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treatment, Native Americans (including Alaska Natives), morbidly obese individuals, and residents of nursing homes or chronic-care facilities. This list resembles that of candidates whose vaccination is a high priority (Table 206-2). Use of neuraminidase inhibitors should be considered in selected high-risk cases despite a history of vaccination.

The available neuraminidase inhibitors are oral oseltamivir, nasal-spray zanamivir, and intravenous peramivir. Oseltamivir, which is most widely used, is an orally absorbed drug that is con verted to its active component, oseltamivir carboxylate, in the liver. Gastrointestinal symptoms, especially nausea, may accompany the administration of oseltamivir. Because zanamivir is not orally bio available, it is given as an inhaled dry powder dispersed through a Diskhaler device. The usual duration of therapy with either oral oseltamivir or intranasal zanamivir is 5 days, with twice-a-day dosing. Oseltami vir is preferred for treatment of pregnant women and is approved for treatment at any age, beginning at 14 days of life in infants. Poor oral intake or absorption is a contraindication to the use of oseltamivir, although this drug can also be given by oro/nasal tube. Asthma and COPD are relative contraindications to the use of intranasal zanamivir; this agent is approved for treatment in persons 7 years and older. For hospitalized patients with suspected or confirmed influenza, initiation of antiviral treatment with oral or enterically administered oseltamivir is recommended as soon as possible. For patients who cannot tolerate or absorb oral or enterically administered oseltamivir, the use of a single infusion of intravenous peramivir should be considered. Peramivir is licensed for individuals ≥2 years of age. The most current recommendations and details on influenza antiviral drug use and release are available through the CDC (https://www.cdc.gov/flu/professionals/antivirals/ summary-clinicians.htm). PART 5 Infectious Diseases In 2018, a first-in-class compound, baloxavir marboxil (XOFLUZA), was approved by the FDA for persons 12 years and older for prophylaxis or treatment of uncomplicated influenza within 2 days of onset of illness. Baloxavir inhibits cap-dependent endonuclease, has activity against influenza A and B, and is a singledose formulation. In clinical studies, if given within 48 h of symp toms, baloxavir decreased symptom duration, viral shedding, and antibiotic use in healthy individuals with uncomplicated influenza. However, development of resistance is a concern, with 2–10% of the trial participants who received baloxavir showing viral escape with reduced drug susceptibility. CDC does not recommend use of bal oxavir in pregnant women, breastfeeding mothers, outpatients with complicated or progressive illness, severely immunosuppressed people, or hospitalized patients because of lack of information on use of baloxavir for these groups. Other critical aspects of treatment include maintenance of fluid and electrolyte balance, oxygen supplementation, fever control with nonsteroidal anti-inflammatory drugs, and treatment of suspected secondary bacterial complications with antibiotics. Appropriate respiratory isolation of patients should be practiced in accordance with local hospital guidelines. ■ ■FURTHER READING

Barry JM: The Great Influenza: The Story of the Deadliest Pandemic in History. New York, Penguin Books, 2005. Chung JR: Effects of influenza vaccination in the United States during the 2018–2019 influenza season. Clin Infect Dis 71:e368, 2020. Erbelding EJ: A universal influenza vaccine: The strategic plan for the National Institute of Allergy and Infectious Diseases. J Infect Dis 218:347, 2018. Fineberg HV: Pandemic preparedness and response—lessons from the H1N1 influenza of 2009. N Engl J Med 370:1335, 2014. Kash JC, Taubenberger JK: The role of viral, host, and secondary bacterial factors in influenza pathogenesis. Am J Pathol 185:1528, 2015. Osterholm MT et al: Efficacy and effectiveness of influenza vaccines: A systemic review and meta-analysis. Lancet Infect Dis 12:36, 2012.

Treanor JJ: Influenza vaccination. N Engl J Med 375:1261, 2016. Uyeki TM et al: Influenza. Lancet 400:693, 2022. Watanabe T et al: 1918 influenza virus hemagglutinin (HA) and the viral RNA polymerase complex enhance viral pathogenicity, but only HA induces aberrant host responses in mice. J Virol 87:5239, 2013. Wright PF et al: Correlates of immunity to influenza as determined by challenge of children with live, attenuated influenza vaccine. Open Forum Infect Dis 3:108, 2016.

Section 14 Infections Due to Human Immunodeficiency Virus and Other Human Retroviruses Dan L. Longo, Anthony S. Fauci

The Human

Retroviruses The retroviruses, which make up a large family (Retroviridae), infect mainly vertebrates. These viruses have a unique replication cycle whereby their genetic information is encoded by RNA rather than DNA. Retroviruses contain an RNA-dependent DNA polymerase (a reverse transcriptase) that directs the synthesis of a DNA form of the viral genome after infection of a host cell. The designation retro virus denotes that information in the form of RNA is transcribed into DNA in the host cell—a sequence that overturned a central dogma of molecular biology: that information passes unidirectionally from DNA to RNA to protein. The observation that RNA was the source of genetic information in the causative agents of certain animal tumors led to a number of paradigm-shifting biologic insights regarding not only the direction of genetic information passage but also the viral etiology of certain cancers and the concept of oncogenes as normal host genes scavenged and altered by a viral vector. The family Retroviridae includes seven subfamilies (Table 207-1). Members of two of the families infect humans with pathologic con sequences: the deltaretroviruses, of which human T-cell lymphotropic virus (HTLV) type 1 is the most important in humans; and the lentivi ruses, of which HIV is the most important in humans. The wide variety of interactions of a retrovirus with its host range from completely benign events (e.g., silent carriage of endogenous retroviral sequences in the germline genome of many animal species) to rapidly fatal infections (e.g., exogenous infection with an onco genic virus such as Rous sarcoma virus in chickens). The ability of TABLE 207-1 Classification of Retroviruses: The Family Retroviridae GENUS EXAMPLE(S) FEATURE Alpharetrovirus Rous sarcoma virus Contains src oncogene Betaretrovirus Mouse mammary tumor virus Exogenous or endogenous Gammaretrovirus Abelson murine leukemia virus Contains abl oncogene Deltaretrovirus HTLV-1 Causes T-cell lymphoma and neurologic disease Epsilonretrovirus Walleye dermal sarcoma virus Not known to be pathogenic in humans Lentivirus HIV-1, HIV-2 Causes AIDS Spumavirus Simian foamy virus Not known to be pathogenic in humans

retroviruses to acquire and alter the structure and function of host cell genetic sequences has revolutionized our understanding of molecular carcinogenesis. The viruses can insert into the germline genome of the host cell and behave as a transposable or movable genetic element. They can activate or inactivate genes near the site of integration into the genome. They can rapidly alter their own genome by recombina tion and mutation under selective environmental stimuli. Most human viral diseases occur as a consequence of tissue destruction either directly by the virus itself or indirectly by the host's response to the virus. Although these mechanisms are opera tive in retroviral infections, retroviruses have additional mechanisms of inducing disease, including the malignant transformation of an infected cell and the induction of an immunodeficiency state through selective destruction or dysfunction of immune-competent cells that renders the host susceptible to opportunistic diseases (infections and neoplasms; Chap. 208). In addition to their role as acquired causes of infections, retroviruses and lentiviruses are employed as tools to alter gene expression in target cells. Gene therapy applications are expanding, and in addition to the benefits they bestow, a new set of viral-mediated adverse events have emerged. STRUCTURE AND LIFE CYCLE All retroviruses are similar in structure, genome organization, and mode of replication. Retroviruses are 70–130 nm in diameter and have a lipid-containing envelope surrounding an icosahedral capsid with a dense inner core. The core contains two identical copies of the singlestrand RNA genome. The RNA molecules are 8–10 kb long and are complexed with reverse transcriptase and tRNA. Other viral proteins, such as integrase, are also components of the virion particle. The RNA has features usually found in mRNA: a cap site at the 5′ end of the mol ecule, which is important in the initiation of mRNA translation, and a polyadenylation site at the 3′ end, which influences mRNA turnover (i.e., messages with shorter polyA tails turn over faster than messages with longer polyA tails). However, the retroviral RNA is not translated; instead, it is transcribed into DNA. The DNA form of the retroviral genome is called a provirus. The replication cycle of retroviruses proceeds in two phases (Fig. 207-1). In the first phase, the virus enters the cytoplasm after binding to one or more specific cell-surface receptors; the viral RNA and reverse transcriptase synthesize a double-strand DNA version of the RNA template; and the provirus moves into the nucleus and integrates into the host cell genome. This proviral integration is per manent. Although some animal retroviruses integrate into a single specific site of the host genome in every infected cell, the human ret roviruses integrate randomly. This first phase of replication depends entirely on gene products in the virus. The second phase includes the synthesis and processing of viral genomes, mRNAs, and proteins using host cell machinery, often under the influence of viral gene products. Virions are assembled and released from the cell by budding from the membrane; host cell membrane proteins are frequently incorporated into the envelope of the virus. Proviral integration occurs during the S-phase of the cell cycle; thus, in general, nondividing cells are resistant to retroviral infection. Only the lentiviruses are able to infect nondivid ing cells. Once a host cell is infected, it is infected for the life of the cell. Retroviral genomes include both coding and noncoding sequences (Fig. 207-2). In general, noncoding sequences are important rec ognition signals for DNA or RNA synthesis or processing events and are located in the 5′ and 3′ terminal regions of the genome. All retroviral genomes are terminally redundant, containing identical sequences called long terminal repeats (LTRs). The ends of the retrovi ral RNA genome differ slightly in sequence from the integrated retro viral DNA. In the latter, the LTR sequences are repeated in both the 5′ and the 3′ terminus of the virus. The LTRs contain sequences involved in initiating the expression of the viral proteins, the integration of the provirus, and the polyadenylation of viral RNAs. The primer binding site, which is critical for the initiation of reverse transcription, and the viral packaging sequences are located outside the LTR sequences. The coding regions include the gag (group-specific antigen, core protein),

Adsorption to specific receptor Penetration Reverse transcription Integration Translation Transcription Capsid assembly Budding Provirus A gag pol env Transcription m7G Polyadenylation m7G m7G gag pol env Splicing env mRNA m7G gag pol env env proteins gag pol mRNA CHAPTER 207 m7G gag pol env Genomes m7G gag gag pol env m7G pol gag pol env Proteins The Human Retroviruses B FIGURE 207-1 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 reversetranscribed 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. (Reproduced with permission from JM Coffin, in BN Fields, DM Knipe [eds]: Fields Virology. New York, Raven, 1990.) pol (RNA-dependent DNA polymerase), and env (envelope) genes. The gag gene encodes a precursor polyprotein that is cleaved to form three to five capsid proteins; a fraction of the Gag precursor proteins also contain a protease responsible for cleaving the Gag and Pol polyprot eins. A Gag-Pol polyprotein gives rise to the protease that is responsible for cleaving the Gag-Pol polyprotein. The pol gene encodes three pro teins: the reverse transcriptase, the integrase, and the protease. The reverse transcriptase copies the viral RNA into the double-strand DNA provirus, which inserts itself into the host cell DNA via the action of integrase. The protease cleaves the Gag-Pol polyprotein into smaller protein products. The env gene encodes the envelope glycoproteins: one protein that binds to specific surface receptors and determines what cell types can be infected and a smaller transmembrane protein that anchors the complex to the envelope. Fig. 207-3 shows how the retroviral gene products make up the virus structure. HTLVs have a region between env and the 3′ LTR that encodes sev eral proteins and transcripts in overlapping reading frames (Fig. 207-2). Tax is a 40-kDa protein that does not bind to DNA but induces the expres sion of host cell transcription factors that alter host cell gene expression

LTR MuLV GAG POL LTR MA CA NC RT PR p14 p95 HTLV-I,II p19 p24 p15 GAG LTR MA CA NC p17 p24 p7 HIV-1 RT IN p10 POL p66 p32 GAG PR LTR HIV-2 GAG POL FIGURE 207-2 Genomic structure of retroviruses. The murine leukemia virus MuLV has the typical three structural genes: gag, pol, and env. The gag region gives rise to three proteins: matrix (MA), capsid (CA), and nucleic acid–binding (NC) proteins. The pol region encodes both a protease (PR) responsible for cleaving the viral polyproteins and a reverse transcriptase (RT). In addition, HIV pol encodes an integrase (IN). The env region encodes a surface protein (SU) and a small transmembrane protein (TM). The human retroviruses have additional gene products translated in each of the three possible reading frames. HTLV-1 and HTLV-2 have tax and rex genes with exons on either side of the env gene. HIV-1 and HIV-2 have six accessory gene products: tat, rev, vif, nef, vpr, and either vpu (in HIV-1) or vpx (in HIV-2). The genes for these proteins are located mainly between the pol and env genes. GP, glycoprotein; HBZ, HTLV-1 basic leucine zipper domain–containing protein; LTR, long terminal repeat. PART 5 Infectious Diseases and is capable of inducing cell transformation under certain circum stances. Rex is a 27-kDa protein that regulates the expression of viral mRNAs. Other transcripts from this region (p12, p13, and 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. HTLV-I HIV-1 SU gp46 gp120 TM p21 gp41 NC p15 p7 PR p14 p10 RT p95 p66 IN –– p32 MA p19 p17 CA p24 p24 RNA 9kb 10kb FIGURE 207-3 Schematic structure of human retroviruses. The surface glycoprotein (SU) is responsible for binding to receptors of host cells. The transmembrane protein (TM) anchors SU to the virus. NC is a nucleic acid–binding protein found in association with the viral RNA. A protease (PR) cleaves the polyproteins encoded by the gag, pol, and env genes into their functional components. RT is reverse transcriptase, and IN is an integrase present in some retroviruses (e.g., HIV-1) that facilitates insertion of the provirus into the host genome. The matrix protein (MA) is a Gag protein closely associated with the lipid of the envelope. The capsid protein (CA) forms the major internal structure of the virus, the core shell.

ENV LTR LTR GP46 p21 SU TM TAX, p40 REX, p27 POL p30 p12 p13 HBZ p23 VIF VPR VPU NEF p27 LTR GP120 GP41 SU ENV TM p15 p16 TAT, p14 REV, p19 ENV NEF LTR VIF VPX VPR TAT REV 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 polypep tide, a cytidine deaminase that mutates the viral sequence) for pro teasomal 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 G2 growth arrest and differentiation of some target cells. Vpx is structurally related to Vpr, but its functions are not fully defined. Vpu promotes the degra dation 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 transforma tion 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 unregu lated expression. For example, avian leukosis virus causes B-cell leu kemia 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 experimen tal 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 unpre dictable 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. Lentiviruses are being widely examined as gene therapy tools to cor rect genetic defects (e.g., thalassemia, sickle cell disease, hemophilia) and to generate effective cancer therapies (e.g., chimeric antigen recep tor T cells, natural killer [NK] cells, and macrophages). The success of these therapies has been variable. Gene therapy interventions are often not permanent as expression of the introduced gene wanes over time. The random insertion of genetic material into multiple sites of the genome in some cells has resulted in insertional mutagenesis and the generation of novel malignancies. While gene therapies are overall only rarely associated with second malignancies, the expectation is that the use of directed insertion of genetic material into a specific site in the genome (e.g., with CRISPR technology) will reduce the risk. HUMAN T-CELL LYMPHOTROPIC VIRUS HTLV-1, a delta retrovirus, was isolated in 1980 from a T-cell lym phoma cell line from a patient originally thought to have cutaneous T-cell lymphoma. Later it became clear that the patient had a dis tinct 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 called HTLV-1-associated myelopathy (HAM). HTLV-1 may also play a role in infective dermatitis, arthritis, uveitis, and Sjögren’s syndrome. Two years after the isolation of HTLV-1, HTLV-2 was isolated from a patient with an unusual form of hairy cell leukemia that affected T cells. Epidemiologic studies of HTLV-2 failed to reveal a consistent disease association. Similarly, HTLV-3 and HTLV-4 have been identified but have no known disease association. ■ ■BIOLOGY AND MOLECULAR BIOLOGY Because the biology of HTLV-1 and that of HTLV-2 are similar, the following discussion will focus on HTLV-1. Human glucose transporter protein 1 (GLUT-1) functions as a receptor for HTLV-1, probably acting together with neuropilin-1 (NRP1) and heparan sulfate proteoglycans. The heparan sulfate proteoglycans do not appear to be involved with HTLV-2 cell entry. Generally, only T cells are productively infected, but infection of B cells and other cell types is occasionally detected. The most common outcome of HTLV-1 infection is latent carriage of randomly integrated provirus in CD4+ T cells. HTLV-1 does not contain an oncogene and does not insert into a unique site in the genome. Indeed, most infected cells express no viral gene products. The only viral gene product that is routinely expressed in tumor cells transformed by HTLV-1 in vivo is hbz. The tax gene is thought to be critical to the transformation process but is not expressed in the tumor cells of many ATL patients, possibly because of the immunogenicity of tax-expressing cells. Cells

transformed in vitro, by contrast, actively transcribe HTLV-1 RNA and produce infectious virions. Most HTLV-1-transformed cell lines are the result of the infection of a normal host T cell in vitro. It is difficult to establish cell lines derived from authentic ATL cells.

Although tax does not itself bind to DNA, it is located in the nucleus and induces the expression of a wide range of host cell gene products, including transcription factors (especially c-rel/nuclear factor κB [NF-κB], ets-1 and -2, and members of the fos/jun family), cytokines (e.g., interleukin [IL] 2, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor), membrane proteins and receptors (major histocompatibility [MHC] molecules and IL-2 receptor α), and chromatin remodeling complexes. The genes activated by tax are gen erally controlled by transcription factors of the c-rel/NF-κB and cyclic AMP response element binding (CREB) protein families. It is unclear how this induction of host gene expression leads to neoplastic trans formation; tax can interfere with G1 and mitotic cell-cycle checkpoints, block apoptosis, inhibit DNA repair, and promote antigen-independent T-cell proliferation. Induction of a cytokine-autocrine loop has been proposed; however, IL-2 is not the crucial cytokine. The involvement of IL-4, IL-7, and IL-15 has been proposed. In light of the irregular expression of tax in ATL cells, it has been suggested that tax is important in the early phases of transformation but is not essential for the maintenance of the transformed state. The maintenance role is thought to be due to hbz expression. As is clear from the epidemiology of HTLV-1 infection, transformation of an infected cell is a rare event and may depend on heterogeneous second, third, or fourth genetic hits. No consistent chromosomal abnormali ties have been described in ATL; however, aneuploidy is common, and individual cases with p53 mutations and translocations involving the T-cell receptor genes on chromosome 14 have been reported. Tax may repress certain DNA repair enzymes, permitting the accumula tion of genetic damage that would normally be repaired. However, the molecular pathogenesis of HTLV-1-induced neoplasia is not fully understood. CHAPTER 207 The Human Retroviruses ■ ■FEATURES OF HTLV-1 INFECTION Epidemiology HTLV-1 infection is transmitted in at least three ways: from mother to child, especially via breast milk; through sexual activity, more commonly from men to women; and through the blood—via contaminated transfusions or contaminated needles. The virus is most commonly transmitted perinatally. Compared with HIV, which can be transmitted in cell-free form, HTLV-1 is less infectious, and its transmission usually requires cell-to-cell contact. HTLV-1 is endemic in southwestern Japan and Okinawa, where

> 1 million persons are infected. Antibodies to HTLV-1 are present in the serum of up to 35% of Okinawans, 10% of residents of the Japanese island of Kyushu, and <1% of persons in nonendemic regions of Japan. Despite this high prevalence of infection, only ~500 cases of ATL are diagnosed in this area each year. Clusters of infection have been noted in other areas of eastern Asia, such as Taiwan; in the Caribbean basin, including northeastern South America; in northwestern South America; in central and southern Africa; in Italy, Israel, Iran, and Papua New Guinea; in the Arctic; and in the southeastern part of the United States (Fig.

> 207-4). An estimated 10–20 million persons have HTLV-1 infection worldwide. Progressive spastic or ataxic myelopathy developing in an indi vidual who is HTLV-1 positive (i.e., who has serum antibodies to HTLV-1) may be due to direct infection of the nervous system with the virus, but destruction of the pyramidal tracts appears to involve HTLV-1-infected CD4+ T cells; a similar disorder may result from infection with HIV or HTLV-2. In rare instances, patients with HAM are seronegative but have detectable antibody to HTLV-1 in cerebro spinal fluid (CSF). The cumulative lifetime risk of developing ATL is 3% among HTLV1-infected patients, with a threefold greater risk among men than among women; a similar cumulative risk is projected for HAM (4%), but with women more commonly affected than men. The distribution of these two diseases overlaps the distribution of HTLV-1, with >95%

FIGURE 207-4 Global distribution of HTLV-1 infection. Countries with a prevalence of HTLV-1 infection of 1–5% are shaded darkly. Note that the distribution of infected patients is not uniform in endemic countries. For example, the people of southwestern Japan and northeastern Brazil are more commonly affected than those in other regions of those countries. of affected patients showing serologic evidence of HTLV-1 infection. The latency period between infection and the emergence of disease is 20–30 years for ATL. For HAM, the median latency period is ~3.3 years (range, 4 months to 30 years). The development of ATL is rare among persons infected by blood products; however, ~20% of patients with HAM acquire HTLV-1 from contaminated blood. ATL is more com mon among perinatally infected individuals, whereas HAM is more common among persons infected via sexual transmission. PART 5 Infectious Diseases Associated Diseases • ATL Four clinical types of HTLV-1-induced neoplasia have been described: acute, lymphomatous, chronic, and smoldering. All of these tumors are monoclonal proliferations of CD4+ postthymic T cells with clonal proviral integrations and clonal T-cell receptor gene rearrangements. ACUTE ATL About 60% of patients who develop malignancy have classic acute ATL, which is characterized by a short clinical pro drome (~2 weeks between the first symptoms and the diagnosis) and an aggressive natural history (median survival period, 6 months). The clinical picture is dominated by rapidly progressive skin lesions, pulmonary involvement, hypercalcemia, and lymphocytosis with cells containing lobulated or “flower-shaped” nuclei (see Fig. 113-7). The malignant cells have monoclonal proviral integrations and express CD4, CD3, and CD25 (low-affinity IL-2 receptors) on their surface. Serum levels of CD25 can be used as a tumor marker. Anemia and thrombocytopenia are rare. The skin lesions may be difficult to distin guish from those in mycosis fungoides. Lytic bone lesions, which are common, do not contain tumor cells but rather are composed of osteo lytic cells, usually without osteoblastic activity. Despite the leukemic picture, bone marrow involvement is patchy in most cases. The hypercalcemia of ATL is multifactorial; the tumor cells produce osteoclast-activating factors (tumor necrosis factor α, IL-1, lympho toxin) and can also produce a parathyroid hormone–like molecule. Affected patients have an underlying immunodeficiency that makes them susceptible to opportunistic infections similar to those seen in patients with AIDS (Chap. 208). The pathogenesis of the immunodefi ciency is unclear. Pulmonary infiltrates in ATL patients reflect leukemic infiltration half the time and opportunistic infections with organisms such as Pneumocystis and other fungi the other half. Gastrointestinal symptoms are nearly always related to opportunistic infection. Stron gyloides stercoralis is a gastrointestinal parasite that has a pattern of endemic distribution similar to that of HTLV-1. HTLV-1-infected persons also infected with this parasite may develop ATL more often or more rapidly than those without Strongyloides infections. Serum concentrations of lactate dehydrogenase and alkaline phosphatase are often elevated in ATL. About 10% of patients have leptomeningeal involvement leading to weakness, altered mental status, paresthesia, and/or headache. Unlike other forms of central nervous system (CNS) lymphoma, ATL may be accompanied by normal CSF protein levels.

The diagnosis depends on finding ATL cells in the CSF (Chap. 113). LYMPHOMATOUS ATL The lymphomatous type of ATL occurs in ~20% of patients and is similar to the acute form in its natural history and clinical course, except that cir culating abnormal cells are rare and lymph adenopathy is evident. The histology of the lymphoma is variable but does not influence the natural history. In general, the diagnosis is suspected on the basis of the patient’s birthplace (see “Epidemiology,” above) and the presence of skin lesions and hypercal cemia. The diagnosis is confirmed by the detection of antibodies to HTLV-1 in serum. CHRONIC ATL Patients with the chronic form of ATL generally have normal serum levels of calcium and lactate dehydrogenase and no involvement of the CNS, bone, or gastrointestinal tract. The median duration of survival for these patients is 2 years. In some cases, chronic ATL progresses to the acute form of the disease. SMOLDERING ATL Fewer than 5% of patients have the smolder ing form of ATL. In this form, the malignant cells have monoclonal proviral integration; <5% of peripheral-blood cells exhibit typical morphologic abnormalities; hypercalcemia, adenopathy, and hepato splenomegaly do not develop; the CNS, the bones, and the gastroin testinal tract are not involved; and skin lesions and pulmonary lesions may be present. The median survival period for this small subset of patients appears to be ≥5 years. HAM (TROPICAL SPASTIC PARAPARESIS) In contrast to ATL, in which there is a slight predominance of male patients, HAM affects female patients disproportionately. HAM resembles multiple sclerosis in certain ways (Chap. 455). The onset is insidious. Symptoms include weakness or stiffness in one or both legs, back pain, and urinary incontinence. Sen sory changes are usually mild, but peripheral neuropathy may develop. The disease generally takes the form of slowly progressive and unremit ting thoracic myelopathy; one-third of patients are bedridden within 10 years of diagnosis, and one-half are unable to walk unassisted by this point. Patients display spastic paraparesis or paraplegia with hyperre flexia, ankle clonus, and extensor plantar responses. Cognitive function is usually spared; cranial nerve abnormalities are unusual. Magnetic resonance imaging (MRI) reveals lesions in both the white matter and the paraventricular regions of the brain as well as in the spi nal cord. Pathologic examination of the spinal cord shows symmetric degeneration of the lateral columns, including the corticospinal tracts; some cases involve the posterior columns as well. The spinal meninges and cord parenchyma contain an inflammatory infiltrate that includes CD8+ T cells with myelin destruction. HTLV-1 is not usually found in cells of the CNS but may be detected in a small population of lymphocytes present in the CSF. In general, HTLV-1 replication is greater in HAM than in ATL, and patients with HAM have a stronger immune response to the virus. Antibodies to HTLV-1 are present in the serum and appear to be produced in the CSF of HAM patients, where titers are often higher than in the serum. The pathophysiology of HAM may involve the induction of autoim mune destruction of neural cells by T cells with specificity for viral components such as Tax or Env proteins. One theory is that suscep tibility to HAM may be related to the presence of human leukocyte antigen (HLA) alleles capable of presenting viral antigens in a fashion that leads to autoimmunity. Insufficient data are available to confirm an HLA association. However, antibodies in the sera of HAM patients have been shown to bind a neuron-specific antigen (heteronuclear ribonuclear protein A1 [hnRNP A1]) and to interfere with neurotrans mission in vitro. It is unclear what factors influence whether HTLV-1 infection will cause disease and, if it does, whether it will induce a neoplasm (ATL)

or an autoimmune disorder (HAM). Differences in viral strains, the susceptibility of particular MHC haplotypes, the route of HTLV-1 infection, the viral load, and the nature of the HTLV-1-related immune response are putative factors, but few definitive data are available. OTHER PUTATIVE HTLV-1-RELATED DISEASES Even in the absence of the full clinical picture of HAM, bladder dysfunction is common in HTLV-1-infected women. In areas where HTLV-1 is endemic, diverse inflammatory and autoimmune diseases have been attributed to the virus, including uveitis, dermatitis, pneumonitis, rheumatoid arthritis, and polymyositis. However, a causal relationship between HTLV-1 and these illnesses has not been established. Prevention Women in endemic areas should not breast-feed their children, and blood donors should be screened for serum antibodies to HTLV-1. As in the prevention of HIV infection, the practice of safe sex and the avoidance of needle sharing are important. A B Smouldering (5–10% of all cases) Chronic (10–20% of all cases) Features • ≥5% abnormal T cells • ≤4 × 109 lymphocytes per L • Calcium <2·74 mmol per L • LDH ≤1·5 × upper limit of normal • Skin and lung involvement only Features • ≥5% abnormal T cells • ≥4 × 109 lymphocytes per L • Calcium <2·74 mmol per L • LDH ≤2 × upper limit of normal • Lymphadenopathy and involvement of spleen, skin, liver, and lung only Prognosis • 4-year overall survival 52% • Median overall survival 55 months
Prognosis • 4-year overall survival 36% • Median overall survival 31·5 months Symptomatic IFN-α and AZTbased therapy, with or without ATO and topical therapies Asymptomatic Active monitoring Unfavourable chronic Favourable chronic If IFN-`and AZT-based therapy is  unavailable and tumorous lesions are present: Chemotherapy with or without topical therapies, followed by allogeneic HSCT IFN-α and AZT-based therapy with or without ATO, continued indefinitely If IFN-` and AZT-based therapy is unavailable and non-tumorous lesions are present: Skin-directed therapies and active monitoring If IFN-`and AZT-based therapy is  unavailable, or PD on therapy: Chemotherapy followed by allogeneic HSCT If PD with tumorous lesions or  progression during active monitoring or IFN-` and AZT-based therapy: Switch strategy for aggressive disease Patients with ATLL who are older or unsuitable for transplantation: Following first-line therapy (reduced dose of chemotherapy or IFN-α and AZT-based therapy, if available), consider maintenance strategies such as sobuzoxane or etoposide, or IFN-α and AZT-based therapy with or without ATO (if available) FIGURE 207-5 An approach to HTLV-1-associated adult T-cell leukemia/lymphoma. ATLL, adult T-cell leukemia or lymphoma; ATO, arsenic trioxide; AZT, azidothymidine; CHOEP, cyclophosphamide, vincristine, doxorubicin, etoposide, and prednisolone; CHOP, cyclophosphamide, vincristine, doxorubicin, and prednisolone; DA-EPOCH, dose-adjusted etoposide, prednisolone, vincristine, and cyclophosphamide; HSCT, hematopoietic stem cell transplantation; Hyper-CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone with alternating high-dose methotrexate and cytarabine; LDH, lactate dehydrogenase; PD, progressive disease; VCAP-AMP-VECP, vincristine, cyclophosphamide, doxorubicin, and prednisolone; doxorubicin, ranimustine, and prednisolone; vindesine, etoposide, carboplatin, and prednisolone. (Reproduced with permission from JS O'Donnell et al: Integrated molecular and immunological features of human T-lymphotropic virus type 1 infection and disease progression to adult T-cell leukaemia or lymphoma. Lancet Haematology 10:e539, 2023.)

TREATMENT HTLV-1 Infection For the small number of patients who develop HTLV-1–related disease, therapies are not curative. In patients with the acute and lymphomatous types of ATL, the disease progresses rapidly. Hyper calcemia is generally controlled by glucocorticoid administration and cytotoxic therapy directed against the neoplasm. The tumor is highly responsive to combination chemotherapy that is used against other forms of lymphoma; however, patients are susceptible to over whelming bacterial and opportunistic infections, and ATL relapses within 4–10 months after remission in most cases (Fig. 207-5). The combination of interferon α and zidovudine may extend sur vival. Because viral replication is not clearly associated with ATL progression, zidovudine is probably effective through its cytotoxic C D Lymphoma (20–25% of all cases) Acute (55–60% of all cases) Features • ≤4 × 109 lymphocytes per L • ≤1% abnormal T cells • Lymphadenopathy diagnosed by histology with or without extranodal lesions Features • All remaining patients with leukaemic manifestations and tumour lesions not classified under any other subtype Prognosis • 4-year overall survival 11% • Median overall survival 8·3 months Prognosis • 4-year overall survival 16% • Median overall survival 10·6 months CHAPTER 207 If non-bulky lymph nodes or tumours: Either IFN-α and AZT-based therapy or intensive chemotherapy Extranodal primary cutaneous variant Intensive chemotherapy The Human Retroviruses If available: Concurrent or sequential lowdose IFN-α and AZT-based therapy If IFN-` and AZT-based therapy is unavailable, or PD on therapy, or if patient has bulky disease: Intensive chemotherapy If available: Early up-front allogeneic HSCT If available: Early up-front allogeneic HSCT Intensive chemotherapy with or without skin-directed therapy, followed by allogeneic HSCT or IFN-α and AZT-based therapy with or without ATO Chemotherapy: Japan: VCAP-AMP-VECP (modified LSG15), or EPOCH Elsewhere: CHOP, CHOEP, DA-EPOCH, or hyper-CVAD Relapsed and refractory disease: • Single-agent or alternative combination chemotherapy containing platinum, etoposide, and high-dose cytarabine • Localised radiotherapy (palliation) In Japan: Mogamulizumab and lenalidomide

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