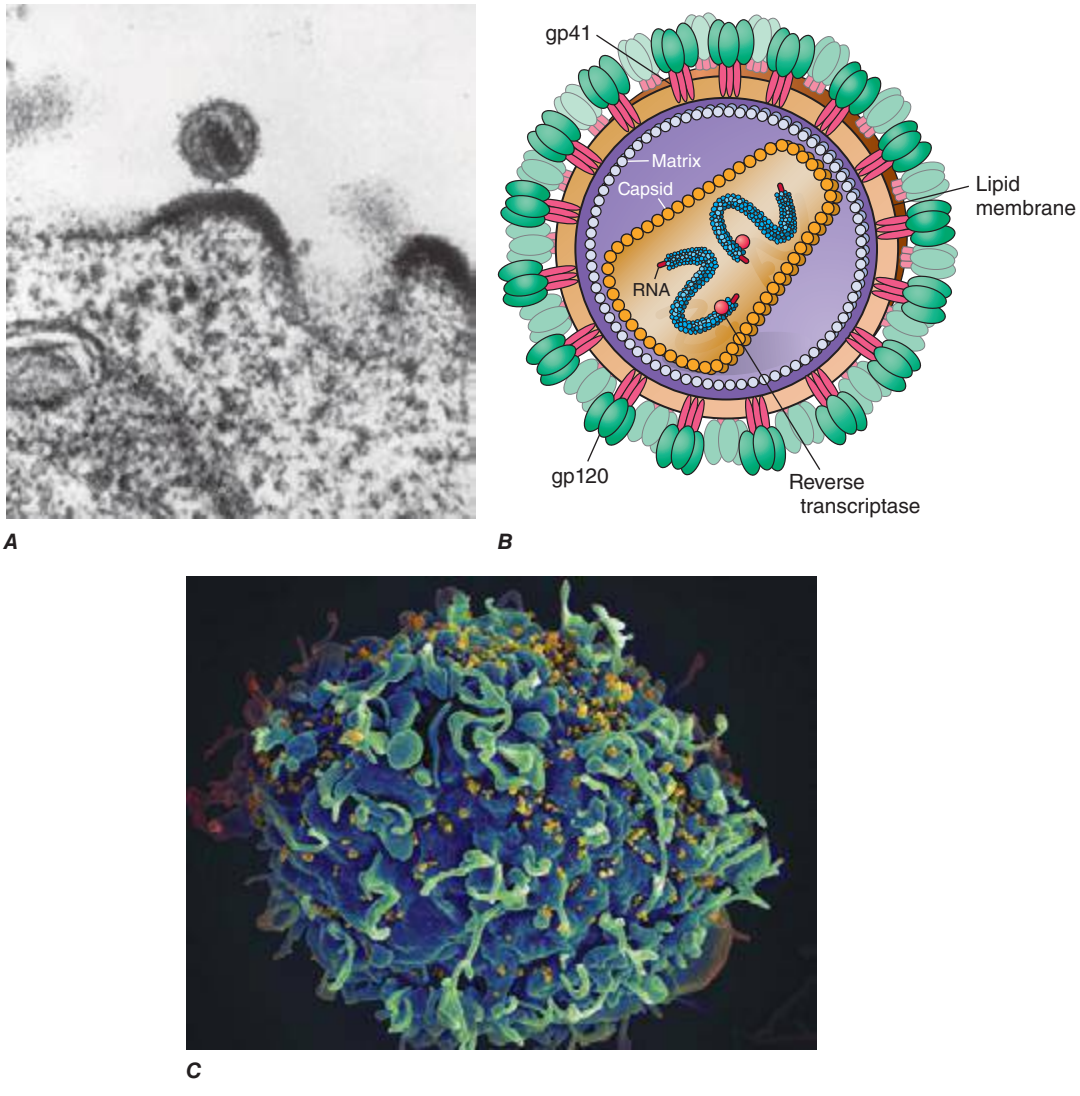

FIGURE 226-2 ***A.*** Electron micrograph of HIV. Figure illustrates a typical virion following budding from the surface of a CD4+ T lymphocyte, together with two additional incomplete virions in the process of budding from the cell membrane. ***B.*** Structure of HIV-1, including the gp120 envelope, gp41 transmembrane components of the envelope, genomic RNA, enzyme reverse transcriptase, p18(17) inner membrane (matrix), and p24 core protein (capsid). *(Copyright by George V. Kelvin.) (Adapted from RC Gallo: Sci Am 256:46, 1987.)* ***C.*** Scanning electron micrograph of HIV-1 virions infecting a human CD4+ T lymphocyte. The original photograph was imaged at 8000× magnification. *(Courtesy of Elizabeth R. Fischer, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases; with permission.)*

the cytoplasm to reach the nucleus, the viral reverse transcriptase enzyme catalyzes the reverse transcription of the genomic RNA into DNA, resulting in the formation of double-stranded proviral HIV-DNA. At the preintegration steps of the replication cycle, the viral genome is vulnerable to cellular factors that can block the progression of infection. In particular, the cytoplasmic tripartite motif-containing protein 5-α (TRIM5-α) is a host restriction factor that interacts with retroviral capsids (Fig. 226-3). Although the exact mechanisms of action of TRIM5-α remain unclear, the HIV-1 capsid is not recognized by the human form of TRIM5-α. Thus this host factor is not effective in restricting HIV-1 replication in human cells. The apolipoprotein B mRNA editing enzyme (catalytic polypeptide-like 3 [APOBEC3]) family of cellular proteins also inhibits progression of virus infection after virus has entered the cell and prior to entering the nucleus (Fig. 226-3). APOBEC3 proteins, which are incorporated into virions and released into the cytoplasm of a newly infected cell, bind to the single minus-strand DNA intermediate and deaminate viral cytidine, causing hypermutation of retroviral genomes. HIV has evolved a powerful strategy to protect itself from APOBEC. The viral protein Vif targets APOBEC3 for proteasomal degradation.

With activation of the cell, the viral DNA accesses the nuclear pore and is exported from the cytoplasm to the nucleus, where it is integrated into the host cell chromosomes through the action of another virally encoded enzyme, *integrase* (Fig. 226-3). HIV provirus (DNA) integrates into the nuclear DNA preferentially within introns of active genes and regional hotspots. This provirus may remain transcriptionally inactive (latent) or it may manifest varying levels of gene expression, up to active production of virus.

Cellular activation plays an important role in the replication cycle of HIV and is critical to the pathogenesis of HIV disease (see "Pathogenesis and Pathophysiology," below). Following initial binding, fusion, and internalization of the nucleic acid contents of virions into the target cell, incompletely reverse-transcribed DNA intermediates are labile in quiescent cells and do not integrate efficiently into the host cell genome unless cellular activation occurs shortly after infection. Furthermore, some degree of activation of the host cell is required for the initiation of transcription of the integrated proviral DNA into either genomic RNA or mRNA. This latter process may not necessarily be associated with the detectable expression of the classic cell-surface markers of activation. In this regard, activation of HIV expression from the latent state depends on the interaction of a number of cellular and viral factors. Following transcription, HIV mRNA is translated into proteins that undergo modification through glycosylation, myristoylation, phosphorylation,