**TABLE 226-2 CDC HIV INFECTION STAGES 1–3 BASED ON AGE-SPECIFIC CD4+ T LYMPHOCYTE COUNT OR CD4+ T LYMPHOCYTE PERCENTAGE OF TOTAL LYMPHOCYTES[a]**

| | Age on Date of CD4 T+ Lymphocyte Test | | | | | |
|---|---|---|---|---|---|---|
| | <1 Year | | 1–5 Years | | 6 Years through Adult | |
| Stage[a] | Cells/μL | % | Cells/μL | % | Cells/μL | % |
| 1 | ≥1,500 | ≥34 | ≥1,000 | ≥30 | ≥500 | ≥26 |
| 2 | 750–1,499 | 26–33 | 500–999 | 22–29 | 200–499 | 14–25 |
| 3 | <750 | <26 | <500 | <22 | <200 | <14 |

[a]The stage is based primarily on the CD4+ T-lymphocyte count; the CD4+ T-lymphocyte count takes precedence over the CD4 T-lymphocyte percentage, and the percentage is considered only if the count is missing.

***Source:*** MMWR 63(No. RR-03), April 11, 2014.

on whether the patient fulfills the strict definition of AIDS, but should view HIV disease as a spectrum ranging from primary infection, with or without the acute syndrome, to the asymptomatic stage, to advanced stages associated with opportunistic diseases (see "Pathophysiology and Pathogenesis," below).

## ETIOLOGIC AGENT

HIV is the etiologic agent of AIDS; it belongs to the family of human retroviruses (Retroviridae) and the subfamily of lentiviruses (Chap. 225e). Nononcogenic lentiviruses cause disease in other animal species, including sheep, horses, goats, cattle, cats, and monkeys. The four retroviruses known to cause human disease belong to two distinct groups: the human T lymphotropic viruses (HTLV)-1 and HTLV-2, which are transforming retroviruses; and the human immunodeficiency viruses, HIV-1 and HIV-2, which cause cytopathic effects either directly or indirectly (Chap. 225e). The most common cause of HIV disease throughout the world, and certainly in the United States, is HIV-1, which comprises several subtypes with different geographic distributions (see "Molecular Heterogeneity of HIV-1," below). HIV-2 was first identified in 1986 in West African patients and was originally confined to West Africa. However, a number of cases that generally can be traced to West Africa or to sexual contacts with West Africans have been identified throughout the world. The currently defined groups of HIV-1 (M, N, O, P) and the HIV-2 groups A through H each are likely derived from a separate transfer to humans from a nonhuman primate reservoir. HIV-1 viruses likely came from chimpanzees and/or gorillas, and HIV-2 from sooty mangabeys. The AIDS pandemic is primarily caused by the HIV-1 M group viruses. Although HIV-1 group O and HIV-2 viruses have been found in numerous countries, including those in the developed world, they have caused much more localized epidemics. The taxonomic relationship between primate lentiviruses is shown in Fig. 226-1.

## MORPHOLOGY OF HIV

Electron microscopy shows that the HIV virion is an icosahedral structure (Fig. 226-2) containing numerous external spikes formed by the two major envelope proteins, the external gp120 and the transmembrane gp41. The HIV envelope exists as a trimeric heterodimer. The virion buds from the surface of the infected cell and incorporates a variety of host proteins into its lipid bilayer. The structure of HIV-1 is schematically diagrammed in Fig. 226-2*B*.

## REPLICATION CYCLE OF HIV

HIV is an RNA virus whose hallmark is the reverse transcription of its genomic RNA to DNA by the enzyme *reverse transcriptase*. The replication cycle of HIV begins with the high-affinity binding of the gp120 protein via a portion of its V1 region near the N terminus to its receptor on the host cell surface, the CD4 molecule (Fig. 226-3). The CD4 molecule is a 55-kDa protein found predominantly on a subset of T lymphocytes that are responsible for helper function in the immune system (Chap. 372e). It is also expressed on the surface of monocytes/macrophages and dendritic/Langerhans cells. Once it binds to CD4, the gp120 protein undergoes a conformational change that facilitates binding to one of two major co-receptors. The two major co-receptors for HIV-1 are CCR5 and CXCR4. Both receptors belong to the family of seven-transmembrane-domain G protein–coupled cellular receptors, and the use of one or the other or both receptors by the virus for entry into the cell is an important determinant of the cellular tropism of the virus. Certain dendritic cells (DCs) express a diversity of C-type lectin receptors on their surface—one of which is called *DC-SIGN*—that also bind with high affinity to the HIV gp120 envelope protein, allowing DCs to facilitate virus spread to CD4+ T cells. Following binding of the envelope protein to the CD4 molecule associated with the above-mentioned conformational change in the viral envelope gp120, fusion with the host cell membrane occurs via the newly exposed gp41 molecule penetrating the plasma membrane of the target cell and then coiling upon itself to bring the virion and target cell together (Fig. 226-4). Following fusion, uncoating of the capsid protein shell is initiated—a step that facilitates reverse transcription and leads to formation of the preintegration complex, composed of viral RNA, enzymes, and accessory proteins and surrounded by capsid and matrix proteins (Fig. 226-3). As the preintegration complex traverses

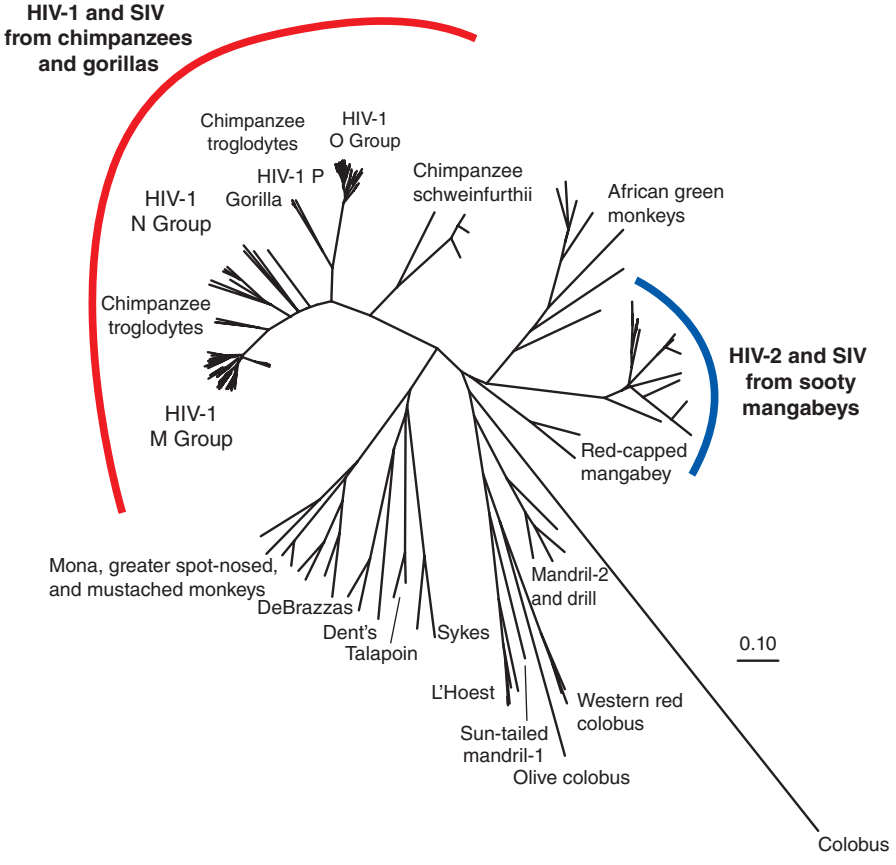


**FIGURE 226-1 A phylogenetic tree based on the complete genomes of primate immunodeficiency viruses.** The scale (0.10) indicates a 10% difference at the nucleotide level. *(Prepared by Brian Foley, PhD, of the HIV Sequence Database, Theoretical Biology and Biophysics Group, Los Alamos National Laboratory; additional information at www.hiv.lanl.gov/content/sequence/HelpDocs/subtypes.html.)*