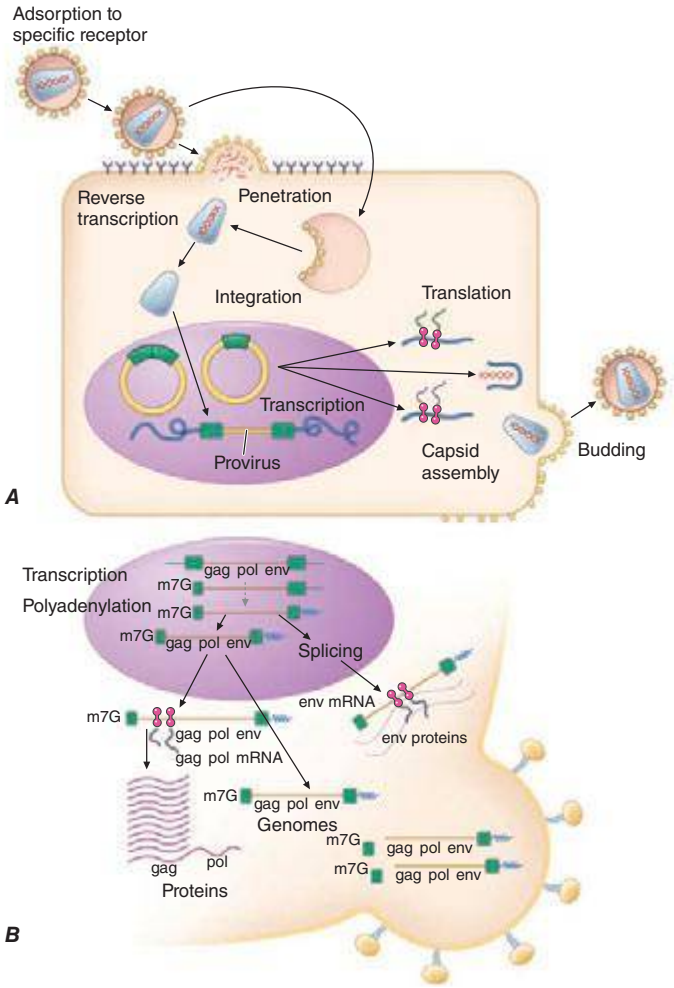

FIGURE 225e-1 **The life cycle of retroviruses. *A.*** Overview of virus replication. The retrovirus enters a target cell by binding to a specific cell-surface receptor; once the virus is internalized, its RNA is released from the nucleocapsid and is reverse-transcribed into proviral DNA. The provirus is inserted into the genome and then transcribed into RNA; the RNA is translated; and virions assemble and are extruded from the cell membrane by budding. ***B.*** Overview of retroviral gene expression. The provirus is transcribed, capped, and polyadenylated. Viral RNA molecules then have one of three fates: they are exported to the cytoplasm, where they are packaged as the viral RNA in infectious viral particles; they are spliced to form the message for the envelope polyprotein; or they are translated into Gag and Pol proteins. Most of the messages for the Pol protein fail to initiate Pol translation because of a stop codon before its initiation; however, in a fraction of the messages, the stop codon is missed and the Pol proteins are translated. *(Modified from JM Coffin, in BN Fields, DM Knipe [eds]: Fields Virology. New York, Raven, 1990; with permission.)*

HTLVs have a region between *env* and the 3′ LTR that encodes several proteins and transcripts in overlapping reading frames (Fig. 225e-2). Tax is a 40-kDa protein that does not bind to DNA but induces the expression of host cell transcription factors that alter host cell gene expression and is capable of inducing cell transformation under certain circumstances. Rex is a 27-kDa protein that regulates the expression of viral mRNAs. Other transcripts from this region (p12, p13, p30) tend to restrict expression of viral genes and diminish the immunogenicity of infected cells. The protein of *HBZ*, a product of the complementary proviral DNA strand, interacts with many cellular transcription factors and signaling proteins. It stimulates proliferation of infected cells and is the only viral product universally expressed in HTLV-1-infected tumor cells. These proteins are produced from messages that are similar but that are spliced differently from overlapping but distinct exons.

The lentiviruses in general, and HIV-1 and -2 in particular, contain a larger genome than other pathogenic retroviruses. They contain an untranslated region between *pol* and *env* that encodes portions of several proteins, varying with the reading frame into which the mRNA is spliced. Tat is a 14-kDa protein that augments the expression of virus from the LTR. The Rev protein of HIV-1, similar to the Rex protein of HTLV, regulates RNA splicing and/or RNA transport. The Nef protein downregulates CD4, the cellular receptor for HIV; alters host T cell–activation pathways; and enhances viral infectivity. The Vif protein is necessary for the proper assembly of the HIV nucleoprotein core in many types of cells; without Vif, proviral DNA is not efficiently produced in these infected cells. In addition, the Vif protein targets APOBEC (apolipoprotein B mRNA-editing enzyme catalytic polypeptide, a cytidine deaminase that mutates the viral sequence) for proteasomal degradation, thus blocking its virus-suppressing effect. Vpr, Vpu (HIV-1 only), and Vpx (HIV-2 only) are viral proteins encoded by translation of the same message in different reading frames. As noted above, oncogenic retroviruses depend on cell proliferation for their replication; lentiviruses can infect nondividing cells, largely through effects mediated by Vpr. Vpr facilitates transport of the provirus into the nucleus and can induce other cellular changes, such as G_2 growth arrest and differentiation of some target cells. Vpx is structurally related to Vpr, but its functions are not fully defined. Vpu promotes the degradation of CD4 in the endoplasmic reticulum and stimulates the release of virions from infected cells.

Retroviruses can be either exogenously acquired (by infection with an infected cell or a free virion capable of replication) or transmitted in the germline as endogenous virus. Endogenous retroviruses are often replication defective. The human genome contains endogenous retroviral sequences, but there are no known replication-competent endogenous retroviruses in humans.

In general, viruses that contain only the *gag, pol*, and *env* genes either are not pathogenic or take a long time to induce disease; these observations indicate the importance of the other regulatory genes in viral disease pathogenesis. The pathogenesis of neoplastic transformation by retroviruses relies on the chance integration of the provirus at a spot in the genome resulting in the expression of a cellular gene (protooncogene) that becomes transforming by virtue of its unregulated expression. For example, avian leukosis virus causes B cell leukemia by inducing the expression of *myc*. Some retroviruses possess captured and altered cellular genes near their integration site, and these viral oncogenes can transform the infected host cell. Viruses that have oncogenes often have lost a portion of their genome that is required for replication. Such viruses need helper viruses to reproduce, a feature that may explain why these acute transforming retroviruses are rare in nature. All human retroviruses identified to date are exogenous and are not acutely transforming (i.e., they lack a transforming oncogene).

These remarkable properties of retroviruses have led to experimental efforts to use them as vectors to insert specific genes into particular cell types, a process known as *gene therapy* or *gene transfer*. The process could be used to repair a genetic defect or to introduce a new property that could be used therapeutically; for example, a gene (e.g., thymidine kinase) that would make a tumor cell susceptible to killing by a drug (e.g., ganciclovir) could be inserted. One source of concern about the use of retroviral vectors in humans is that replication-competent viruses might rescue endogenous retroviral replication, with unpredictable results. This concern is not merely hypothetical: the detection of proteins encoded by endogenous retroviral sequences on the surface of cancer cells implies that the genetic events leading to the cancer were able to activate the synthesis of these usually silent genes.

HUMAN T CELL LYMPHOTROPIC VIRUS

HTLV-1 was isolated in 1980 from a T cell lymphoma cell line from a patient originally thought to have cutaneous T cell lymphoma. Later it became clear that the patient had a distinct form of lymphoma (originally reported in Japan) called *adult T cell leukemia/lymphoma* (ATL). Serologic data have determined that HTLV-1 is the cause of at least two important diseases: ATL and tropical spastic paraparesis, also