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effects (as a chain-terminating thymidine analogue) rather than its antiviral effects. Selected series have reported high rates of response and a 40% rate of 5-year survival; however, this level of response has not been universal. LSG15, a multidrug chemotherapy program developed in Japan, induces complete responses in about one-third of patients, about half of whom survive for >2 years; however, the median survival time is about 13 months. High-dose therapy with bone marrow transplantation has been widely tested in Japan. Median survival has not been influenced by this treat ment; however, up to 25% of patients survive free of disease for

4 years. Lenalidomide has been reported to have a 42% response rate in patients with relapsed ATL, extending median survival to

20 months despite a short 4-month progression-free survival period. Mogamulizumab, an antibody to CCR4 (a receptor for a number of chemokines, including RANTES and TARC), improved response rates when added to chemotherapy. An experimental approach using an yttrium-90-labeled or toxin-conjugated antibody to the IL-2 receptor appears promising but is not widely available. Patients with the chronic or smoldering form of ATL may be managed with an expectant approach: treat any infections, and watch and wait for signs of progression to acute disease.

Patients with HAM may obtain some benefit from the use of glucocorticoids to reduce inflammation during acute episodes of myelopathy. Antiretroviral regimens have not been effective. In one study, danazol (200 mg three times daily) produced significant neu rologic improvement in five of six treated patients, with resolution of urinary incontinence in two cases, decreased spasticity in three, and restoration of the ability to walk after confinement to a wheel chair in two. Antibody to IL-15 receptor β chain has been tested with some promising clinical effects in small numbers of

patients. Physical therapy and rehabilitation are important components of management. PART 5 Infectious Diseases ■ ■FEATURES OF HTLV-2 INFECTION Epidemiology HTLV-2 is endemic in certain Native American tribes and in Africa. It is generally considered to be a New World virus that was brought from Asia to the Americas 10,000–40,000 years ago during the migration of infected populations across the Bering land bridge. The mode of transmission of HTLV-2 is probably the same as that of HTLV-1 (see above). HTLV-2 may be less readily transmitted sexually than HTLV-1. Studies of large cohorts of injection drug users with serologic assays that reliably distinguish HTLV-1 from HTLV-2 indicated that the vast majority of HTLV-positive cohort members were infected with HTLV-2. The seroprevalence of HTLV in a cohort of 7841 injection drug users from drug treatment centers in Baltimore, Chicago, Los Angeles, New Jersey (Asbury Park and Trenton), New York City (Brooklyn and Harlem), Philadelphia, and San Antonio was 20.9%, with >97% of cases due to HTLV-2. The seroprevalence of HTLV-2 was higher in the Southwest and the Midwest than in the Northeast. In contrast, the seroprevalence of HIV-1 was higher in the Northeast than in the Southwest or the Midwest. Approximately 3% of the cohort mem bers were infected with both HTLV-2 and HIV-1. The seroprevalence of HTLV-2 increased linearly with age. Women were significantly more likely than men to be infected with HTLV-2; the virus is thought to be more effi ciently transmitted from male to female than from female to male. Associated Diseases Although HTLV-2 was isolated from a patient with a T-cell variant of hairy cell leukemia, this virus has not been consistently associated with a particular disease and in fact has been thought of as “a virus searching for a disease.” However, evidence is accumulating that HTLV-2 may play a role in certain neurologic, hematologic, and dermatologic diseases. These data require confirma tion, particularly in light of the previous confusion regarding the rela tive prevalences of HTLV-1 and HTLV-2 among injection drug users. Prevention Avoidance of needle sharing, adherence to safe-sex practices, screening of blood (by assays for HTLV-1, which also detect

HTLV-2), and avoidance of breast-feeding by infected women are important principles in the prevention of spread of HTLV-2. HUMAN IMMUNODEFICIENCY VIRUS HIV-1 and HIV-2 are members of the lentivirus subfamily of Retro viridae and are the only lentiviruses known to infect humans. The lentiviruses are slower-acting than viruses that cause acute infection (e.g., influenza virus) but not than other retroviruses. The features of acute primary infection with HIV resemble those of more classic acute infections. The characteristic chronicity of HIV disease is consistent with the designation lentivirus. For a detailed discussion of HIV, see Chap. 208. ■ ■FURTHER READING Forlani G et al: HTLV-1 infection and pathogenesis: New insights from cellular and animal models. Int J Mol Sci 22:8001, 2021. Katsuya H et al: Treatment and survival among 1594 patients with ATL. Blood 126:2570, 2015. Letafati A et al: Therapeutic approaches for HTLV-1-associated adult T-cell leukemia/lymphoma: A comprehensive review. Med Oncol 40:295, 2023. Ma G et al: Multifaceted functions and roles of HBZ in HTLV-1 patho genesis. Retrovirology 13:16, 2016. Moir S et al: Pathogenic mechanisms of HIV disease. Annu Rev Pathol 6:223, 2011. Ohmoto A, Fuji S: Non-cancerous complications in HTLV-1 carriers. Expert Rev Anti Infect Ther 22:307, 2024. Yamauchi J et al: An update on human T-cell leukemia virus type I (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/ TSP) focusing on clinical and laboratory biomarkers. Pharmacol Ther 218:107669, 2021.

Human Immunodeficiency

Virus Disease: AIDS and

Related Disorders Anthony S. Fauci, Gregory K. Folkers,

H. Clifford Lane The Acquired Immune Deficiency Syndrome (AIDS) was first rec ognized in the United States in the summer of 1981, when the U.S. Centers for Disease Control and Prevention (CDC) reported the unex plained occurrence of Pneumocystis jirovecii (formerly P. carinii) pneu monia in five previously healthy homosexual men in Los Angeles and of Kaposi's sarcoma (KS) with or without P. jirovecii pneumonia and other opportunistic infections in 26 previously healthy homosexual men in New York, San Francisco, and Los Angeles. The disease was soon recognized in male and female injection drug users; in hemophil iacs and blood transfusion recipients; among female sexual partners of men with AIDS; and among infants born to mothers with AIDS. In 1983, what became known as human immunodeficiency virus (HIV) was isolated from a patient with lymphadenopathy, and by 1984 HIV was demonstrated clearly to be the causative agent of AIDS. In 1985, a sensitive enzyme-linked immunosorbent assay (ELISA) was developed to detect antibodies to HIV. This led to an appreciation of the scope and evolution of the HIV epidemic at first in the United States and other developed nations and ultimately among developing nations throughout the world (see "HIV Infection and AIDS Worldwide," below). The staggering worldwide evolution of the HIV pandemic has been matched by an explosion of information in the areas of HIV virology, pathogenesis (both immunologic and virologic), treatment of

HIV infection, treatment and prophylaxis of the opportunistic diseases associated with HIV infection, and prevention of HIV infection. The information flow related to HIV disease is enormous and continues to expand, and it has become almost impossible for the health care generalist to stay abreast of the literature. The purpose of this chapter is to present the most current information available on the scope of the pandemic, as well as the pathogenesis, treatment, and prevention of HIV disease. Above all, the aim is to provide a solid scientific basis and practical clinical guidelines for a state-of-the-art approach to the care of persons with HIV. ■ ■DEFINITION The current CDC classification system for HIV infection and AIDS categorizes patients based on clinical conditions associated with HIV infection together with the level of the CD4+ T lymphocyte count. A confirmed HIV case can be classified in one of three clinical stages (A, B, or C) and one of three CD4+ T lymphocyte categories (1, 2, or 3). Advanced HIV disease (AIDS) is classified as stage C, requiring the diagnosis of one or more specific opportunistic illnesses (Table 208-1), and as stage 3 in anyone over 6 years of age if the CD4+ T lymphocyte count is below 200 cells/μL (Table 208-2). The definition and staging criteria of AIDS are complex and com prehensive and were established for surveillance purposes rather than for the practical care of patients. Thus, the clinician should not focus 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 relatively asymptomatic stage, to advanced stages associated with opportunistic diseases (see "Patho physiology and Pathogenesis," below). TABLE 208-1 CDC Stage 3 (AIDS)-Defining Opportunistic Illnesses in HIV Infection Bacterial infections, multiple or recurrenta Candidiasis of bronchi, trachea, or lungs Candidiasis of esophagus Cervical cancer, invasiveb Coccidioidomycosis, disseminated or extrapulmonary Cryptococcosis, extrapulmonary Cryptosporidiosis, chronic intestinal (>1 month's duration) Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month Cytomegalovirus retinitis (with loss of vision) Encephalopathy attributed to HIV Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month) Histoplasmosis, disseminated or extrapulmonary Isosporiasis, chronic intestinal (>1 month's duration) Kaposi's sarcoma Lymphoma, Burkitt's (or equivalent term)

Lymphoma, immunoblastic (or equivalent term) Lymphoma, primary, of brain Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary Mycobacterium tuberculosis of any site, pulmonary,b disseminated, or extrapulmonary Mycobacterium, other species or unidentified species, disseminated or extrapulmonary Pneumocystis jirovecii (previously known as Pneumocystis carinii) pneumonia Pneumonia, recurrentb Progressive multifocal leukoencephalopathy Salmonella septicemia, recurrent Toxoplasmosis of brain, onset at age >1 month Wasting syndrome attributed to HIV aOnly among children age <6 years. bOnly among adults, adolescents, and children age ≥6 years. Source: MMWR 63(RR-03), April 11, 2014.

TABLE 208-2 CDC HIV Infection Stages 1–3 Based on Age-Specific CD4+ T Lymphocyte Count or CD4+ T Lymphocyte Percentage

of Total Lymphocytesa AGE ON DATE OF CD4 T+ LYMPHOCYTE TEST 6 YEARS

THROUGH ADULT <1 YEAR 1–5 YEARS STAGEa CELLS/lL % CELLS/lL % CELLS/lL %

≥1500 ≥34 ≥1000 ≥30 ≥500 ≥26

750–1499 26–33 500–999 22–29 200–499 14–25

<750 <26 <500 <22 <200 <14 aThe 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(RR-03), April 11, 2014. ETIOLOGIC AGENT HIV is the etiologic agent of AIDS; it belongs to the family of human retroviruses (Retroviridae) and the subfamily of lentiviruses (Chap. 207). 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 immunodefi ciency viruses, HIV-1 and HIV-2, which cause cytopathic effects either directly or indirectly (Chap. 207). 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, cases traced to West Africa or to sexual contacts with West Africans have been identified throughout the world. HIV-1 strains are broken down into one major group (M) and three minor groups (N, O, P), and HIV-2 viruses are divided into groups A through H. Each group likely derives 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 mang abeys. 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. Reported infections with group N and group P viruses are rare and confined almost entirely to residents of Cameroon or travelers from Cameroon. The taxonomic relationship between primate lentiviruses is shown in Fig. 208-1. CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders

■ ■MORPHOLOGY OF HIV Electron microscopy shows that the HIV virion is an icosahedral struc ture (Fig. 208-2) containing numerous external spikes formed by the two major envelope proteins that exist as a trimeric heterodimer, the external gp120 and the transmembrane gp41. The virion buds from the surface of the infected cell (Fig. 208-2A) and incorporates a variety of host cellular proteins into its lipid bilayer. The structure of HIV-1 is schematically diagrammed in Fig. 208-2B. ■ ■REPLICATION CYCLE OF HIV HIV is an RNA virus whose hallmark is the reverse transcription of its genomic RNA to proviral DNA by the enzyme reverse transcriptase. The replication cycle of HIV begins with the high-affinity binding via surface-exposed residues within the gp120 protein to its receptor on the host cell surface, the CD4 molecule (Fig. 208-3). 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. 360). Once it binds to CD4, the gp120 protein under goes 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-transmem brane-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. Cell-to-cell

SIV-SYK SIV-TAL SIV-MUS SIV-GSN HIV-2 and SIV-SMM/MAC A B SIV-VER SIV-GRI SIV-TAN SIV-DRL SIV-RCM SIV-MND2 SIV-SAB SIV-CPZ Pan troglodytes schweinfurthii HIV-1 P and O groups and SIV_Gorilla HIV-1 M and N groups and SIV-CPZ Pan troglodytes troglodytes 0.25 PART 5 Infectious Diseases FIGURE 208-1 A phylogenetic tree based on the nearly complete genomes (gag through nef genes) of primate immunodeficiency viruses. The scale (0.25) indicates a 25% phylogenetically corrected genetic distance at the nucleotide level. Clades in color represent viruses (HIV-1, HIV-2) identified in humans after relatively recent transfers from chimpanzee, gorilla, and sooty mangabey reservoirs. (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.) spread is also facilitated by accessory molecules such as the C-type lectin receptor DC-SIGN expressed on certain dendritic cells (DCs) that bind to the HIV gp120 envelope protein, allowing virus captured on DCs to 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, which facilitates binding to a co-receptor, fusion with the host cell membrane occurs as the newly exposed gp41 molecule penetrates the plasma membrane of the target cell and then folds upon itself to bring the virion and target cell together (Fig. 208-4). 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. 208-3). All these post-fusion viral components constitute the HIV replication complex, including the outer capsid shell, which plays an integral role in supporting reverse transcription of viral RNA. As the preintegration complex traverses 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 HIV proviral DNA. At several steps of the replication cycle, the virus is vulnerable to various cellular factors that can block the progression of infection. The cytoplasmic tripartite motif-containing protein 5α (TRIM5α) is a host restriction factor that interacts with retroviral capsids, causing their premature disassembly and induction of innate immune responses. The apolipoprotein B mRNA editing enzyme (catalytic polypeptidelike 3 [APOBEC3]) family of cellular proteins also inhibits progression of virus infection

after virus has entered the cell and prior to entering the nucleus. 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 APO BEC. The viral protein Vif targets APOBEC3 for proteasomal degradation. SAMHD1 is another post-entry host factor that prevents reverse transcription by depleting pools of deoxynucleotides (dNTPs). The type I inter feron (IFN)-induced myxovirus resistance protein 2 (MX2) is another restriction factor associated with innate immunity that inhib its HIV-1 nuclear entry. SIV-MON SIV-ASC SIV-DEN SIV-DEB SIV-COL SIV_LST SIV-SUN SIV-MND1 Following reverse transcription, the pro viral DNA accesses the nuclear pore and is transferred from the cytoplasm to the nucleus, where it is integrated into a host cell chromo some through the action of another virally encoded enzyme, integrase (Fig. 208-3). HIV proviral DNA preferentially integrates into the host genomic DNA in regions of active transcription. This provirus may remain tran scriptionally inactive (latent) or may manifest varying levels of gene expression, up to active transcription and production of virus. SIV-OLC SIV-WRC Cellular activation plays an important role in the replication cycle of HIV and is critical to the pathogenesis of HIV disease (see “Pathophysiology and Pathogenesis,” 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 infec tion. 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 detect able expression of the classic cell-surface markers of activation. This is reflected in the fact that cell-associated HIV RNA transcribed from competent or defective proviruses can be detected in infected resting CD4+ T cells. In this regard, activation of HIV expression from the latent state depends on the interaction of various cellular and viral fac tors. Following transcription, HIV mRNA is translated into proteins that undergo modification through glycosylation, myristoylation, phosphorylation, and cleavage. The viral particle is formed by the assembly of HIV proteins, enzymes, and genomic RNA at the plasma membrane of the cells. Budding of the progeny virion through the lipid bilayer of the host cell membrane is the point at which the core acquires its external envelope and where the host restriction factor tetherin can inhibit the release of budding particles. Tetherin is an IFN-induced type II transmembrane protein that interferes with virion detachment. The HIV accessory protein vpu counteracts this effect through direct interactions with tetherin. During or soon after budding, the virally encoded protease catalyzes the cleavage of the gag-pol precursor to yield the mature virion. Progression through the virus replication cycle is profoundly influenced by a variety of viral regulatory gene products. Likewise, each point in the replication cycle of HIV is a real or potential target for therapeutic intervention. Thus far, the reverse transcriptase, protease, and integrase enzymes as well as the process of virus–target cell binding and fusion have proved to be susceptible to pharmacologic disruption. ■ ■HIV GENOME Figure 208-5 illustrates schematically the arrangement of the HIV genome. Like other retroviruses, HIV-1 has genes that encode the structural proteins of the virus: gag encodes the proteins that form the core of the virion (including p24 antigen); pol encodes the enzymes responsible for protease processing of viral proteins, reverse

A B C FIGURE 208-2 A. Transmission electron micrograph of HIV-1 virus particles (colorized yellow/gold) replicating from an HIV-infected H9 T cell (purple). Budding virus particles that have not yet separated from the cell appear as semicircles. A separated, spherical immature particle is seen at the center of the image. (Image captured at the NIAID Integrated Research Facility [IRF] in Fort Detrick, Maryland. Courtesy of NIAID.) 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). (Courtesy of George V. Kelvin. Adapted from RC Gallo: Sci Am 256:46, 1987.) C. Scanning electron micrograph of a human H9 T cell (blue/green) infected with HIV-1 virus particles (yellow). (Image captured at NIAID Rocky Mountain Laboratories in Hamilton, Montana. Courtesy of NIAID.) transcription, and integration; and env encodes the envelope glycopro teins. However, HIV-1 is more complex than other retroviruses, par ticularly those of the nonprimate group, in that it also contains at least six other regulatory genes (tat, rev, nef, vif, vpr, and vpu), which code for proteins involved in the modification of the host cell to enhance virus growth and the regulation of viral gene expression. Several of these proteins are thought to play a role in the pathogenesis of HIV disease; their various functions are listed in Fig. 208-5. Flanking these genes are long terminal repeats (LTRs), which contain regulatory ele ments involved in gene expression (Fig. 208-5). The major difference between the genomes of HIV-1 and HIV-2 is the fact that HIV-2 lacks the vpu gene and has a vpx gene not contained in HIV-1. ■ ■MOLECULAR HETEROGENEITY OF HIV-1 Molecular analyses of HIV isolates reveal varying levels of sequence diversity over all regions of the viral genome. For example, the degree of difference in the coding sequences of the viral envelope protein ranges from a few percent (very close, among isolates from the same infected individual) to more than 50% (extreme diversity, between isolates from the different groups of HIV-1: M, N, O, and P). The changes tend to cluster in hypervariable regions. HIV can evolve by several means, including simple base substitution, insertions and

gp41 Matrix Lipid membrane Capsid RNA gp120 Reverse transcriptase CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders
deletions, recombination, and gain and loss of glycosylation sites. HIV sequence diversity arises directly from the limited fidelity of the reverse transcriptase, i.e., a tendency toward copying errors. The balance of immune pressure and functional constraints on proteins influences the regional level of variation within proteins. For example, envelope, which is exposed on the surface of the virion and is under immune selective pressure from both antibodies and cytolytic T lymphocytes, is extremely variable, with clusters of mutations in hypervariable domains. In contrast, reverse transcriptase, with important enzymatic functions, is relatively conserved in the absence of drug-induced selec tive pressure, particularly around the active site. The extraordinary variability of HIV-1 contrasts markedly with the relative stability of HTLV-1 and 2. The four groups (M, N, O, and P) of HIV-1 are the result of four separate chimpanzee-to-human (or possibly gorilla-to-human for groups O and P) transfers. Group M (major), which is responsible for most infections in the world, has diversified into subtypes and inter subtype recombinant forms, due to “sub-epidemics” within humans after one of those transfers. Among primate lentiviruses, HIV-1 is most closely related to viruses isolated from chimpanzees and gorillas (Fig. 208-1). The chimpanzee subspecies Pan troglodytes troglodytes has been established to be a

1 Binding and fusion to the host cell surface. HIV gp120 CD4 Co-receptor (CCR5 or CXCR4) Host Cell

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Viral DNA is
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transported across the nucleus and integrates into the host DNA. PART 5 Infectious Diseases Mature Virion

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The virus matures
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after protease cleaves long precursor proteins

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New viral RNA
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and proteins move to the cell surface and an immature virion begins to form. Protease FIGURE 208-3 The replication cycle of HIV. See text for description. (From the National Institute of Allergy and Infectious Diseases.) HIV virion gp41 gp120 CD4 CCR5/ CXCR4 Membrane fusion CD4+ T cell Receptor binding

HIV RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell. Preintegration complex

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Viral DNA is
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formed by reverse transcription. Viral RNA Reverse transcriptase Integrase Viral DNA Host DNA New viral RNA

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New viral RNA is
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used as genomic RNA and to make viral proteins. FIGURE 208-4 Binding and fusion of HIV-1 with its target cell. HIV-1 binds to its target cell via the CD4 molecule, leading to a conformational change in the gp120 molecule that allows it to bind to the co-receptor CCR5 (for R5-using viruses). The virus then firmly attaches to the host cell membrane in a coiled-spring fashion via the newly exposed gp41 molecule. Virus–cell fusion occurs as the transitional intermediate of gp41 undergoes further changes to form a hairpin structure that draws the two membranes into close proximity (see text for details). (Adapted from D Montefiori, JP Moore: HIV vaccines. Magic of the occult? Science 283:336, 1999.)

LTR Long terminal repeat vif Viral infectivity factor (p23) Overcomes inhibitory effects of APOBEC3, preventing hypermutation and viral DNA degradation Contains control regions that bind host transcription factors (NF-κβ, NFAT, Sp. 1, TBP) Required for the initiation of transcription Contains RNS trans-acting response element (TAR) that binds Tat R U5 U3

R U5 U3

pol Polymerase Encodes a variety of viral enzymes, including PR (p10), RT and RNAase H (p66/51), and IN (p32) all processed by PR gag Pr55gag Polyprotein processed by PR MA, matrix (p17) Undergoes myristoylation that helps target gag polyprotein to lipid rafts CA capsid (p24) Binds

cyclophilin A and CPSF6 Target of TRIM5α NC, nucleocapsid (p7) Zn finger, RNA-binding protein p6 Regulates the terminal steps in virion budding through interactions with TSG101 and ALIX 1 Incorporates Vpr into viral particles FIGURE 208-5 Organization of the genome of the HIV provirus together with a summary description of its 9 genes encoding 15 proteins. (Reproduced with permission from WC Greene et al: Charting HIV's remarkable voyage through the cell: Basic science as a passport to future therapy. Nat Med 8:673, 2002.) natural reservoir of the HIV-1 M and N groups. The rare viruses of the HIV-1 O and P groups are most closely related to viruses found in Cameroonian gorillas. The M group comprises ten subtypes, or clades, designated A, B, C, D, F, G, H, J, K, and L, as well as more than 150 known circulating recombinant forms (CRFs) and numerous unique recombinant forms. Inter-subtype recombinants are generated by infection of an individual with two subtypes that then recombine and create a virus with a selective advantage. These CRFs range from highly prevalent forms—such as CRF01_AE, common in southeast Asia, and CRF02_AG in west and central Africa—to numerous CRFs that are relatively rare, either because they are of a more recent origin (newly recombined) or because they have not broken out into a major population. The subtypes and CRFs constitute the major lineages of the M group of HIV-1. HIV-1 M group subtype C dominates the global pandemic, and although there is speculation that it is more transmis sible than other subtypes, solid data on variations in transmissibility between subtypes are lacking. Human population densities, access to prevention and treatment, prevalence of genital ulcers, iatrogenic transmissions, and other confounding host factors are all possible rea sons why one subtype has spread more than another. Figure 208-6 schematically diagrams the worldwide distribution of HIV-1 subtypes by region. Nine strains account for most new HIV infections globally: HIV-1 subtypes A, B, C, D, F, and G and three of the CRFs, CRF01_AE, CRF02_AG, and CRF07_BC. Subtype C viruses (of the M group) are by far the most common form, likely accounting for ~50% of infections worldwide. In sub-Saharan Africa, home to approx imately two-thirds of all people living with HIV/AIDS, most infections

vpu Viral protein U Promotes CD4 degradation and influences virion release Overcomes inhibitory effects of tetherin env gp160 envelope protein Cleaved in endoplasmic reticulum to gp120 (SU) and gp 41 (TM) gp120 mediates CD4 and chemokine receptor binding, while gp41 mediates fusion Contains RNA response element (RRE) that binds Rev nef Negative effector (p27) Promotes downregulation of surface CD4 and MHC 1 expression Blocks apoptosis Enhances viron activity Alters state of cellular activation Progression to disease slowed significantly in absence of Nef vpr Viral protein R (p15) Promotes G2 cell-cycle arrest Facilitates HIV infection of macrophages tat Transcriptional activator (p14) Binds TAR In presence of host cyclin T1 and CDK9 enhances RNA Pol II elongation on the viral DNA template rev Regulator of viral gene expression (p19) Binds RRE Inhibits viral RNA splicing and promotes nuclear export of incompletely spliced viral RNAs CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders
are caused by subtype C, with smaller proportions of infections caused by subtype A, subtype D, CRF02_AG, and other subtypes and recombinants. In South Africa, the country with the largest number of prevalent infections (7.7 million in 2023), 98% of all HIV-1 isolates sequenced are of subtype C. In Asia, HIV-1 isolates of the CRF01_AE lineage and subtypes B and C predominate. CRF01_AE accounts for most infections in south and southeast Asia, while ~97% of infections in India, home to an estimated 2.5 million people with HIV, are of sub type C (see "HIV Infection and AIDS Worldwide," below). Subtype B viruses are overwhelmingly predominant in the United States, Canada, certain countries in South America, western Europe, and Australia. It is thought that, purely by chance, subtype B was seeded into the United States and Europe in the late 1970s,

thereby establishing an overwhelming founder effect. Many countries have co-circulating viral subtypes that are giving rise to new CRFs. Sequence analyses of HIV-1 isolates from infected individuals indicate that recombination among viruses of different clades likely occurs when an individual is infected with viruses of more than one subtype, particularly in geographic areas where subtypes overlap, and more often in sub-epidemics driven by injection drug use than in those driven by sexual transmission. The extraordinary diversity of HIV, reflected by the presence of multiple subtypes, circulating recombinant forms, and continuous viral evolution, has implications for possible differential rates of transmission, rates of disease progression, and the development of resistance to antiret roviral drugs. This diversity may also prove to be a formidable obstacle to HIV vaccine development, as a broadly useful vaccine would need to induce protective responses against a wide range of viral strains.

76° 76° 38° 38° 0° 0° –38° –38° 5000 km –76° –76° PART 5 Infectious Diseases World FIGURE 208-6 Global geographic distribution of HIV-1 subtypes and recombinant forms. Distributions derived from relative frequency of subtypes among >1.16 million HIV genomic sequences in the Los Alamos National Laboratory HIV Sequence Database. (Additional information available at www.hiv.lanl.gov/components/sequence/HIV/geo/ geo.comp.) TRANSMISSION HIV is transmitted primarily by sexual contact (both heterosexual and male to male); by blood and blood products; and by infected mothers to infants intrapartum, perinatally, or via breast milk. After four decades of experience and observations, there is no evidence that HIV is trans mitted by any other modality. Table 208-3 lists the estimated risk of HIV transmission for various types of exposures. ■ ■SEXUAL TRANSMISSION HIV infection is predominantly a sexually transmitted infection (STI) worldwide. By far the most common mode of infection, particularly in developing countries, is heterosexual transmission, although in many western countries male-to-male sexual transmission dominates. Although a wide variety of factors including viral load and the presence of ulcerative genital diseases influence the efficiency of heterosexual transmission of HIV, such transmission is generally inefficient. A systemic review found a low per-act risk of heterosexual transmission in the absence of antiretrovi rals: 0.04% for female-to-male transmission and 0.08% for male-to-female transmission during vaginal intercourse in the absence of antiretroviral therapy or condom use (Table 208-3). As discussed below, this risk approaches zero in settings where the infected partner is on effective antiretroviral therapy or when the uninfected partner is on a program of pre-exposure or postexposure prophylaxis (PrEP or PEP). HIV has been demonstrated in seminal fluid both within infected mononuclear cells and in cell-free material. The virus appears to

01_AE

7.9% 02_AG

2.6% 07_BC

2.3% A

5.1% A6

1.8% B 629459 54.0% BF1

1.0% C 169330 14.5% D

2.8% F

1.2% Other

6.7% Total 1166040 100.0% TABLE 208-3 Estimated Per-Act Probability of Acquiring HIV from an Infected Source, By Exposure Act TYPE OF EXPOSURE RISK PER 10,000 EXPOSURES Parenteral Blood transfusion

Needle-sharing during injection drug use

Percutaneous (needle-stick)

Sexual Receptive anal intercourse

Insertive anal intercourse

Receptive penile-vaginal intercourse

Insertive penile-vaginal intercourse

Receptive oral intercourse Low Insertive oral intercourse Low Othera Biting Negligible Spitting Negligible Throwing body fluids (including semen or saliva) Negligible Sharing sex toys Negligible aHIV transmission through these exposure routes is technically possible but unlikely and not well documented. Source: CDC, www.cdc.gov/hivpartners/php/riskandprevention/.

concentrate in the seminal fluid, particularly in situations where there are increased numbers of lymphocytes and monocytes in the fluid, as seen in genital inflammatory states such as urethritis and epididymitis, conditions closely associated with other STIs. The virus has also been demonstrated in cervical smears and vaginal fluid. There is an elevated risk of HIV transmission associated with unprotected receptive anal intercourse (URAI) among both men and women compared to the risk associated with unprotected receptive vaginal intercourse. Although data are limited, the per-act risk for HIV transmission via URAI has been estimated to be ~1.4% (Table 208-3). The risk of HIV acquisition associated with URAI is higher than that seen in penile–vaginal inter course probably because only a thin, fragile rectal mucosal membrane separates the deposited semen from potentially susceptible cells in and beneath the mucosa, and microtrauma of the mucosal membrane has been associated with anal intercourse. Anal douching and sexual prac tices that traumatize the rectal mucosa also increase the likelihood of infection. It is likely that anal intercourse provides at least two modali ties of infection: (1) direct inoculation into blood in cases of traumatic tears in the mucosa; and (2) infection of susceptible target cells, such as Langerhans cells, in the mucosal layer in the absence of trauma. Insertive anal intercourse also confers an increased risk of HIV acqui sition compared with insertive vaginal intercourse in the receptive partner since the vaginal mucosa is several layers thicker than the rectal mucosa and less likely to be traumatized during intercourse. Nonethe less, the virus can be transmitted to either partner through vaginal intercourse. As noted in Table 208-3, male-to-female HIV transmission is more efficient than female-to-male transmission. The differences in reported transmission rates between men and women may be due in part to the prolonged exposure of the vaginal and cervical mucosa to infected seminal fluid; the endometrium also can be exposed to virus when semen enters

through the cervical os. By comparison, the penis and urethral orifice of the uninfected male partner are only exposed relatively briefly to infected vaginal fluid. Among various cofactors examined in studies of heterosexual HIV transmission, the presence of other STIs has been strongly associated with HIV transmission. In this regard, there is a close association between genital ulcerations and transmission, owing to both susceptibility to infection and infectivity. Infections with micro organisms such as Treponema pallidum (Chap. 187), Haemophilus ducreyi (Chap. 162), and herpes simplex virus (HSV; Chap. 197) are important causes of genital ulcerations linked to transmission of HIV. In addition, pathogens responsible for non-ulcerative inflam matory STIs such as those caused by Chlamydia trachomatis (Chap. 194), Neisseria gonorrhoeae (Chap. 161), and Trichomonas vaginalis (Chap. 236) also are associated with an increased risk of transmission of HIV infection. Bacterial vaginosis, an infection related to sexual behavior, but not strictly an STI, also may be linked to an increased risk of transmission of HIV infection. Multiple studies have suggested that treating STIs and genital tract syndromes may help decrease transmission of HIV. This effect is most prominent in populations in which the prevalence of HIV infection is relatively low. It is notewor thy that this principle may not apply to the treatment of HSV infec tions since it has been shown that even following anti-HSV therapy with resulting healing of HSV-related genital ulcers, HIV acquisition is not reduced. Biopsy studies revealed that the likely explanation is that HIV receptor–positive inflammatory cells persisted in the genital tissue despite the healing of ulcers, and so HIV-susceptible targets remained at the site. The quantity of HIV-1 in plasma (viral load) is a primary deter minant of the risk of HIV-1 transmission. In a cohort of heterosexual couples in Uganda discordant for HIV infection and not receiving anti retroviral therapy, the mean serum HIV RNA level was significantly higher among individuals with HIV whose partners seroconverted than among those whose partners did not seroconvert. In fact, trans mission was rare when the infected partner had a plasma level of <1700 copies of HIV RNA per milliliter, even when genital ulcer disease was present (Fig. 208-7). The rate of HIV transmission per coital act was highest during the early stage of HIV infection when plasma HIV RNA levels were high and in advanced disease with high viral set points.

No genital ulcer disease Genital ulcer disease Probability of transmission

per 10,000 coital acts

<1700 <1700– 12,499 12,500– 38,499 ≥38,500 HIV load of infected partner, RNA copies/mL FIGURE 208-7 Probability of HIV transmission per coital act among monogamous, heterosexual, HIV-serodiscordant couples in Uganda. (From RH Gray et al: Lancet 357:1149, 2001.) Antiretroviral therapy dramatically reduces plasma viremia in most people with HIV (see “Antiretroviral Therapy” and “HIV Prevention,” below) and is associated with a dramatic reduction in risk of transmis sion, an approach widely referred to as treatment as prevention or TasP. Multiple studies have demonstrated that if the viral load of a person with HIV is reduced by antiretroviral therapy to <20 copies/mL as measured by conventional commercial assays, there is essentially no chance of sexual transmission to the person’s sexual partner. This is true for heterosexuals as well as men who have sex with men, leading to the commonly used description of this phenomenon as “undetectable equals untransmittable” or “U = U.” CHAPTER 208 Multiple studies including large, randomized, controlled trials clearly have indicated that male circumcision is associated with a lower risk of acquisition of HIV infection for heterosexual men. Studies also suggest that circumcision is protective against HIV acquisition for men who have sex with men reporting mainly

or only insertive sex. The benefit of circumcision may be due to increased susceptibility of uncircumcised men to ulcerative STIs, as well as to other factors such as microtrauma to the foreskin and glans penis. In addition, the highly vascularized inner layer of foreskin tissue contains a high density of Langerhans cells as well as increased numbers of CD4+ T cells, macro phages, and other cellular targets for HIV. Finally, the moist environ ment under the foreskin may promote the presence or persistence of microbial flora that, via inflammatory changes, may lead to even higher concentrations of target cells for HIV in the foreskin. In addition, ran domized clinical trials have demonstrated that male circumcision also reduces HSV type 2, human papillomavirus virus (HPV), and genital ulcer disease in men as well as HPV, genital ulcer disease, bacterial vaginosis, and Trichomonas vaginalis infections among female partners of circumcised men. Thus, there may be an added indirect benefit of diminution of risk for HIV acquisition to the female sexual partners of circumcised men. Human Immunodeficiency Virus Disease: AIDS and Related Disorders
In some studies, the use of oral contraceptives was associated with an increase in incidence of HIV infection over and above that which might be expected by not using a condom for birth control. This phe nomenon may be due to drug-induced changes in the cervical mucosa, rendering it more vulnerable to penetration by the virus. Adolescent girls might also be more susceptible to infection upon exposure due to the properties of an immature genital tract with increased cervical ectopy or exposed columnar epithelium. Oral sex is a much less efficient mode of transmission of HIV than is anal intercourse or vaginal intercourse (Table 208-3). Multiple studies have reported that the incidence of transmission of infection by oral sex among couples discordant for HIV is extremely low. However, there have been well-documented reports of HIV transmission that likely resulted from fellatio or cunnilingus. Therefore, the assumption that oral sex is completely safe is not warranted. The association of alcohol consumption and illicit drug use with unsafe sexual behavior, both homosexual and heterosexual, leads to an increased

risk of sexual transmission of HIV. Methamphetamine and other so-called “club drugs” such as 3,4-methylenedioxymethamphetamine (MDMA; also known as “ecstasy”), ketamine, gamma-hydroxybutyrate (GHB), and inhaled nitrites (known as “poppers”), sometimes taken in conjunction with PDE-5 inhibitors such as sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra), have been associated with risky sexual practices and increased risk of HIV infection, particularly among men who have sex with men.

■ ■TRANSMISSION THROUGH INJECTION

DRUG USE HIV can be transmitted to injection drug users (IDUs) who are exposed to HIV while sharing injection paraphernalia such as needles, syringes, the water in which drugs are mixed, or the cotton through which drugs are filtered. Parenteral transmission of HIV during injec tion drug use does not require IV puncture; subcutaneous (“skin pop ping”) or intramuscular (“muscling”) injections can transmit HIV as well, even though these behaviors are sometimes erroneously perceived as low risk. Among IDUs, the risk of HIV infection increases with the duration of injection drug use; the frequency of needle sharing; the number of partners with whom paraphernalia are shared; comorbid psychiatric conditions such as antisocial personality disorder; the use of cocaine in injectable form or smoked as “crack”; and the use of injection drugs in a geographic location with a high prevalence of HIV infection. As noted in Table 208-3, the per-act risk of transmission from injection drug use with a contaminated needle has been estimated to be approximately 0.6%.
■ ■TRANSMISSION BY TRANSFUSED BLOOD

AND BLOOD PRODUCTS HIV can be transmitted to individuals who receive HIV-contaminated blood transfusions, blood products, or transplanted tissue. The vast majority of HIV infections acquired via contaminated blood trans fusions, blood components, or transplanted tissue in resource-rich countries occurred prior to the spring of 1985, when mandatory test ing of donated blood for HIV-1 was initiated. It is estimated that >90% of individuals exposed to HIV-contaminated blood products become infected (Table 208-3). Transfusions of whole blood, packed red blood cells, platelets, leukocytes, and plasma are all capable of transmitting HIV infection. In contrast, hyperimmune gamma globulin, hepatitis B

immune globulin, plasma-derived hepatitis B vaccine, and Rho immune globulin have not been associated with transmission of HIV infection. The procedures involved in processing these products either inactivate or remove the virus. PART 5 Infectious Diseases Currently, in the United States and in most developed countries, the following measures have made the risk of transmission of HIV infection by transfused blood or blood products extremely small: the screening of blood donations for antibodies to HIV-1 and HIV-2 and determination of the presence of HIV nucleic acid usually in minipools of several specimens; the careful selection of potential blood donors with health history questionnaires to exclude individuals with risk behaviors; and opportunities for self-deferral and the screening out of HIV-negative individuals with serologic testing for infections that have shared risk factors with HIV, such as hepatitis B and C and syphilis. The chance of infection of a hemophiliac via clotting factor concen trates has essentially been eliminated because of standard screening of blood together with the added layer of safety resulting from heat treatment of the concentrates. It is currently estimated that the risk of infection with HIV in the United States via transfused screened blood is approximately 1 in 2 million units. Since nearly 21 million blood components are transfused in the United States each year, eliminat ing the risk of transfusion-related HIV transmission likely will not be possible. Transmission of HIV (both HIV-1 and HIV-2) by blood or blood products is still an ongoing threat in certain developing coun tries where routine screening of blood is not universally practiced. Furthermore, there have been reports in certain countries of sporadic breakdowns in routinely available screening procedures in which con taminated blood or plasma was transfused, resulting in small clusters of patients becoming infected.

■ ■OCCUPATIONAL TRANSMISSION OF HIV:

HEALTH CARE WORKERS, LABORATORY

WORKERS, AND THE HEALTH CARE SETTING There is a small but definite occupational risk of HIV transmission to health care workers and laboratory personnel and potentially others who work with HIV-containing materials, particularly when sharp objects are used. More than 300,000 health care workers are stuck with needles or other sharp medical instruments in the United States each year. The global number of HIV infections among health care workers attributable to sharps injuries has been estimated to be 1000 cases (range, 200–5000) per year. In the United States, a total of 58 documented cases of occupational HIV transmission to health care workers, and 150 possible transmissions, have been reported by the CDC. Since 1999, only one confirmed case (a laboratory technician sustaining a needle puncture while working with a live HIV culture in 2008) has been reported. Exposures that place a health care worker at potential risk of HIV infection are percutaneous injuries (e.g., a needle stick or cut with a sharp object) or contact of mucous

membrane or nonintact skin (e.g., exposed skin that is chapped, abraded, or afflicted with dermatitis) with blood, tissue, or other potentially infectious body fluids. Large, multi-institutional studies have indicated that the risk of HIV trans mission following skin puncture from a needle or a sharp object that was contaminated with blood from a person with documented HIV infection is ~0.23%, and after a mucous membrane exposure it is ~0.09% (see “HIV and the Health Care Worker,” below) if the injured and/or exposed person is not treated within 24 hours with antiretro viral drugs. The risk of hepatitis B virus (HBV) infection following a similar type of exposure is ~6–30% in nonimmune individuals. If a susceptible worker is exposed to HBV, postexposure prophylaxis with hepatitis B immune globulin and initiation of HBV vaccine is >90% effective in preventing HBV infection. The risk of HCV infection fol lowing percutaneous injury is ~1.8% (Chap. 350). Rare HIV transmission after nonintact skin exposure has been documented. The average risk for transmission by this route has not been precisely determined; however, it is estimated to be less than the risk for mucous membrane exposure. Transmission of HIV through intact skin has not been documented. All health care workers experi encing a puncture wound or mucous membrane exposures involving blood from a patient with documented HIV infection should be treated prophylactically with combination antiretroviral therapy (ART). This practice, referred to as postexposure prophylaxis or PEP, has dramati cally reduced the occurrence of puncture-related transmissions of HIV to health care workers. In addition to blood and visibly bloody body fluids, semen and vaginal secretions also are considered potentially infectious; however, they have not been implicated in occupational transmission from patients to health care workers. The following fluids also are consid ered potentially infectious: cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid. The risk for transmission after exposure to fluids or tissues other than HIV-infected blood has not been quantified, but it is probably considerably lower than the risk after blood exposures. Feces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus are not considered potentially infectious for HIV unless they are visibly bloody. Rare cases of HIV transmission via human bites have been reported, but not in the setting of occupational exposure. An increased risk for HIV infection following percutaneous expo sures to HIV-infected blood is associated with exposures involving a relatively large quantity of blood, as in the case of a device visibly contaminated with the patient’s blood, a procedure that involves a hollow-bore needle placed directly in a vein or artery, or a deep injury. Factors that might be associated with mucocutaneous transmission of HIV include exposure to an unusually large volume of blood and pro longed contact. In addition, the risk increases for exposures to blood from untreated patients with high levels of HIV in the blood. Since the beginning of the HIV epidemic, there have been rare instances where transmission of infection from a health care worker to patients seemed highly probable. Despite this small number of documented cases, the

risk of HIV transmission involving infected health care workers to patients is extremely low in developed countries—in fact, too low to be measured accurately. In this regard, several retrospective epide miologic studies have been performed tracing thousands of patients of dentists, physicians, surgeons, obstetricians, and gynecologists with HIV, and no cases of HIV transmission that could be linked to the health care providers were identified other than the already identified documented cases. Breaches in infection control and the reuse of contaminated syringes, failure to properly sterilize surgical instruments, and/or hemodialysis equipment also have resulted rarely in the transmission of HIV from patient to patient in hospitals, nursing homes, and out patient settings. Finally, these very rare occurrences of transmission of HIV as well as HBV and HCV to and from health care workers in the workplace underscore the importance of the use of

universal precau tions when caring for all patients (see below and Chap. 147). ■ ■MOTHER-TO-CHILD TRANSMISSION OF HIV HIV infection can be transmitted from an infected mother to her fetus during pregnancy, during delivery, or by breast-feeding. This remains a persistent form of transmission of HIV infection in certain developing countries. Virologic analyses of aborted fetuses indicate that HIV can be transmitted to the fetus during the first or second trimesters of preg nancy. However, maternal transmission occurs most commonly during birth. Two studies performed in Rwanda and the Democratic Republic of Congo (then called Zaire) indicated that among all mother-to-child transmissions of HIV, the relative proportions were 23–30% before birth, 50–65% during birth, and 12–20% via breast-feeding. In the absence of antiretroviral therapy for the mother during preg nancy, labor, and delivery, and for the infant prophylactically following birth, the overall probability of transmission of HIV from mother to infant/fetus ranges from 15% to 25% in industrialized countries and from 25% to 35% in developing countries. These differences may relate to the adequacy of prenatal care as well as to the stage of HIV disease and the general health of the mother during pregnancy. Higher rates of transmission have been reported to be associated with many

factors—the best documented of which is the presence of high mater nal levels of plasma viremia, with the risk increasing linearly with the level of maternal plasma viremia. It is very unlikely that mother-tochild transmission will occur if the mother’s level of plasma viremia is <1000 copies of HIV RNA/mL of blood and extremely unlikely if the level is <50 copies/mL. Increased mother-to-child transmission is also correlated with closer human leukocyte antigen (HLA) match between mother and child. A prolonged interval between membrane rupture and delivery is another well-documented risk factor for transmission of HIV. Other conditions that are potential risk factors, but that have not been consistently demonstrated, are the presence of chorioamnionitis at delivery; STIs during pregnancy; illicit drug use during pregnancy; cigarette smoking; preterm delivery; and obstetric procedures such as amniocentesis, amnioscopy, fetal scalp electrodes, and episiotomy. Today, the rate of mother-to-child transmission has fallen to <1% in pregnant women who are receiving ART for their HIV infection. Such treatment, combined with cesarean section delivery, has rendered mother-to-child transmission of HIV an extremely unusual event in the United States and other developed nations. In this regard, both the United States Public Health Service and the World Health Organiza tion guidelines recommend that all pregnant women with HIV receive lifelong ART for the health of the mother (regardless of plasma HIV RNA copy number or CD4+ T cell count) as well as to prevent perinatal transmission. Breast-feeding is an important modality of transmission of HIV infection in certain developing countries, particularly where untreated mothers continue to breast-feed for prolonged periods. The risk factors for mother-to-child transmission of HIV via breast-feeding by an untreated mother include detectable levels of HIV in breast milk, the presence of mastitis, low maternal CD4+ T cell counts, and maternal vitamin A deficiency. The risk of HIV infection via breastfeeding is highest in the early months of breast-feeding. In addition, exclusive breast-feeding has been reported to carry a lower risk of

HIV transmission than mixed feeding. In developed countries, breastfeeding of babies by a mother with HIV is contraindicated since alter native forms of adequate nutrition, i.e., formulas, are readily available. In developing countries, where breast-feeding may be essential for the overall health of the infant, the continuation of ART in the infected mother during the period of breastfeeding markedly diminishes the risk of transmission of HIV to the infant. In fact, treatment of a pregnant woman with ART should be provided for the benefit of the woman as much as for the prevention of

mother-to-child transmission and should be continued beyond the pregnancy, for life.

■ ■TRANSMISSION OF HIV BY OTHER BODY FLUIDS Although HIV can be isolated typically in low titers from saliva of a small proportion of infected individuals, there is no convincing evidence that saliva can transmit HIV infection, either through kiss ing or through other exposures, such as occupationally to health care workers. Saliva contains endogenous antiviral factors; among these factors, HIV-specific immunoglobulins of IgA, IgG, and IgM isotypes are detected readily in salivary secretions of infected individuals. It has been suggested that large glycoproteins such as mucins and throm bospondin 1 sequester HIV into aggregates for clearance by the host. In addition, multiple soluble salivary factors inhibit HIV to various degrees in vitro, probably by targeting host cell receptors rather than the virus itself. Perhaps the best studied of these, secretory leukocyte protease inhibitor (SLPI), blocks HIV infection in several cell culture systems, and it is found in saliva at levels that approximate those required for inhibition of HIV in vitro. In this regard, higher salivary levels of SLPI in breast-fed infants were associated with a decreased risk of HIV transmission through breast milk. It has also been suggested that submandibular saliva reduces HIV infectivity by stripping gp120 from the surface of virions, and that saliva-mediated disruption and lysis of HIV-infected cells occurs because of the hypotonicity of oral secretions. Transmission of HIV by a human bite can occur but is a rare event. Although virus can be detected, if not isolated, from virtually any body fluid, there is no evidence that HIV transmission can occur as a result of exposure to tears, sweat, or urine. However, there have been isolated cases of transmission of HIV infection by body fluids that may or may not have been contaminated with blood. Most of these situations occurred in the setting of a close relative providing intensive nursing care for a person with HIV without observing universal pre cautions, underscoring the importance of adhering to such precautions in the handling of body fluids and wastes from people with HIV. CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders
EPIDEMIOLOGY ■ ■HIV INFECTION AND AIDS WORLDWIDE HIV infection/AIDS is a global pandemic, with cases reported from virtually every country. In 2023, an estimated 39.9 million individuals were living with HIV infection, according to the Joint United Nations Programme on HIV/AIDS (UNAIDS). An estimated 95% of people liv ing with HIV/AIDS reside in low- and middle-income countries; ~53% are female, and 1.4 million are children <15 years. The regional distri bution of these cases is illustrated in Fig. 208-8. The estimated number North America and Western and North America and Western and Central Europe Eastern Europe and Central Asia Eastern Europe and Central Asia Central Europe 2.3 million [2.0 million–2.7 million] 2.3 million [2.0 million–2.7 million] 2.1 million [1.9 million–2.3 million] Middle East and 2.1 million [1.9 million–2.3 million] Middle East and North Africa North Africa Caribbean Caribbean 210,000 [170,000–280,000] Western and Central 210,000 [170,000–280,000] Western and Central Africa 5.1 million [4.5 million–5.9 million] 340,000 [280,000–390,000] 340,000 [280,000–390,000] Asia and the Pacific Asia and the Pacific 6.7 million [6.0 million–7.5 million] 6.7 million [6.0 million–7.5 million] Africa 5.1 million [4.5 million–5.9 million] Latin America Latin America 2.3 million [2.0 million–2.5 million] 2.3 million [2.0 million–2.5 million] Eastern and Southern Africa Eastern and Southern Africa 20.8 million [19.2 million–23.0 million] 20.8 million [19.2 million–23.0 million] FIGURE 208-8 Estimated number of adults and children living with HIV infection as of December 2023. Total: 39.9 million (36.1 million–44.6 million). (From Joint United Nations Programme on HIV/AIDS [UNAIDS].)

3,500,000 45,000,000 New HIV infections and AIDS-related deaths 3,000,000 2,500,000 2,000,000 1,500,000 1,000,000 15,000,000 500,000 – –

FIGURE 208-9 Global estimates of new HIV cases, AIDS-related deaths, and HIV prevalence, 1990–2023. (From UNAIDS.) of people living with HIV—i.e., the global prevalence—has increased more than fourfold since 1990, reflecting the combined effects of con tinued high rates of new HIV infections and the life-prolonging impact of antiretroviral therapy (Fig. 208-9). The overall global prevalence of HIV infection among persons 15–49 years of age is ~0.7%, with rates varying widely by country and region as illustrated in Fig. 208-10. The WHO Eastern and Southern Africa region remains most severely affected, with more than 1 in 20 adults (5.7%) living with HIV and accounting for more than half of the people with HIV worldwide. An estimated 88.4 million people have become infected with HIV since the start of the pandemic. PART 5 Infectious Diseases In 2023, an estimated 1.3 million new cases of HIV infection occurred worldwide, including 120,000 among children <15 years; about one-third of new infections were among people age 15–24 years. The regional distribution of new HIV cases in 2023 is shown No data 0% 0.1% 0.2% 0.5% 1% 2% 5% 10% 20% 50% FIGURE 208-10 Adult HIV prevalence rates by country, 2021. Data are estimates for adults age 15–49 years. (Reproduced from IHME, Global Burden of Disease with major processing by Our World in Data; 2024.)

People living with HIV 40,000,000 35,000,000 People living with HIV 30,000,000 25,000,000 New HIV infections 20,000,000 AIDS-related deaths 10,000,000 5,000,000

in Fig. 208-11. Globally, members of certain high-risk populations are disproportionately affected by HIV infection, often because of factors such as marginalization, discrimination, and in some cases criminalization. Sex workers, people who inject drugs, transgender people, prisoners, gay men and other men who have sex with men, the clients of sex workers, and the sexual partners of these key populations accounted for 55% of all new HIV infections in 2022 (Fig. 208-12). New HIV infections globally have fallen by 60% since their peak in 1995 (Fig. 208-9). In 2023, 1.3 million people were newly infected with HIV, compared with 3.3 million people in 1995. Reductions in global HIV incidence likely reflect progress with HIV prevention efforts and the increased provision to HIV-infected people of antiretroviral ther apy, which makes them much less likely to transmit the virus to sexual partners. Between 2010 and 2023, new HIV infections declined by 39%, from 2.1 million to 1.3 million. During the same period a ~62%

FIGURE 208-11 Distribution of new HIV infections, by region, 2023. (Reproduced with permission from UNAIDS.) reduction in HIV infections among children <15 years was observed, from 300,000 in 2010 to 120,000 in 2023. This progress is due largely to the increasing availability of antiretroviral medications to prevent the transmission of HIV from mother to infant. An estimated 30.7 million people with HIV globally, 77% of all people living with HIV, were accessing antiretroviral therapy as of December 2023, up from 7.7 million people in 2010. Among pregnant women with HIV, 84% had access to antiretroviral medicines to prevent transmission of HIV to their child in 2023. In 2023, global AIDS deaths totaled 630,000 (including 76,000 chil dren <15 years), a 65% decrease since 2000 that coincides with a rapid expansion of access to antiretroviral therapy (Fig. 208-13). Since the beginning of the HIV pandemic, an estimated 42.3 million persons globally have died of an AIDS-related illness. The HIV epidemic has occurred in “waves” in different regions of the world, each wave having somewhat different characteristics depending on the demographics of the country and region in question and the tim ing of the introduction of HIV into the population. Although the AIDS epidemic was first recognized in the United States and shortly thereaf ter in Western Europe, it very likely began in sub-Saharan Africa (see above), a region particularly

devastated by the epidemic. The 21 countries of the Eastern and Southern Africa region are home to about 7% of the world's population but had 20.8 million peo ple living with HIV in 2023, >50% of the global total (Fig. 208-8). HIV prevalence among adults age 15–49 years across the region is 5.7%. Of 21 countries in the region, 17 have generalized epidemics, that is, their national prevalence is >1%. In 6 countries in the region, >10% of Sex workers (8%) Gay men and men who have sex with other men (20%) Remaining population (45%) Transgender women (1%) People who inject drugs (8%) Clients of sex workers (10%) Sex partners of key populations (non-clients) (8%) FIGURE 208-12 Global distribution of new HIV infections by population. Data for 2022. (From UNAIDS.)

Asia and the Pacific 300,000 Caribbean 15,000 Eastern Europe and central Asia 140,000 Latin America 120,000 Middle East and North Africa 23,000 Western and central Europe and North America 56,000 Eastern and southern Africa 450,000 Western and central Africa 190,000 the adult population age 15–49 has HIV infection (Fig. 208-10). South Africa has the highest number of people living with HIV in the world (7.7 million); Eswatini (formerly known as Swaziland) has the highest adult HIV prevalence globally (25.1%). Heterosexual exposure is the primary mode of HIV transmission in most countries in this region, as is the case throughout sub-Saharan Africa. Women and girls age 15 years and older account for ~63% of all HIV infections in the region. Key populations, notably sex workers and clients of sex workers, accounted for 23% of new infections in the region in 2022. CHAPTER 208 Major progress in the HIV response has been made in the Eastern and Southern Africa region in recent years. The annual number of people acquiring HIV in the region fell by 59% between 2010 and 2023, from 1.1 million to 450,000. AIDS-related deaths decreased by 57% in that period, from 600,000 in 2010 to 260,000 in 2023. As of 2023, 93% of people living with HIV in the region knew their infections status; 83% of those living with HIV (17.4 million people) were on antiretro viral therapy, and 78% had suppressed viral loads. Human Immunodeficiency Virus Disease: AIDS and Related Disorders
The 25 countries of the Western and Central Africa region are home to 5.1 million people living with HIV, of whom 3.1 million are women age ≥15 years and 380,000 are children. HIV prevalence in most countries is relatively low compared with Eastern and Southern Africa. HIV prevalence among adults across the region overall stands at 1.2%. About 40% of new infections in the region in 2023 occurred in Nigeria, a large country with an HIV seroprevalence rate of 1.3%. As in Eastern and Southern Africa, heterosexual transmission accounts for most HIV transmission in West and Central Africa, with sex workers and their clients accounting for about one-fifth of new infections. The Middle East and North Africa region has one of the lowest HIV prevalence rates in the world (<0.1%), although annual new infections more than doubled between 2010 and 2023, from 11,000 to 23,000. In 2023, an estimated 230,000 people were living with HIV in the 19 countries in the region. Cases are largely concentrated among IDUs, men who have sex with men, and sex workers and their clients. In Asia and the Pacific, an estimated 6.7 million people were living with HIV at the end of 2023, with an overall adult prevalence rate of 0.2%. With 300,000 new infections in 2023, the region accounted for one-quarter of all new infections globally that year. The region saw a 13% decrease in new infections between 2010 and 2023, with reduc tions in Thailand and Vietnam offset by increases in Afghanistan, Bangladesh, Fiji, the Lao People's Democratic Republic, Papua New Guinea, and the Philippines. In the same time frame, AIDS-related deaths in the region fell by 51% to 150,000. Among countries in this region, only Thailand has an adult seroprevalence rate that reaches 1%. However, the populations of many countries are so large that even low infection and seroprevalence rates result in large numbers of people living with HIV. In this regard, three

populous countries—China, India, and Indonesia—account for around three-quarters of all people living with HIV in the region. Key populations (Fig. 208-11) and their

3,000,000 2,500,000 Number of AIDS–related deaths 2,000,000 1,500,000 1,000,000 500,000 0

FIGURE 208-13 Global antiretroviral therapy coverage and number of AIDS-related deaths, 1990-2023. (Data from The Urgency of Now: AIDS at a Crossroads. Geneva: Joint United Nations Programme on HIV/AIDS; 2024.) partners accounted for ~80% of new HIV infections in the region in 2022. Rising numbers of new infections among gay men and other men who have sex with men in this region are a major concern. The HIV epidemic continues to expand in Eastern Europe and Central Asia, with a 20% increase in annual new HIV infections and 34% increase in AIDS deaths between 2010 and 2023. There are about 2.1 million people living with HIV in the region, where the epidemic has been driven by injection drug use but has an increasing proportion of new HIV infections transmitted sexually. Members of key popula tions and their sexual partners account for ~94% of new infections in the region. The Russian Federation, Ukraine, Kazakhstan, and Uzbekistan reported 92% of all registered cases in the region in 2023. PART 5 Infectious Diseases Approximately 2.3 million people were living with HIV/AIDS in Latin America at the end of 2023. The annual number of new infec tions in the region increased by 9% between 2010 and 2023 to 120,000. About two-thirds of new infections were among key populations and their sex partners, with increasing rates among men who have sex with men, sex workers, and transgender women. AIDS-related deaths declined by 28% to 30,000 from 2010 to 2023. Brazil is home to the largest number of HIV-infected persons (1,00,000) in the region. In the Caribbean, an estimated 340,000 people were living with HIV in 2023, with 15,000 new infections that year. New infections have declined by 22% in the region since 2010. About 90% of new infections in the region in 2023 were in Cuba, the Dominican Republic, Haiti, and Jamaica. People from key populations and their sex partners accounted for almost half of new infections in the region in 2023. Approximately 2.3 million people were living with HIV/AIDS in North America and Western and Central Europe in 2023. While modes of transmission vary greatly by country, HIV in the region dis proportionately affects men who have sex with men. New infections in the region fell by 24% between 2010 and 2023 to 56,000, while AIDSrelated deaths fell 34%, to 13,000. Key populations accounted for ~83% of new infections in the region in 2022. ■ ■HIV INFECTION IN THE UNITED STATES As of 2022, an estimated 1.2 million individuals in the United States were living with HIV infection, ~13% of whom were unaware of their infection. Among people with diagnosed HIV in 2022, about 76% have received some HIV care, and about 65% have achieved viral suppres sion (see below). Nearly 40% of people living with HIV in the United States are Black/ African American and 26% are Hispanic/Latino; ~60% are men who have sex with men, according to CDC estimates. The HIV prevalence

Percentage of people living with HIV receiving treatment Percentage of people living with HIV receiving treatment

Number of AIDS–related deaths

target

rate among all individuals age 13 years or older in the United States is 0.4%. Approximately 1.4% of Black/African-American adults are living with HIV in the United States, more than any other racial/ethnic group. The estimated annual number of new HIV infections in the United States has fallen by more than two-thirds since its height in the late 1980s of about 130,000 per year. CDC data indicate further progress in recent years, as overall incidence fell 12% from 2018 to 2022, from 36,200 new infections to 31,800. The estimated distribution of new infections in 2022, broken down by transmission category, is shown in Fig. 208-14. In the United States, the burden of HIV infection is not evenly dis tributed across states and regions. In most areas of the country, HIV is concentrated in urban areas. In the southern United States, larger per centages of diagnoses are in smaller metropolitan and nonmetropolitan areas. HIV has disproportionately affected minority populations in the United States in both urban and rural areas. Among new HIV infec tions from 2018 to 2022 in the United States, 37% were among Blacks/ African Americans, a group that constitutes only 12% of the U.S. popu lation. Hispanics/Latinos, 18% of the U.S. population, accounted for 33% of new HIV infections. The rate of new HIV infections in 2022 by race/ethnicity in the United States is shown in Fig. 208-15. Perinatal HIV transmission, from an HIV-infected mother to her baby, has declined significantly in the United States, largely due to the implementation of guidelines for the universal counseling and voluntary HIV testing of pregnant women and the use of antiretroviral Heterosexual contact 7000 infections (22%) Male-to-male sexual contact and injection drug use 1100 infections (3%) Injection drug use 2300 infections (7%) Male-to-male sexual contact 21,400 infections (67%) FIGURE 208-14 Estimated distribution of new HIV infections in the United States among people age ≥13 years, by transmission category, 2022. Total: 31,800. (From CDC: HIV Surveillance Supplemental Report 29 [No. 1], 2024.)

Black/African American Multiple races 21.6 Hispanic/Latino 20.7 American Indian/ Alaska Native 9.8 White 4.4 Asian 2.2

Rate/100,000 population FIGURE 208-15 Estimated rate of new HIV infections in the United States among people age ≥13 years, by race/ethnicity (per 100,000 population), 2022. (From CDC: HIV Surveillance Supplemental Report 29 [No. 1], 2024.) therapy for pregnant women and newborn infants to prevent infection. In 2022, 62 children were newly diagnosed with HIV infection in the United States, down from a peak of ~1750 in 1991. The rate of HIV-related deaths in the United States rose steadily through the 1980s, peaked around 1994, and fell rapidly through 1997 (Fig. 208-16). Since then, the rate of death due to HIV disease con tinues to decline, decreasing from 2.6 deaths per 100,000 in 2010 to 1.3 deaths per 100,000 in 2022. This trend is likely due to several fac tors, including improved prophylaxis and treatment of opportunistic infections, growing experience among the health professions in caring for HIV-infected individuals, improved access to health care, and a decrease in new infections. However, the most influential factor clearly has been the increased use—and continued refinement—of antiretro viral therapy (ART), generally administered in a combination of two, three, or four agents. Despite much progress, HIV disease continues to remain among the leading causes of death among all persons age 25–44 years in the United States, ranking 13th in 2022. HIV disease as an underlying cause of death is particularly high among Black/AfricanAmerican persons age 25–44 years, ranking as the 8th leading cause among Black males and the 12th leading cause among Black females in 2022. PATHOPHYSIOLOGY AND PATHOGENESIS The hallmark of HIV disease is a profound immunodeficiency result ing primarily from a progressive quantitative and qualitative deficiency of the subset of T lymphocytes referred to as helper T cells occurring

Deaths, No. (in thousands)

Year of death FIGURE 208-16 Trends in annual age-adjusted rates of death in the general population with HIV infection as the underlying cause, United States, 1987–2022. (From CDC.)

in a setting of aberrant immune activation creating a state of immuno suppression. The helper subset of T cells is defined phenotypically by the presence on its surface of the CD4 molecule (Chap. 360), which serves as the primary cellular receptor for HIV. A co-receptor also must be present together with CD4 for efficient binding, fusion, and entry of HIV-1 into its target cells (Figs. 208-3 and 208-4). HIV-1 uses two major co-receptors, CCR5 and CXCR4, for fusion and entry; these co-receptors are also the primary receptors for certain chemoattractant cytokines termed chemokines and belong to the seven-transmembranedomain G protein–coupled family of receptors. Multiple mechanisms responsible for cellular depletion and/or immune dysfunction of CD4+ T cells have been demonstrated in vitro. These include direct infection and destruction of these cells by HIV, as well as indirect effects such as immune clearance of infected cells; cell death associated with aberrant immune activation and inflammation, including caspase 1–mediated pyroptosis prompted by tissue CD4+ T cells undergoing abortive/

nonproductive HIV infection; and immune exhaustion due to per sistent cellular activation with resulting cellular dysfunction. Patients with CD4+ T cell levels below certain thresholds are at high risk of developing a variety of opportunistic diseases, particularly the infec tions and neoplasms that are AIDS-defining illnesses. Some features of AIDS, such as Kaposi’s sarcoma and certain neurologic abnormalities, cannot be explained completely by the immunodeficiency caused by HIV infection, since these complications may occur prior to the devel opment of severe immunologic impairment.

34.1 The combination of viral pathogenic and immunopathogenic events that occur during the course of HIV disease from the moment of initial (primary) infection through the development of advanced-stage dis ease is complex and varied. It is important to appreciate that the patho genic mechanisms of HIV disease are multifactorial and multiphasic and are different at different stages of the disease. Therefore, it is essen tial to consider the typical clinical course of an untreated individual with HIV to better appreciate these pathogenic events (Fig. 208-17). CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders

■ ■EARLY EVENTS IN HIV INFECTION:

PRIMARY INFECTION AND INITIAL DISSEMINATION OF VIRUS Using rectal or vaginal mucosal transmission in nonhuman primates as a model, the earliest events (within hours) that occur following expo sure of HIV to the mucosal surface determine whether an infection will be established or aborted as well as the subsequent course of events following infection. Although the mucosal barrier is relatively effective in limiting access of HIV to susceptible targets in the submucosal tis sue, the virus can cross the barrier by transport on Langerhans cells, an epidermal type of DC, just beneath the surface or through microscopic rents in the mucosa. Significant disruptions in the mucosal barrier as seen in ulcerative genital disease facilitate viral entry and increase the

Death ±Acute HIV syndrome Wide dissemination of virus Seeding of lymphoid organs Primary infection Constitutional symptoms

CD4+ T lymphocyte count (cells/µL)

Clinical latency

Weeks Years FIGURE 208-17 Typical course of an untreated HIV-infected individual. See text for detailed description. (From G Pantaleo, C Graziosi, AS Fauci: The Immunopathogenesis of Human Immunodeficiency Virus Infection. N Engl J Med 328:327, 1993. Copyright © 1993 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.) PART 5 Infectious Diseases efficiency of infection. Viruses then seek susceptible targets, which are primarily CD4+ T cells that are spatially dispersed in the mucosa. This spatial dispersion of targets provides a significant obstacle to the estab lishment of infection. Such obstacles account for the low efficiency of sexual transmission of HIV (see “Sexual Transmission,” above). Both “partially” resting CD4+ T cells and activated CD4+ T cells serve as early amplifiers of infection. Resting CD4+ T cells are more abundant; however, activated CD4+ T cells support productive infection and thus generate larger amounts of virus. For infection to become established, the basic reproductive rate (R0) must become equal to or greater than 1,

i.e., each infected cell would infect at least one other cell. Once infec tion is established, the virus replicates in lymphoid cells in the mucosa, the submucosa, and to some extent the lymphoreticular tissues that drain the gut or genital tissues. For a variable period up to several days, the virus is typically not detected in the plasma. This period is Lamina propria Lymphoid tissue Infected “resting” CD4+ T cells PD-1+CD8+ T cells “Resting” CD4+ T cells HIV virions Crossing the barrier Activated CD4+ T cell DC Infected activated CD4+ T cell Infected cell Macrophage Hours Days Weeks Years FIGURE 208-18 Summary of early events in HIV infection. See text for detailed description. CTLs, cytolytic T lymphocytes; HIV, human immunodeficiency virus. (Adapted from AT Haase: Nat Rev Immunol 5:783, 2005.)

called the “eclipse” phase of infection. As more virus is produced within several days to weeks, it is disseminated, first to the draining lymph nodes and then to other lymphoid compartments where it has easy access to dense concentrations of CD4+ T cell targets, allowing for a burst of high-level plasma viremia that is readily detectable by currently available assays measuring viral RNA (Fig. 20818). The gut-associated lymphoid tissue (GALT) is one target of HIV infection and a location where CD4+ T cells (pri marily memory cells) are infected and depleted, both by direct viral effects and by activation-associated apoptosis. Once virus replication reaches this threshold and virus is widely disseminated, infec tion is firmly established throughout the lymphoid tissues of the body and persists for the life of the individual. It is important to point out that the effi ciency of initial infection of susceptible cells may vary somewhat with the route of infection. Virus that enters directly into the bloodstream via infected blood or blood products (i.e., transfusions, use of contaminated needles for injection drugs, sharp-object injuries, maternalto-fetal transmission either intrapartum or perinatally, or sexual inter course where there is enough trauma to cause bleeding) is likely first cleared from the circulation to the spleen and other lymphoid organs, where primary focal infections begin, followed by wider dissemination throughout other lymphoid tissues as described above. Opportunistic diseases HIV RNA copies per mL plasma

It has been demonstrated that sexual transmission of HIV is the result of a single infectious event and that a viral genetic bottleneck exists for transmission with selective transmission of certain viruses. In this regard, certain characteristics of the HIV envelope glycoprotein have a major influence on transmission, at least in subtype A and C viruses. Transmitting viruses, often referred to as “founder viruses,” are typically a small fraction of the circulating viremia of the transmit ting partner and are less-diverged viruses with signature sequences including shorter V1–V2 loop sequences and fewer predicted N-linked glycosylation sites relative to the major circulating variants. These Late-responding CTLs Establishment of lymphoidtissue viral reservoir Partial control Immune activation Dissemination of virus Sustained HIV production Regulatory T cells

Founder Replicating virus FIGURE 208-19 As HIV diverges from founder to chronically replicating virus, it accumulates N-linked glycosylation sites. See text for detailed description. (Adapted from CA Derdeyn et al: Science 303:2019, 2004; B Chohan et al: J Virol 79:6528, 2005; and BF Keele et al: Proc Natl Acad Sci USA 105:7552, 2008.) viruses are almost exclusively R5 strains and are usually sensitive to neutralizing antibody. Once replication proceeds in the newly infected partner, the founder virus diverges and accumulates glycosylation sites, becoming progressively more resistant to neutralization (Fig. 208-19). The acute burst of viremia and wide dissemination of virus in pri mary HIV infection may be associated with an acute HIV syndrome, which occurs to varying degrees in ~50% of individuals within 2 to

4 weeks of initial infection (see below). This syndrome is usually associated with high levels of plasma viremia reflected in millions of copies of HIV RNA per milliliter of plasma that can last for several weeks. Acute mononucleosis-like symptoms are well correlated with the presence of high levels of plasma viremia. Virtually all patients develop some degree of plasma viremia during primary infection, which contributes to virus dissemination throughout the lymphoid tissue, even though they may remain asymptomatic or not recall experiencing symptoms. The peak level of plasma viremia in primary HIV infection does not necessarily determine the rate of disease progression; however, the set point of the level of steady-state plasma viremia after ~1 year correlates with the rate of disease progression in the untreated patient and with immunologic and virologic aberrancies that may persist in the treated patient. The strikingly high levels of viremia observed in many patients during acute HIV infection is felt to be associated with a higher likelihood of transmission of the virus to others by a variety of routes including sexual transmission, shared needles and syringes, and mother-to-child transmission intrapartum, perinatally, or via breast milk. ■ ■ESTABLISHMENT OF CHRONIC INFECTION Persistence of Virus Replication HIV infection is unique among human viral infections. Despite the robust cellular and humoral immune responses that are mounted following primary infection (see “Immune Response to HIV,” below), once infection has been estab lished the virus succeeds in escaping complete immune-mediated clearance, paradoxically seems to thrive on immune activation, and is never eliminated completely from the body. Rather, a chronic infection develops and persists with varying degrees of continual virus replica tion in the untreated patient for a median of ~10 years before the patient becomes clinically ill (see “Advanced HIV Disease,” below). It is this establishment of a chronic, persistent infection that is the hallmark of HIV disease. Throughout the often-protracted course of chronic infection, virus replication can invariably be detected in untreated patients by widely available molecular assays that measure copies of virion-associated HIV RNA in plasma (copies per milliliter). Levels of virus vary greatly in most untreated patients, usually ranging from fewer than 50 to greater than a million copies of HIV RNA per milliliter of plasma. Studies using highly sensitive

molecular techniques have demonstrated that even in treated patients in whom plasma viremia is suppressed to below detection limits of commercial assays (20–50 copies of HIV RNA per milliliter depending on assay kit manufacturer)

by ART, there is a continual low level of virion production in most infected patients. In other human viral infections (with some excep tions) if the host survives, the virus is completely cleared from the body and a state of immunity against subsequent infection develops. HIV infection very rarely kills the host during primary infection. Certain viruses, such as HSV (Chap. 197), are not completely cleared from the body after infection, but instead enter a latent state; in these cases, clinical latency is accompanied by microbiologic latency. This is not the case with HIV infection as described above. Chronicity associated with persistent virus replication can also be seen in certain cases of HBV and HCV infections (Chap. 352); however, in these infections the immune system is not a target of the virus.

Escape of HIV from Effective Immune System Control Inher ent to the establishment of chronicity of HIV infection is the ability of the virus to evade adequate control and elimination by the cellular and humoral immune responses. There are several mechanisms whereby the virus accomplishes this evasion. Paramount among these is the establishment of a sustained level of replication associated with the generation of viral diversity via mutation and recombination. The selec tion of mutants that escape control by CD8+ cytolytic T lymphocytes (CTLs) is critical to the propagation and progression of HIV infection. The high rate of virus replication associated with inevitable mutations also contributes to the inability of antibody to neutralize and/or clear the autologous virus. Furthermore, for reasons that remain unclear, the humoral immune system does not readily produce classic neutralizing antibodies against the HIV envelope and does so only after years of persistent virus replication and after the infection is firmly established (see below). Extensive analyses of sequential HIV isolates and host responses have demonstrated that viral escape from B cell and CD8+ T cell responses occurs early after infection and allows the virus to con tinually evade effective immune responses. Virus-specific CD8+ CTLs expand greatly during primary HIV infection, and they likely represent the high-affinity responses that would be expected to be most efficient in eliminating virus-infected cells; however, with very rare exceptions, viral control is incomplete as viral replication persists at relatively high levels in the majority of individuals. In addition to viral escape from CTLs through high rates of mutation, it is thought that the initially strong immune response becomes qualitatively dysfunctional owing to the overwhelming immune activation associated with persistent viral replication, leading to immune “exhaustion” that affects both arms of adaptive immunity. Several studies have indicated that exhaustion of HIV-specific CD8+ T cells during prolonged immune activation is associated with upregulation of several inhibitory receptors, such as the programmed death (PD) 1 molecule (of the B7-CD28 family of mol ecules), T cell immunoreceptor with Ig and ITIM domains (TIGIT),

T cell immunoglobulin and mucin domain–containing molecule 3 (Tim-3), and lymphocyte activating gene 3 (Lag-3), collectively referred to as immune-checkpoint receptors. Upregulation of these surface proteins restricts polyreactivity and proliferative capacity, func tional attributes of CD8+ T cells that are essential for effective killing of pathogens. Another mechanism contributing to the evasion by HIV of immune system control is the downregulation of HLA class I molecules on the surface of HIV-infected cells by the viral proteins Nef, Tat, and Vpu, resulting in the lack of ability of CD8+ CTLs to recognize and kill infected target cells. Although this downregulation of HLA

class I mol ecules would seem to favor elimination of HIV-infected cells by natural killer (NK) cells, this latter mechanism does not remove HIV-infected cells effectively (see below). Another potential means of escape of HIVinfected cells from elimination by CD8+ CTLs is the sequestration of infected cells in immunologically privileged sites such as the central nervous system (CNS), as well as the low frequency of virus-specific CD8+ CTLs in areas of lymphoid tissues, namely germinal centers, where HIV actively replicates. CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders
The principal targets of neutralizing antibodies against HIV are the envelope proteins gp120 and gp41. HIV employs at least three mechanisms to evade neutralizing antibody responses: hypervariability in the primary sequence of the envelope, extensive glycosylation of the envelope, and conformational masking of neutralizing epitopes.

Several studies that have followed the evolution of the humoral immune response to HIV from the earliest points after primary infec tion indicate that the virus continually mutates to escape the emerging antibody response such that the sequential antibodies that are induced do not neutralize the currently autologous virus. Broadly neutralizing antibodies capable of neutralizing a wide range of primary HIV isolates in vitro occur in only about 20% of people with HIV, and, when they do occur, 2–3 years of infection with continual virus replication are generally required to drive the affinity maturation of the antibodies. Unfortunately, by the time these broadly neutralizing antibodies are formed, they are ineffective in containing the virus currently replicat ing in the patient. Persistent viremia also results in exhaustion of B cells like the exhaustion reported for CD8+ T cells, adding to the defects in the humoral response to HIV.

CD4+ T cell help is essential for the integrity of both humoral and cell-mediated antigen-specific immune responses. HIV preferentially infects activated CD4+ T cells including HIV-specific CD4+ T cells, and so this loss of viral-specific helper T cell responses has profoundly negative consequences for the immunologic control of HIV replica tion. Furthermore, this loss occurs early in the course of infection, and animal studies indicate that 40–70% of all memory CD4+ T cells in the GALT are eliminated during acute infection. During chronic HIV viremia, CD4+ T cells also exhibit evidence of exhaustion, reflected in upregulation of the cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), also a member of the B7-CD28 family. Finally, the escape of HIV from immune-mediated elimination dur ing primary infection allows the formation of a pool of latently infected CD4+ T cells, referred to as the viral reservoir, which may not be rec ognized or completely eliminated by virus-specific CTLs or by ART (see below). Thus, despite a potent immune response and the marked downregulation of virus replication following primary HIV infection, HIV succeeds in establishing a state of chronic infection with a variable degree of persistent virus replication. During this period most patients make the clinical transition from acute primary infection to variable periods of clinical latency or smoldering disease activity (see below). PART 5 Infectious Diseases The HIV Reservoir: Obstacles to the Eradication of Virus

A pool of latently infected, resting CD4+ T cells that serves as at least one component of the persistent reservoir of virus exists in virtually all people with HIV, including those who are receiving ART. Such cells carry an integrated form of HIV DNA in the genome of the host and can remain in this state until an activation signal drives the expres sion of HIV transcripts. Only a small fraction of the latently infected cells in the viral reservoir contains replication-competent virus, with the overwhelming majority of cells containing defective proviruses incapable of a full replication cycle.

However, upon activation of the reservoir variable degrees of sustained virus replication invariably occur. This form of latency is to be distinguished from preintegration latency, in which HIV enters a resting CD4+ T cell and, in the absence of an activation signal, reverse transcription of the HIV genome occurs to a certain extent but the resulting proviral DNA fails to integrate into the host genome. This period of preintegration latency may last hours to days, and if no activation signal is delivered to the cell, the proviral DNA loses its capacity to initiate a productive infection. If these cells do become activated prior to decay of the preintegration complex, reverse transcription proceeds to completion and the virus continues along its replication cycle (see above and Fig. 208-20). The pool of cells that are in the postintegration state of latency is established early dur ing primary HIV infection. Despite the suppression of plasma viremia to <20–50 copies per milliliter by potent regimens of ART adminis tered over several years, this pool of latently infected cells persists and can give rise to replication-competent virus upon cellular activation ex vivo. Modeling studies built on projections of decay curves have estimated that in such a setting of prolonged viral suppression, it would require many years to the entire life of the host for the pool of latently infected cells to be eliminated. This has not been documented to occur spontaneously in any patients very likely because the latent viral reservoir is long-lived and is continually replenished by the low levels of persistent virus replication that may remain below the limits

Resting CD4+ T cell Preintegration latency (unstable) T-cell activation (Ag, cytokines) Degradation of unintegrated HIV DNA T-cell activation (Ag, cytokines) CTLs Resting CD4+ T cell Active Virus Replication Postintegration latency (stable) Cytopathic effect of virus Resting latently infected CD4+ memory T cells T-cell activation (Ag, cytokines) Virus spread FIGURE 208-20 Generation of latently infected, resting CD4+ T cells in people with HIV. See text for details. Ag, antigen; CTLs, cytolytic T lymphocytes. (Courtesy of TW Chun.) of detection of current assays (see below) as well as by the expansion by proliferation of the pool of latently infected cells (Fig. 208-20), even in patients who for the most part are treated successfully. Reservoirs of HIV-infected cells, latent or otherwise, can exist in multiple com partments including the lymphoid tissue, peripheral blood, and CNS (likely in cells of the monocyte/macrophage lineage) as well as in other unidentified locations. Over the past several years attempts have been made to eliminate HIV in the latent viral reservoir using agents that activate resting CD4+ T cells and/or reinitiate viral expression without systemic activation during the course of ART; however, such attempts, referred to as “shock and kill,” have thus far been unsuccessful. This persistent reservoir of infected cells remains a major obstacle to the goal of eradication of virus from infected individuals and hence a clas sic “cure,” despite the favorable clinical outcomes that have resulted from ART. Consequently, intense efforts are being directed toward investigating the feasibility of achieving ART-free HIV remission through passive transfer of long-acting broadly neutralizing antibodies and therapeutic agents that could enhance the host immune responses against the virus. Viral Dynamics The dynamics of viral production and turnover have been quantified using mathematical modeling in the setting of the administration of reverse transcriptase and protease inhibitors to people with HIV in clinical studies. Treatment with these drugs resulted in a precipitous decline in the level of plasma viremia, which typically fell by well over 90% within 2 weeks. It was determined on the basis of modeling the kinetics of viral decline and the emergence of resistant mutants during therapy that 93–99% of the circulating virus originated from recently infected, rapidly turning over CD4+ T cells and that ~1–7% of circulating virus originated from longer-lived cells, likely monocytes/macrophages. A negligible amount of circulating virus originated from the pool of latently infected cells (Fig. 208-21).

Replication cycle ~2 days Latently infected CD4+ T cells Rapidly turning over infected CD4+ T cells Half life 1.0 day Uninfected, activated CD4+ T cells ≤1% 93–99% Uninfected CD4+ T cells Circulating HIV virions Half life ~30–60 min 1–7% CD4+ T cells infected with defective viruses Longer-lived cells FIGURE 208-21 Dynamics of HIV infection in vivo. See text for detailed description. (Adapted from Perelson AS et al: HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time. Science 271:1582, 1996.) It was also determined that the half-life of a circulating virion was ~30–60 min and that of productively infected cells was 1 day. Given the relatively steady level of plasma viremia and of infected cells, it appears that extremely large amounts of virus (~1010–1011 virions) are produced and cleared from the circulation each day. In addition, data suggest that the minimal duration of the HIV-1 replication cycle in vivo is ~2 days. Other studies have demonstrated that the decrease in plasma viremia that results from treatment with ART correlates closely with a decrease in virus replication in lymph nodes, further confirming that lymphoid tissue is the main site of HIV replication and the main source of plasma viremia. The level of steady-state viremia, called the viral set point, at ~1 year following acquisition of HIV infection has important prognostic impli cations for the progression of HIV disease in the untreated patient. It has been demonstrated that, as a group, untreated people with HIV who have a low set point at 6 months to 1 year following infection prog ress to AIDS much more slowly than do individuals whose set point is very high at that time (Fig. 208-22). Clinical Latency versus Microbiologic Latency With the exception of certain long-term nonprogressors and “elite controllers” of HIV replication, the level of CD4+ T cells in the blood inevitably decreases progressively in viremic people with HIV in the absence of ART. The decline in CD4+ T cells may be gradual or abrupt, the latter usually reflecting a significant spike in the level of plasma vire mia. Most patients are relatively asymptomatic while this progressive 1.0 Proportion remaining AIDS-free 0.8 0.6 0.4 0.2 0.0 0

Time, years FIGURE 208-22 Relationship between levels of virus and rates of disease progression. Kaplan-Meier curves showing proportion of 1604 untreated patients remaining AIDS-free over 10 years, stratified by baseline HIV-1 RNA categories (copies per milliliter). (From Multicenter AIDS Cohort Study; JW Mellors, A Muñoz, JV Giorgi, JB Margolick, CJ Tassoni, P Gupta, LA Kingsley, JA Todd, AJ Saah, R Detels, JP Phair, CR Rinaldo, Jr.)

decline is taking place (see below) and are often described as being in a state of clinical latency. However, this term is misleading; it does not mean disease latency, since progression, although slow in many cases and often without symptoms, is generally relentless as evidenced by readily detectable plasma viremia, during this period. Furthermore, clinical latency should not be confused with microbiologic latency since varying levels of virus replica tion inevitably occur during this period of clinical latency. Even in those rare patients, such as elite controllers, who have <50 copies of HIV RNA per milliliter in the absence of therapy, there is virtually always some degree of lowlevel ongoing virus replication.

■ ■ADVANCED HIV DISEASE In untreated patients or in patients in whom therapy has not adequately controlled virus replication, after a vari able period, usually measured in years, the CD4+ T cell count falls below a critical level (<200/μL) and the patient becomes highly susceptible to opportunistic disease (Fig. 208-17). For this reason, the CDC case definition of stage 3 (AIDS) includes all people with HIV >5 years of age with CD4+ T cell counts below this level (Table 208-2). Patients may experience constitutional signs and symptoms or may develop an opportunistic

disease abruptly without any prior symptoms. The depletion of CD4+ T cells continues to be progressive and unrelenting in this phase. It is not uncommon for CD4+ T cell counts in the untreated patient to drop to as low as 10/μL or even to zero. In countries where ART as well as prophylaxis and treatment for opportunistic infections are readily accessible, survival is increased dramatically even in those patients with advanced HIV disease. In contrast, untreated patients who prog ress to this severest form of immunodeficiency usually succumb to opportunistic infections or neoplasms (see below). CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders

■ ■LONG-TERM SURVIVORS, LONG-TERM NONPROGRESSORS, AND ELITE CONTROLLERS It is important to distinguish between the terms long-term survivor and long-term nonprogressor. Long-term nonprogressors are by definition long-term survivors; however, the reverse is not always true. Predic tions from one study that antedated the availability of effective ART estimated that ~13% of homosexual/bisexual men who were infected at an early age may remain free of clinical AIDS for >20 years. Many of these individuals may have gradually progressed in their degree of immune deficiency; however, they certainly survived for a considerable period. With the advent of effective ART, the survival of people with HIV has dramatically increased. Early in the AIDS pandemic, prior to the availability of antiretroviral therapy, if a patient presented with a life-threatening opportunistic infection, the median survival was 26 weeks from the time of presentation. Currently, a 20-yearold individual with HIV who is appropri ately treated with ART can expect to live at least 50 years according to mathematical model projections. In the face of ART, longterm survival is now commonplace. Defi nitions of long-term nonprogressors have varied considerably over the years, and so such individuals constitute a heterogeneous group. Long-term nonprogressors were first described in the 1990s. Originally, individu als were considered to be long-term nonpro gressors if they had been infected with HIV for a long period (≥10 years), their CD4+ T cell counts were in the normal range, their plasma viremia remained relatively low (undetectable to several thousand copies of HIV RNA/mL plasma), and they remained clinically stable over years without receiv ing ART. Approximately 5–15% of people <500 500 to 3000 3001 to 10,000 10,001 to 30,000

> “ 30,000

with HIV fell into this broader nonprogressor category. However, this group was rather heterogeneous and over time a significant proportion of these individuals progressed and ultimately required antiretroviral therapy. From this broader group, a much smaller subgroup of “elite” controllers was identified, and they constituted a fraction of 1% of people with HIV. These elite controllers, by definition, have extremely low levels of plasma viremia that is often undetectable by standard assays and normal CD4+ T cell counts. It is noteworthy that their HIV-specific immune response, especially HIV-specific CD8+ CTLs that can clear infected CD4+ T cells, is robust and distinctly superior to those of progressors with HIV infection. In this group of elite control lers, certain HLA class I haplotypes are overrepresented, particularly HLA-B57-01 and HLA-B27-05. Outside of the subgroup of elite con trollers, multiple other genetic factors have been shown to be involved to a greater or lesser degree in the control of virus replication and thus in the rate of HIV disease progression (see “Genetic Factors in HIV-1 and AIDS Pathogenesis,” below).

■ ■LYMPHOID ORGANS AND HIV PATHOGENESIS Regardless of the portal of entry of HIV, lymphoid tissues are the major anatomic sites for the establishment and propagation of HIV infection. Despite the use of measurements of plasma viremia to determine the level of disease activity, virus replication occurs mainly in lymphoid tissue and not in blood; indeed, the level of plasma viremia directly reflects virus production in lymphoid tissue. Some patients experience progressive generalized lymphadenopathy early in the course of the infection; others experience varying degrees of transient lymphadenopathy. Lymphadenopathy reflects the cellular activation and immune response to the virus in the lymphoid tis sue, which is generally characterized by follicular or germinal center hyperplasia. Lymphoid tissue involvement is a common denominator of virtually all patients with HIV infection, even those without easily detectable lymphadenopathy. PART 5 Infectious Diseases Examinations of lymph tissue and peripheral blood in patients and monkeys during various stages of HIV and simian immunodeficiency virus (SIV) infection, respectively, have led to substantial insight into the pathogenesis of HIV disease. In most of the original human stud ies, peripheral lymph nodes were the predominant sources for analyses into changes in lymphoid tissues associated with HIV and SIV infec tion, whereas more recent studies have expanded to include the GALT, where the earliest burst of virus replication occurs associated with marked depletion of CD4+ T cells. A variety of techniques, including sensitive molecular and imaging approaches to visualize virus and cells in location or suspension, have been employed to describe events associated with HIV disease. During acute HIV infection resulting from mucosal transmission, virus replication progressively amplifies from scattered lymphoid cells in the lamina propria of the gut to drain ing lymph nodes, leading to high levels of plasma viremia. The GALT plays a major role in the amplification of virus replication, and virus is disseminated from replication in the GALT to peripheral lymphoid tis sues. A profound degree of cellular activation occurs within lymphoid tissues (see below) and is reflected in follicular or germinal center hyperplasia. At this time copious amounts of extracellular virions (both infectious and defective) are trapped on the processes of the follicular dendritic cells (FDCs) that form the stromal cell network in the light zones of lymph node germinal centers. Virions that have bound com plement components on their surfaces attach to the surface of FDCs via interactions with complement receptors and likely via Fc receptors that bind to antibodies that are attached to the virions. The use of in situ hybridization techniques, including those that allow detection of viral RNA in the context of tissue architecture, has revealed that HIV is primarily expressed in CD4+ T cells of the paracortical area and, to a lesser extent, in specialized CD4+ T cells (see below) in light zones of germinal centers (Fig. 208-23). The persistence of trapped virus on the surface of FDC likely reflects both a long-lived viral reservoir and virus that is replaced by continual expression in nearby CD4+ T cells. The trapped virus, either as whole virion or shed envelope, also serves as a continual activator of CD4+ T cells, thus driving further virus replication.

FIGURE 208-23 HIV in the lymph node of an HIV-infected individual. An individual cell infected with HIV shown expressing HIV RNA by in situ hybridization using a radiolabeled molecular probe. Original ×500. (Reproduced with permission from G Pantaleo et al: HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. Nature 362:355, 1993.) During the early stages of HIV disease, the architecture of lymphoid tissues is generally preserved and may even be hyperplastic owing to an increased presence of B cells and specialized CD4+ T cells called follicular helper CD4+ T cells (TFH) in prominent germinal centers. Extracellular virions can be seen by electron microscopy attached to FDC processes. The trapping of antigen is a physiologically normal function for the FDCs, which present antigen to B cells and secrete factors

such as CXCL13 that retain B and TFH cells in the light zones of germinal centers. These FDC functions, along with stimulatory factors produced by TFH cells, contribute to the generation of B cell memory. However, in the case of HIV, persistent cellular activation, resulting in a shift to secretion of proinflammatory cytokines such as interleukin (IL) 1β, tumor necrosis factor (TNF) α, IFN-γ, and IL-6, can induce viral replication (see below) and diminish the effectiveness of the immune response against the virus. In addition, the CD4+ TFH cells that are recruited into the germinal center to provide help to B cells in the generation of an HIV-specific immune response are highly susceptible to infection and may be an important component of the HIV reservoir. Thus, in HIV infection, a normal physiologic function of the immune system, i.e., the generation of an HIV-specific immune response that contributes to the clearance of virus, can also have del eterious consequences. As HIV disease progresses, the architecture of lymphoid tissues begins to disrupt. Confocal microscopy reveals destruction of the fibroblastic reticular cell (FRC) and FDC networks in the T cell zone and B cell follicles/germinal centers, respectively. The mechanisms of destruction are not completely understood, but they are thought to be associated with collagen deposition causing fibrosis and a shift in the expression of certain cytokines, namely decreases in IL-7 and lym photoxin α, which are critical to the maintenance of lymphoid tissues and their lymphocyte constituents, and increased levels of transform ing growth factor (TGF) β. As the disease progresses to an advanced stage, there is complete disruption of the architecture of the lymphoid tissues, accompanied by dissolution of the FRC and FDC networks. At this point, the lymph nodes are “burnt out.” This destruction of lymphoid tissue compounds the immunodeficiency of HIV disease and contributes both to the inability to control HIV replication and to the inability to mount adequate immune responses against opportu nistic pathogens and vaccination. The events from primary infection to the ultimate destruction of the immune system are illustrated in

Fig. 208-24. In nonhuman primate studies and some human studies that have examined GALT following SIV or HIV infection, the basal level of cellular activation combined with virus-mediated activation leads to the rapid infection and elimination of an estimated 50–90% of CD4+ T cells in the gut.

Massive viremia Wide dissemination to lymphoid organs Establishment of infection in GALT Primary infection Partial immunologic control of virus replication Destruction of Immune System Accelerated virus replication Rapid CD4+ T cell turnover FIGURE 208-24 Events that transpire from primary HIV infection through the establishment of chronic persistent infection to the ultimate destruction of the immune system. See text for details. GALT, gut-associated lymphoid tissue. ■ ■THE ROLE OF IMMUNE ACTIVATION AND INFLAMMATION IN HIV PATHOGENESIS Activation of the immune system and variable degrees of inflamma tion are essential components of any appropriate immune response to a foreign antigen. However, immune activation and inflammation, which are aberrant in certain individuals with HIV, play a critical role in the pathogenesis of HIV disease as well as other chronic conditions associated with HIV infection. Immune activation and inflammation in individuals with HIV contribute substantially to (1) the replication of HIV, (2) the induction of immune dysfunction, and (3) the increased incidence of chronic conditions such as premature cardiovascular disease (Table 208-4). INDUCTION OF HIV REPLICATION BY ABERRANT IMMUNE ACTIVATION

The immune system is normally in a state of homeostasis, awaiting per turbation by foreign antigenic stimuli. Once the immune response deals with and clears the antigen, the system returns

to relative quiescence (Chap. 360). This is generally not the case in HIV infection where, in the untreated patient, virus replication is invariably persistent with very few exceptions and as a result immune activation is persistent. HIV replicates most efficiently in activated CD4+ T cells; in HIV infection, chronic activation provides the cell substrates necessary for persistent virus replication throughout the course of HIV disease, particularly in the untreated patient. Even in certain patients receiving ART whose levels of plasma viremia are suppressed to <20 copies per milliliter, there are low but detectable degrees of virus replication that drives lowlevel persistent immune activation. In addition, immune activation may result from RNA transcription of the integrated DNA of defective proviruses. From a virologic standpoint, although quiescent CD4+ T cells can be infected with HIV, albeit inefficiently, reverse transcription, TABLE 208-4 Conditions Associated with Persistent Immune Activation and Inflammation in Patients with HIV Infection Accelerated aging syndrome Bone fragility Cancers Cardiovascular disease Diabetes Kidney disease Liver disease Neurocognitive dysfunction

integration, and virus spread are much more efficient in activated cells. Further more, cellular activation induces expres sion of virus in cells latently infected with HIV. In essence, immune activation and inflammation provide the engine that drives HIV replication. In addition to endogenous factors such as cytokines, multiple exogenous factors such as other microbes that induce cellular activation can enhance HIV replication and thus may play a role in HIV pathogenesis.

HIV-specific immune response Trapping of virus and establishment of chronic, persistent infection Co-infection with a range of viruses, such as HSV types 1 and 2, cytomegalo virus (CMV), human herpesvirus (HHV) 6, Epstein-Barr virus (EBV), HBV, HCV, adenovirus, and HTLV-1 have been shown to upregulate HIV expression. In addition, infestation with nematodes has been shown to be associated with a heightened state of immune activation that facilitates HIV replication; in certain studies, deworming of the infected host has resulted in a decrease in plasma vire mia. Two diseases of great global health significance, malaria and tuberculosis (TB), have been shown to increase HIV viral load in dually infected individuals. Globally, Mycobacterium tuberculosis is the most common opportunistic infection in people with HIV (Chap. 183). In addition to the fact that individuals with HIV are more likely to develop active TB after exposure and to reactivate latent TB, it has been demonstrated that active TB can accelerate the course of HIV infection. It has also been shown that levels of plasma viremia are greatly elevated in indi viduals with HIV who have active TB and who are not receiving ART, compared with pre-TB levels and levels of viremia after successful treatment of the active TB. The situation is similar in the interaction between HIV and malaria parasites (Chap. 231). Acute infection with Plasmodium falciparum of individuals with HIV increases viral load, and the increased viral load is reversed by effective treatment of malaria. Immune activation mediated by cytokines and HIV envelope-mediated aberrant cell signaling CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders MICROBIAL TRANSLOCATION AND PERSISTENT IMMUNE ACTIVATION

One proposed mechanism of persistent immune activation involves the disruption of the mucosal barrier in the gut due to HIV replication in submucosal lymphoid tissue. As a result of this disruption, there is an increase in the products of bacteria, particularly lipopolysaccharide (LPS), that translocate from the bowel lumen through the damaged mucosa to the circulation, leading to persistent systemic immune activation and inflammation. This effect can persist even after the HIV

viral load is brought to <20 copies/mL by ART. Other related factors that are thought to contribute to the pathogenesis of HIV include depletion in the GALT of IL-17–producing T cells, which are responsible for defense against extracellular bacteria and fungi, as well as alterations in gut microbiota and the metabolic pathways involved. PERSISTENT IMMUNE ACTIVATION AND INFLAMMATION INDUCE IMMUNE DYSFUNCTION The immune activated state in HIV infection is reflected by hyperactivation of B cells leading to hypergammaglobu linemia; increased lymphocyte turnover; activation of monocytes; expression of activation markers and immune checkpoint receptors on CD4+ and CD8+ T cells; increased activation-associated cellular apoptosis and pyroptosis; lymph node hyperplasia, particularly during the chronic phase prior to disease progression; increased secretion of proinflammatory cytokines, particularly IL-6 and type I interferons; elevated levels of high-sensitivity C-reactive protein (CRP), CXC che mokine ligand 10 (CXCL10), d-dimer, neopterin, β2-microglobulin, soluble (s) CD14, sTNFR, sCD27, sCD163, and sCD40L; and autoim mune phenomena (see “Autoimmune Phenomena,” below). Even in the absence of direct infection of a target cell, HIV envelope proteins can interact with cellular receptors (CD4 molecules and chemokine

receptors) to deliver potent activation signals resulting in calcium flux, the phosphorylation of certain proteins involved in signal transduc tion, co-localization of cytoplasmic proteins including those involved in cell trafficking, immune dysfunction, and, under certain circum stances, apoptosis and pyroptosis. From an immunologic standpoint, chronic exposure of the immune system to a particular antigen over an extended period may ultimately lead to an inability to sustain an adequate immune response to the antigen in question. In many chronic viral infections, including HIV infection, persistent viremia is associ ated with “functional exhaustion” of virus-specific T cells, decreasing their capacity to proliferate and perform effector functions. It has been demonstrated that this phenomenon of immune exhaustion may be mediated, at least in part, by the upregulation of inhibitory receptors on HIV-specific T cells, such as PD-1, LAG-3, and Tim-3 that are shared by both CD4+ and CD8+ T cells, as well as CTLA-4 on CD4+ and 2B4 and CD160 on CD8+ T cells. Furthermore, the ability of the immune system to respond to a broad spectrum of non-HIV antigens may be compromised if immunocompetent bystander cells are maintained in a state of chronic activation.

The deleterious effects of chronic immune activation on the pro gression of HIV disease are well established. As in most conditions of persistent antigen exposure, the host maintains activation of antigen (HIV)-specific responses but must also prevent excessive activation and potential immune-mediated damage to tissues. Certain studies suggest that normal immunoregulatory mechanisms that act to keep hyperimmune activation in check, particularly CD4+, FoxP3+, and CD25+ regulatory T cells (T-regs), may be dysfunctional or depleted in the context of advanced HIV disease. One possibility is a role for the inhibitory receptor LAG-3 (see below), which is overexpressed on exhausted T cells and shown to inhibit the proliferation of T-regs. PART 5 Infectious Diseases Apoptosis Apoptosis is a form of programmed cell death that is a normal mechanism for the elimination of effete cells in organogenesis as well as in the cellular proliferation that occurs during a normal immune response (Chap. 360). Apoptosis can occur by intrinsic or extrinsic pathways, the latter of which is largely dependent on cellular activation, and in this regard the aberrant cellular activation associated with HIV disease is correlated with a heightened state of apoptosis. HIV can trigger activation-induced cell death through the upregula tion of the death receptors, such as Fas/CD95, TNFR1, or TNF-related apoptosis-inducing ligand (TRAIL) receptors 1

and 2. Their corre sponding ligands FasL, TNF, and TRAIL also are upregulated in HIV disease. HIV-induced stress and alterations in homeostasis also can trigger intrinsic apoptosis due to the downregulation of antiapoptotic proteins such as Bcl-2. Other mechanisms of HIV-induced cell death have been described, including autophagy, necrosis, necroptosis, and pyroptosis. The phenomenon of pyroptosis, an inflammatory form of cell death involving the upregulation of the proinflammatory enzyme caspase 1 and release of the proinflammatory cytokines IL-1β and IL-18, has been linked to a bystander effect of HIV replication on depletion of CD4+ T cells (see "Pathophysiology and Pathogenesis," above). The process of pyroptosis generates multimeric complexes called inflammasomes, which can also be activated by LPS. Certain viral gene products have been associated with enhanced susceptibility to apoptosis; these include Env, Tat, and Vpr. In contrast, Nef has been shown to possess antiapoptotic properties. The intensity of apoptosis correlates with the general state of activation of the immune system and not with the stage of disease or with viral burden. Multiple studies, including those examining lymphoid tissue, have demonstrated that the rate of apoptosis is elevated in HIV infection and that apoptosis is seen in "bystander" cells such as CD8+ T cells and B cells as well as in uninfected CD4+ T cells. It is likely that this bystander apoptosis of immunocompetent cells related to immune activation contributes to the general immunologic abnormalities in HIV disease. MEDICAL CONDITIONS ASSOCIATED WITH PERSISTENT IMMUNE ACTIVATION AND INFLAMMATION IN HIV DISEASE It has become clear, as the survival of people with HIV has increased, that multiple, previously unrecognized medical complications are associated with HIV disease—and that these complications relate to chronic immune

activation and inflammation (Table 208-4). These complications can appear even after patients have experienced years of ART-induced adequate control of viral replication (plasma viremia <50 copies per milliliter of plasma) for several years. Other chronic conditions that have been reported include bone fragility, certain cancers, diabetes, kidney and liver disease, and neurocognitive dysfunction, thus present ing an overall picture of accelerated aging. Autoimmune Phenomena Autoimmune phenomena are com monly observed in people with HIV, and they reflect, at least in part, chronic immune activation and the dysregulation of B and T cells. Although these phenomena usually occur in the absence of autoim mune disease, a wide spectrum of clinical manifestations that may be associated with autoimmunity have been described (see "Immu nologic and Rheumatologic Diseases," below). Autoimmune phe nomena include antibodies against autoantigens expressed on intact lymphocytes and other cells, or against proteins released from dying cells. Antiplatelet and antierythrocyte antibodies have some clinical relevance in that they may contribute to thrombocytopenia and auto immune hemolytic anemia, respectively, in HIV disease (see below). Antibodies to nuclear and cytoplasmic components of cells have been reported, as have antibodies to cardiolipin and phospholipids, as well as surface receptors, including CD4, and serum proteins. However, these manifestations are relatively low in the era of ART. Molecular mimicry, either from opportunistic pathogens or from HIV itself, also is a trigger or cofactor in autoimmunity. Antibodies against the HIV envelope proteins, especially gp41, often cross-react with host proteins; the best-known examples are antibodies directed against the membrane-proximal external region (MPER) of gp41 that also react with phospholipids and cardiolipin. The phenomenon of polyreactive HIV-specific antibodies may be beneficial to the host (see "Immune Response to HIV," below). The increased occurrence and/or exacerbation of certain autoim mune diseases have been reported in HIV infection; these diseases include psoriasis, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, Graves' disease,

antiphospholipid syndrome, and primary biliary cirrhosis. Most of these manifestations were described prior to the advent of ART and have decreased in frequency since its widespread use. However, with increasing availability of ART, an immune reconstitution inflammatory syndrome (IRIS) has been increas ingly observed in infected individuals, particularly those with low CD4+ T cell counts (see below). IRIS is an autoimmune-like phenom enon characterized by a paradoxical deterioration of clinical condition, which is usually compartmentalized to a particular organ system in individuals in whom ART has recently been initiated. It is associated with a decrease in viral load and at least partial recovery of immune competence, which is usually associated with increases in CD4+ T cell counts. The immunopathogenesis of this syndrome is felt to be related to an increase in immune response against the presence of residual antigens that are usually microbial and is most commonly seen with underlying mycobacterial (Mycobacterium tuberculosis [TB] or avium complex [MAC]), fungal (cryptococcal), and viral (CMV, HHV) infec tions. This syndrome is discussed in more detail below. ■ ■CYTOKINES AND OTHER SOLUBLE FACTORS

IN HIV PATHOGENESIS The immune system is homeostatically regulated by a complex network of immunoregulatory cytokines, which are pleiotropic and redun dant and operate in an autocrine and paracrine manner. They are expressed continuously, even during periods of apparent quiescence of the immune system. On perturbation of the immune system by antigenic challenge, the expression of cytokines increases to varying degrees (Chap. 360). Cytokines that are important components of this immunoregulatory network are thought to play major roles in HIV disease, during both the early and chronic phases of infection. A potent proinflammatory “cytokine storm” is induced during the acute phase of HIV infection, likely a response of inflammatory cells to virus replicating at very high levels. Cytokines and chemokines that are induced during this early phase include the type I interferon IFN-α,

IL-15, and CXCL10, followed by IL-6, IL-12, and TNF-α, and a delayed peak of the anti-inflammatory cytokine IL-10. Soluble factors of innate immunity also are induced shortly after infection, including neopterin and β-microglobulin. Several of these early-expressed cytokines and factors are not downregulated following the early phase of HIV infec tion, as seen in other self-resolving viral infections, and persist during the chronic phase of infection and contribute to maintaining high levels of immune activation. Among the cytokines and factors associ ated with early innate immune responses, they are intended to contain viral replication, although paradoxically most are potent inducers of HIV expression/replication because of their ability to induce immune activation that leads to enhanced viral production and an increase in readily available target cells for HIV (activated CD4+ T cells). The induction of IFN-α, one of the first cytokines induced during primary HIV infection and an important element of innate immune sensing, is thought to play a particularly important role in HIV pathogenesis by inducing a large number of IFN-associated genes that activate the immune system, alter the homeostasis of CD4+ T cells, and influ ence the virus variants that are selected during the HIV transmission bottleneck. Other cytokines that are elevated during the chronic phase of HIV infection and linked to immune activation include IFN-γ, the CC-chemokine RANTES (CCL5), macrophage inflammatory protein (MIP) 1β (CCL4), and IL-18. Multiple cytokines and soluble factors have been associated with HIV pathogenesis at various stages of disease, in various tissues or organs, and in the regulation of HIV replication. Plasma levels of IP-10 are predic tive of disease progression, whereas the proinflammatory cytokine IL-6, marker of monocyte/macrophage activation soluble CD14 (sCD14), and coagulation marker d-dimer are associated with increased risk of all-cause mortality in people with HIV. In particular, IL-6,

sCD14, and d-dimer are associated with increased risk of cardiovascular disease and other causes of death, even in individuals receiving ART. IL-18 has also been shown to play a role in the development of the HIV-associated lipodystrophy syndrome. Elevated levels of TNF-α and IL-6 have been demonstrated in plasma and cerebrospinal fluid (CSF), and increased expression of TNF-α, IL-1β, IFN-γ, and IL-6 has been demonstrated in the lymph nodes of people with HIV prior to disease progression and a shift to TGF-β in advanced disease (see “Lymphoid Organs and HIV Pathogenesis,” above). RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4) (Chap. 360) inhibit infection by and spread of R5 HIV-1 strains, while stromal cell–derived factor (SDF) 1 inhibits infection by and spread of X4 strains. The mechanisms whereby the CC-chemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4) inhibit infection of R5 strains of HIV, or SDF-1 blocks X4 strains of HIV, involve blocking of the binding of the virus to its co-receptors, the CC-chemokine receptor CCR5 and the CXC-chemokine receptor CXCR4, respectively. Other soluble factors that have not yet been fully characterized, such as soluble CD8 antiviral factor (CAF), also have been shown to suppress HIV rep lication, independent of co-receptor usage. ■ ■LYMPHOCYTE TURNOVER IN HIV INFECTION The immune systems of patients with HIV infection are characterized by a profound increase in lymphocyte turnover that is immediately reduced with effective ART. Studies utilizing in vivo or in vitro labeling of lymphocytes in the S-phase of the cell cycle have demonstrated a tight correlation between the degree of lymphocyte turnover and plasma vire mia. This increase in turnover is seen in CD4+ and CD8+ T lymphocytes as well as B lymphocytes and can be observed in peripheral blood and lymphoid tissue. Mathematical models derived from these data suggest that one can view the lymphoid pool as consisting of dynamically distinct subpopulations of cells that are differentially affected by HIV infection. A major consequence of HIV infection appears to be a shift in cells from a more quiescent pool to a pool with a higher turnover rate. It is likely that a consequence of a higher rate of turnover is a higher rate of cell death. It has been suggested that the more rapid decline in CD4+ compared with CD8+ T cells may be linked to alterations in inflammatory and homeostatic cytokines that cause increased activation-induced death without replenishment of CD4+ T cells. (See Table 208-5 for additional mechanisms of depletion.)

TABLE 208-5 Proposed Mechanisms of CD4+ T Cell Dysfunction and Depletion DIRECT MECHANISMS INDIRECT MECHANISMS Loss of plasma membrane integrity due to viral budding Aberrant intracellular signaling events Accumulation of unintegrated viral DNA Activation of DNA-dependent protein kinase during viral integration into host genome Autoimmunity Interference with cellular RNA processing Innocent bystander killing of viral

antigen–coated cells Intracellular gp120–CD4 autofusion events Apoptosis, pyroptosis (caspase

1–associated inflammation), autophagy Syncytia formation Inhibition of lymphopoiesis from reduced survival cytokines and lymphoid tissue integrity Activation-induced cell death Elimination of HIV-infected cells by virusspecific immune responses ■ ■THE ROLE OF VIRAL RECEPTORS AND CO-RECEPTORS IN HIV PATHOGENESIS CCR5 AND CXCR4 As mentioned above, HIV-1 utilizes two major coreceptors along with CD4 to bind to, fuse with, and enter target cells; these co-receptors are CCR5 and CXCR4, which are also receptors for certain endogenous chemokines. Strains of HIV that utilize CCR5 as a co-receptor are referred to as R5 viruses. Strains of HIV that utilize CXCR4 are referred to as X4 viruses. Many virus strains are dual tropic in that they utilize both CCR5 and CXCR4; these are referred to as R5X4 viruses. CHAPTER 208 Human Immunodeficiency Virus

The natural chemokine ligands for the major HIV co-receptors can readily block entry of HIV. For example, the CC-chemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4), which are the natu ral ligands for CCR5, block entry of R5 viruses, whereas SDF-1, the natural ligand for CXCR4, blocks entry of X4 viruses. The mechanism of inhibition of viral entry is a steric inhibition of binding that is not dependent on signal transduction (Fig. 208-25). The transmitting virus is almost invariably an R5 virus that pre dominates during the early stages of HIV disease, although in the era of deep sequencing, more X4 variants have been detected in early disease than were previously reported. In the absence of ART or in therapeutic failures, there is a transition to a predominantly X4 virus in approxi mately half of individuals infected with subtype B virus. The transition is often preceded by dual R5X4 strains, and detection of X4 variants is associated with a relatively rapid decline in CD4+ T cell counts, increased HIV plasma viremia, and progression of disease. However, the other half of infected individuals progress in their disease while maintaining predominance of an R5 virus, and individuals infected with non–subtype B clades more rarely switch from CCR5 tropism to CXCR4 tropism than do those infected with subtype B. The reason for this difference is unclear. The basis for the tropism of different envelope glycoproteins for either CCR5 or CXCR4 relates to the ability of the HIV envelope, including the third variable region (V3 loop) of gp120, to interact with these co-receptors. In this regard, binding of gp120 to CD4 induces a conformational change in gp120 that increases its affinity for the relevant co-receptor. Finally, R5 viruses are more efficient in infecting monocytes/macrophages and microglial cells of the brain (see “Neuro pathogenesis in HIV Disease,” below). THE INTEGRIN `4a7 The integrin a4β7 is an accessory receptor for HIV. It is not essential for the binding and infection of a CD4+ T cell by HIV; however, it likely plays an important role in the transmission of HIV at mucosal surfaces such as the genital tract and gut and con tributes somewhat to the pathogenesis of HIV disease. The integrin a4β7, which is the gut homing receptor for peripheral T cells, binds

ENV HIV HIV CD4 CD4+ Target Cell SDF-1 CXCR4 A ENV HIV HIV CD4 CD4+ Target Cell PART 5 Infectious Diseases CC-Chemokine (RANTES, MIP-1α, MIP-1β) CCR5 B FIGURE 208-25 Model for the role of co-receptors CXCR4 and CCR5 in the efficient binding and entry of X4 (A) and R5 (B) strains of HIV-1, respectively, into CD4+ target cells. Blocking of this initial event in the virus life cycle can be accomplished by inhibition of binding to the co-receptor by the normal ligand for the receptor in question. The ligand for CXCR4 is stromal cell–derived factor (SDF-1); the ligands for CCR5 are RANTES, MIP-1a, and MIP-1b. in its activated form to a specific tripeptide in the V2 loop of gp120, resulting in rapid activation of leukocyte function–associated antigen 1 (LFA-1), the central integrin in the establishment of virologic synapses, which facilitate efficient cell-to-cell spread of HIV. It has been demon strated that α4β7high CD4+ T cells are more susceptible to productive infection than are α4β7low–neg CD4+ T cells because this cellular subset is enriched with metabolically active CD4+ T cells that are CCR5high. These cells are present in the mucosal surfaces of the gut and genital tract. Importantly, it has been demonstrated that the virus that is trans mitted during sexual exposure binds much more efficiently to α4β7 than does the virus that diversifies from the transmitting virus over time by mutation, particularly involving the accumulation of glycogens on the surface of the HIV envelope (see “Early Events in HIV Infection: Primary Infection and Initial Dissemination of Virus,” above). ■ ■CELLULAR TARGETS OF HIV CD4+ T lymphocytes and to a lesser extent CD4+ cells of the myeloid lineage are the principal targets of HIV and are the only cells that can be productively infected with HIV. Circulating DCs have been reported to express low levels of CD4, although high expression of the restric tion factor SAMHD1 in myeloid (mDC) and

plasmacytoid (pDC) DCs limits HIV replication in these cells by depleting intracellular pools of dNTPs and directly degrading viral RNA. Epidermal Langerhans cells express CD4 and have been infected by HIV in vivo, although they too restrict replication by high expression of the host restriction fac tor langerin. As has been shown in vivo for DCs, FDCs, and B cells,

Langerhans cells are more likely to bind and transfer virus to activated CD4+ T cells than to be productively infected themselves. Of potential clinical relevance is the demonstration that thymic precursor cells, which were assumed to be negative for CD3, CD4, and CD8 molecules, express low levels of CD4 and can be infected with HIV in vitro. In addition, human thymic epithelial cells trans planted into an immunodeficient mouse can be infected with HIV by direct inoculation of virus into the thymus. Since these cells may play a role in the normal regeneration of CD4+ T cells, it is possible that their infection and depletion contribute, at least in part, to the impaired ability of the CD4+ T cell pool to completely reconstitute itself in certain infected individuals in whom ART has suppressed plasma viremia to below the level of detection (see below). In addition, CD34+ monocyte precursor cells have been shown to be infected in vivo in patients with advanced HIV disease. It is likely that these cells express low levels of CD4, and therefore it is not essential to invoke CD4-independent mechanisms to explain the infection. The clinical relevance of this finding is unclear. ■ ■QUALITATIVE AND QUANTITATIVE ABNORMALITIES OF MONONUCLEAR CELLS CD4+ T Cells The primary immunopathogenic lesion in HIV infection involves CD4+ T cells, and the range of CD4+ T cell abnor malities in advanced HIV infection is broad. The defects are both quantitative and qualitative and ultimately impact virtually every limb of the immune system, indicating the critical dependence of the integ rity of the immune system on the inducer/helper function of CD4+

T cells. In advanced HIV disease, most of the observed immune defects can ultimately be explained by the quantitative depletion of CD4+ T cells. However, T cell dysfunction can be demonstrated in patients early in the course of infection, even when the CD4+ T cell count is in the low–normal range. The degree and spectrum of dysfunctions increase as the disease progresses, reflecting the range of CD4+ T cell functional heterogeneity, especially in lymphoid tissues. One of the first sites of intense HIV replication is in the GALT where CD4+ TH17 cells reside; they are important for host defense against extracellular pathogens in the intestinal mucosa and help maintain the integrity of the gut epithe lium. In HIV infection, they are depleted by direct and indirect effects of viral replication and cause loss of gut homeostasis and integrity, as well as a shift toward a TH1 phenotype. Studies have shown that even after many years of ART, normalization of the CD4+ T cells in the GALT remains incomplete. In lymph nodes, HIV perturbs another important subset of the CD4+ helper T lineage, namely TFH cells (see “Lymphoid Organs and HIV Pathogenesis,” above). TFH cells, which are derived either directly from naïve CD4+ T cells or from other TH precursors, migrate into B cell follicles during germinal center reactions and pro vide help to antigen-specific B cells through cell–cell interactions and secretion of cytokines to which B cells respond, the most important of which is IL-21. In addition, it has been shown that people with HIV who have broadly neutralizing antibodies have higher frequencies of memory TFH CD4+ T cells. As with TH17 cells, TFH cells are highly susceptible to HIV infection. However, in contrast to TH17 and most other CD4+ T cell subsets, the number of TFH cells is increased in lymph nodes of people with HIV, especially those who are viremic. It is unclear whether this increase is helpful to responding B cells, although the likely outcome is that the increase in numbers is detrimental to the quality of the humoral immune response against HIV (see “Immune Response to HIV,” below). In addition, defects of central memory cells are a critical component of HIV immunopathogenesis. The

progressive loss of antigen-specific CD4+ T cells has important implications for the control of HIV infection. In this regard, there is a correlation between the maintenance of HIV-specific CD4+ T cell proliferative responses and improved control of infection. Essentially every T cell function has been reported to be abnormal at some stage of HIV infection. Loss of polyfunctional HIV-specific CD4+ T cells, especially those that produce IL-2, occurs early in disease, whereas IFN-producing CD4+ T cells are maintained longer and do not correlate with control of HIV viremia. Other abnormalities include impaired expression of IL-2 receptors,

defective IL-2 production, reduced expression of the IL-7 receptor (CD127), and a decreased proportion of CD4+ T cells that express CD28, a major co-stimulatory molecule necessary for the normal activation of T cells, which is also depleted due to aging. Cells lacking expression of CD28 do not respond normally to activation signals and may express markers of terminal activation including HLA-DR, CD38, and CD45RO. As mentioned above (“The Role of Immune Activation and Inflammation in HIV Pathogenesis”), a subset of CD4+ T cells referred to as T regulatory cells, or T-regs, may be involved in damp ing aberrant immune activation that propagates HIV replication. The presence of these T-reg cells correlates with lower viral loads and higher CD4+/CD8+ T cell ratios. A loss of this T-reg capability with advanced disease may be detrimental to the control of virus replication. It is difficult to explain completely the profound immunodeficiency noted in people with HIV solely based on direct infection and quantita tive depletion of CD4+ T cells. This is particularly apparent during the early stages of HIV disease, when CD4+ T cell numbers may be only marginally decreased. In this regard, it is likely that CD4+ T cell dysfunc tion results from a combination of depletion of cells due to direct infec tion of the cell and multiple virus-related but indirect effects on the cell (Table 208-5). Several of these effects have been demonstrated ex vivo and/or by the analysis of cells isolated from the peripheral blood. Soluble viral proteins, particularly gp120, can bind with high affinity to the CD4 molecules on uninfected T cells and monocytes; in addi tion, virus and/or viral proteins can bind to DCs or FDCs. HIV-specific antibodies can recognize these bound molecules and potentially collaborate in the elimination of the cells by ADCC. HIV envelope glycoproteins gp120 and gp160 manifest high-affinity binding to the CD4 molecule as well as to various chemokine receptors. Intracellular signals transduced by gp120 through both CD4 and CCR5/CXCR4 have been associated with a number of immunopathogenic processes including anergy, apoptosis, and abnormalities of cell trafficking. The molecular mechanisms responsible for these abnormalities include dysregulation of the T cell receptor–phosphoinositide pathway, p56lck activation, phosphorylation of focal adhesion kinase, activation of the MAP kinase and ras signaling pathways, and downregulation of the co-stimulatory molecules CD40 ligand and CD80. The inexorable decline in CD4+ T cell counts that occurs in most untreated people with HIV may result in part from the inability of the immune system to regenerate over an extended period of time the rap idly turning over CD4+ T cell pool efficiently enough to compensate for both HIV-mediated and naturally occurring attrition of cells. In this regard, the degree and duration of decline of CD4+ T cells at the time of initiation of therapy is an important predictor of the restora tion of these cells. A person who maintains a very low CD4+ T cell count for a considerable period before the initiation of ART almost invariably has an incomplete reconstitution of such cells. At least two major mechanisms may contribute to the failure of the CD4+ T cell pool to reconstitute itself adequately over the course of HIV infection. The first is the destruction of lymphoid precursor cells, including thymic and bone marrow progenitor cells; the other is the gradual disruption of the lymphoid tissue architecture and microenvironment, which is essential for efficient regeneration of immunocompetent cells. Finally, during the advanced stages of CD4+ T lymphopenia, there are

increased serum levels of the homeostatic cytokine IL-7. It was initially felt that this elevation was a homeostatic response to the lymphopenia; however, recent findings suggest that the increase in serum IL-7 was a result of reduced utilization of the cytokine related to the loss of cells expressing the IL-7 receptor, CD127, which serves as a normal physi ologic regulator of IL-7 production. CD8+ T Cells A relative CD8+ T lymphocytosis is generally asso ciated with high levels of HIV plasma viremia and likely reflects an immune response to the virus as well as dysregulated homeostasis asso ciated with generalized immune activation. During the late stages of HIV infection, there may be a significant reduction in the numbers of CD8+ T cells despite the presence of high levels of viremia. HIV-specific CD8+ CTLs have been demonstrated in people with HIV early in the course of disease, and their emergence often coincides with a decrease

in plasma viremia—an observation that is a factor in the proposal that virus-specific CTLs can control HIV disease for a finite period of time in a certain percentage of infected individuals. However, emergence of HIV escape mutants that ultimately evade these HIV-specific CD8+ T cells has been described in most people with HIV who are not receiving ART. In addition, as the disease progresses, the functional capability of these cells gradually decreases, at least in part due to the persistent nature of HIV infection that causes functional exhaustion via the upregulation of inhibitory receptors such as PD-1, TIGIT, LAG-3, and TIM-3 on HIV-specific CD8+ T cells (see “The Role of Immune Activation and Inflammation in HIV Pathogenesis,” above). As chronic immune activation persists, there are also systemic effects on CD8+ T cells, such that as a population they assume an abnormal phenotype characterized by expression of activation markers such as co-expression of HLA-DR and CD38 with an absence of expression of the IL-2 receptor (CD25) and a reduced expression of the IL-7 receptor (CD127). In addition, CD8+ T cells lacking CD28 expression are increased in HIV disease, reflecting a skewed expansion of a less differentiated CD8+ T cell subset. This skewing of subsets is also asso ciated with diminished polyfunctionality, a qualitative difference that distinguishes elite controllers from progressors. Elite controllers can also be distinguished from progressors by the maintenance in the for mer of a high proliferative capacity of their HIV-specific CD8+ T cells coupled to increases in perforin expression and elimination of infected targets, characteristics that are markedly diminished in advanced HIV disease. It has been reported that the phenotype of CD8+ T cells in people with HIV may be of prognostic significance. Those individuals whose CD8+ T cells developed a phenotype of HLA-DR+/CD38–

following seroconversion had stabilization of their CD4+ T cell counts, whereas those whose CD8+ T cells developed a phenotype of HLA-DR+/ CD38+ had a more aggressive course and a poorer prognosis. In addi tion to the defects in HIV-specific CD8+ CTLs, functional defects in other MHC-restricted CTLs, such as those directed against influenza and CMV, have been demonstrated. CD8+ T cells secrete a variety of soluble factors that inhibit HIV replication, including the CC-chemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4) and poten tially several yet-unidentified factors. The presence of high levels of HIV viremia in vivo as well as exposure of CD8+ T cells in vitro to HIV envelope, both of which are associated with aberrant immune activation, have been shown to be associated with a variety of cellular functional abnormalities. Furthermore, since the integrity of CD8+ T cell function depends in part on adequate inductive signals from CD4+ T cells, the defect in CD8+ CTLs is likely compounded by the quantita tive loss and qualitative dysfunction of CD4+ T cells.

B Cells The predominant defect in B cells from people with HIV is one of aberrant cellular activation, which is reflected by increased propensity to terminal differentiation and immunoglobulin secretion, as well as increased expression of markers of activation and exhaustion. As a result of activation and differentiation in vivo and induction of inhibitory pathways of regulation, B cells from HIV viremic patients manifest a decreased capacity to undergo cell signaling and mount a proliferative response ex vivo. B cells from people with HIV manifest enhanced spontaneous secretion of immunoglobulins in vitro, a pro cess that reflects their highly differentiated state in vivo. There is also an increased incidence of EBV-related B cell lymphomas in people with HIV that are likely due to combined effects of defective T cell immune surveillance and increased B cell turnover that increases the risk of oncogenesis. Untransformed B cells cannot be infected with HIV, although HIV or its products can activate B cells directly. B cells from patients with high levels of viremia bind virions to their surface via the CD21 complement receptor. It is likely that in vivo activation of B cells by replication-competent or defective virus as well as viral products during the viremic state accounts at least in part for their activated phe notype. B cell subpopulations from people with HIV undergo a number of changes over the course of HIV disease, including the attrition of resting memory B cells and replacement with several aberrant mem ory and differentiated B cell subpopulations that collectively express reduced levels of CD21 and either increased expression of activation

markers or inhibitory receptors associated with functional exhaustion. The more activated and differentiated B cells are also responsible for increased secretion of immunoglobulins and increased susceptibility to Fas-mediated apoptosis. In more advanced disease, there is also the appearance of immature B cells associated with CD4+ T cell lymphope nia. Despite increased frequencies of germinal center B cells and CD4+ TFH cells, both of which are required for effective humoral immunity, cognate B cell–CD4+ T cell interactions in lymphoid tissues are per turbed in people with HIV, especially those with persistent viremia. In vivo, the aberrant activated state of B cells manifests itself by hypergam maglobulinemia and by the presence of circulating immune complexes that bind the B cells and restrict their capacity to respond to further stimulation. People with HIV respond poorly to primary and secondary immunizations with protein and polysaccharide antigens. Using immu nization with influenza vaccine, it has been demonstrated that there is a memory B cell defect in people with HIV, particularly those with high levels of HIV viremia. There is also evidence that responses to HIV and non-HIV antigens in infected individuals, especially those who remain viremic, are enriched in abnormal subsets of B cells that either are highly prone to apoptosis or show signs of functional exhaustion. Taken together, these B cell defects are likely responsible at least in part for the inadequate humoral response to HIV as well as to decreased response to vaccinations and the increase in certain bacterial infections seen in advanced HIV disease in adults. In addition, they likely contribute to the inadequacy of host defenses against bacterial infections that play a role in the increased morbidity and mortality of children with HIV. The absolute number of circulating B cells also may be depressed in HIV infection; this phenomenon likely reflects increased activation-induced apoptosis as well as a redistribution of cells out of the circulation and into the lymphoid tissue—phenomena that are associated with ongoing viral replication. Monocytes/Macrophages Circulating monocytes are generally normal in number in people with HIV; however, there is evidence of increased activation within this lineage. The increased level of sCD14 and other biomarkers (see above) reported in people with HIV is an indirect marker of monocyte activation in vivo. Levels of sCD14 can remain elevated in individuals

whose plasma viremia has been sup pressed by ART for several years, an indicator of the residual immune activation and inflammation observed in HIV infection and effects on the monocyte/macrophage lineage. Multiple other abnormalities of circulating monocytes have been reported in people with HIV, many of which may be related directly or indirectly to aberrant in vivo immune activation. In this regard, increased levels of lipopolysac charide (LPS) are found in the sera of people with HIV due, at least in part, to translocation across the gut mucosal barrier (see above). LPS is a highly inflammatory bacterial product that preferentially binds to macrophages through CD14 and Toll-like receptors, resulting in cel lular activation. In the peripheral blood, expansion of monocytes that express the intermediate and nonclassical marker CD16 and markers of activation (HLA-DR) and stimulation (CD40 and CD86) has been described, especially in viremic individuals. Activated monocytes are also responsible for secretion of inflammatory cytokines and chemo kines observed in HIV infection, including CXCL10, IL-1β, and IL-6. Monocytes express the CD4 molecule and several co-receptors for HIV on their surface, and thus are potential targets of HIV infection. How ever, in vivo infection of circulating monocytes is difficult to demonstrate, although infection of tissue macrophages and macrophage-lineage cells in the brain (infiltrating macrophages or resident microglial cells) and lung (pulmonary alveolar macrophages) can be demonstrated easily. Tissue macrophages are an important source of HIV during the inflam matory response associated with opportunistic infections and can serve as persistent reservoirs of HIV infection, thus representing an obstacle to the eradication of HIV by antiretroviral drugs. Dendritic and Langerhans Cells DCs and Langerhans cells are not productively infected with HIV, likely in part due to their expres sion of host restriction factors, including APOBEC3G and SAMHD1 (see above). However, they are thought to play an important role in the initiation of HIV infection by virtue of the ability of HIV to bind

to cell-surface C-type lectin receptors, particularly DC-SIGN (see above) and langerin. However, while langerin provides a host barrier for replication by trafficking HIV to acidic compartments for degrada tion, DC-SIGN retains HIV in early endosomal compartments. This allows efficient presentation of intact virus to CD4+ T cell targets that become infected; complexes of infected CD4+ T cells and DCs provide an optimal microenvironment for virus replication. Furthermore, pDCs secrete large amounts of IFN-α in response to viral infections and as such play an important role in innate sensing of HIV during early phase of infection. The numbers of circulating pDCs and mDCs are decreased in HIV infection through mechanisms that remain unclear, although several studies have shown increased lymphoid tissue recruitment of DCs associated with lymphoid hyperplasia and inflammation. The mDCs are also involved in the initiation of adaptive immunity in drain ing lymph nodes by presenting antigen to T cells and B cells, as well as by secreting cytokines such as IL-12, IL-15, and IL-18 that activate other immune cells, although these functions are perturbed in HIV infection. Natural Killer Cells and Innate Lymphoid Cells NK cells represent the prototypical member of innate lymphoid cells (ILCs) that collectively provide tissue homeostasis and immunosurveillance against virus-infected cells, certain tumor cells, and allogeneic cells (Chap. 360). There are no convincing data that HIV productively infects NK cells in vivo; however, functional abnormalities in NK cells have been observed throughout the course of HIV disease, and the severity of these abnormalities increases as disease progresses. NK cells are part of the innate immune system and act by direct killing of infected cells and secretion of antiviral cytokines and chemokines. In early HIV infection there is an increase in the activation of NK cells, and the

capacity to secrete IFN-γ is maintained, although they manifest reduced cytotoxic function as a result of altered maturation. During chronic HIV infection, both NK cell cytotoxicity and cytokine secre tion become impaired. Given that HIV infection of target cells down regulates HLA-A and B, but not HLA-C and D molecules, this may explain in part the relative inability of NK cells to kill HIV-infected tar get cells. However, the NK cell impairments, especially in patients with high levels of virus replication, are associated with an expansion of an “anergic” CD56–/CD16+ NK cell subset. This abnormal subset of NK cells manifests an increased expression of inhibitory NK cell receptors (iNKRs) and a substantial decrease in expression of natural cytotoxic ity receptors (NCRs) and shows a markedly impaired lytic activity. The overrepresentation of this abnormal subset of NK cells may explain in part the observed defects in NK cell function in people with HIV and likely begins to occur during primary infection. The relative expression of iNKRs and NCRs—as well as their ligands, which include HLA class I molecules—has an impact on the antiviral functions associated with NK cells, including direct killing and ADCC. Polymorphisms in iNKR and NCR alleles have been linked to HIV-1 disease outcomes, and there are indications that the early control of HIV may be mediated by cytotoxic NK cell-mediated responses. NK cells may also serve as sources of HIV-inhibitory soluble factors, including CC-chemokines such as MIP-1α (CCL3), MIP-1β (CCL4), and RANTES (CCL5). Finally, both inflammatory cytokines and alterations in the GALT of HIV infected individuals disrupt NK cells and other ILCs. ■ ■GENETIC FACTORS IN HIV-1 AND

AIDS PATHOGENESIS Candidate gene approaches and genome-wide association studies (GWAS) have identified polymorphisms in host genes that contribute to inter-individual variation in (1) the risk of acquiring HIV, (2) the steady-state levels of HIV that are established soon after infection (virologic set point), (3) the rate at which untreated HIV infection progresses to AIDS defined by a CD4+ T cell count that is lower than 200 cells/mm3 and/or development of AIDS-defining illnesses, (4) the level of immune reconstitution (e.g., CD4+ cell counts) achieved and risk of non-AIDS-associated diseases after initiation of virally suppressive antiretroviral therapy (ART), and (5) adverse reactions to antiretroviral agents. The key polymorphisms that influence these five outcomes are summarized in Table 208-6, and their identification has

TABLE 208-6 Host Genetic Factors Influencing HIV/AIDS Pathogenesis and Therapy Responses GENEa GENETIC VARIATION MECHANISMSb GENETIC ASSOCIATIONSc Genes in MHC Locus HLA-B B *27 and B*57 Altered presentation of specific HIV antigens Slower progression to AIDS; lower viral load B*35 Restriction of specific HIV peptide presentation Faster progression to AIDS; higher viral load HLA-Bw4 Providing ligands for activating KIR Slower progression to AIDS B*57:01 Altered presentation of specific HIV antigens (as above); possible abacavir-specific activation of cytokine-producing CD8+ T cells in carriers of this allele HLA-B? 21M allele Enhanced HLA-E expression levels correlated with higher HLA-A expression and inhibition of NKG2Aexpressing cells B*57:03 bearing the rs2523608-A allele Altered presentation of specific HIV antigens Variant overexpressed in HIV-1 controllers of African descent HLA class I allele Homozygosity of HLA-class I alleles Reduced repertoire for epitope recognition Faster progression to AIDS; increased risk of mother-to-child transmission Shared donor–recipient HLA alleles Preadaptation of HIV strains Faster progression to AIDS Rare HLA alleles Limited adaptation of HIV strains; less frequent escape mutants HLA class II allele HLA-DRB1 alleles Influence on protein specificity of CD4+ T cell responses to HIV Gag and Nef proteins HLA extended haplotype A1-B8-DR3-DQ2 (AH 8.1) Increased proinflammatory responses; higher TNF-α production HLA-C rs9264942-C allele (35 kb upstream of HLA-C) in linkage with rs67384697-Del Increased expression of HLA-C by reducing binding of

*miRNA-148a rs5010528-G (1 kb upstream of HLA-C) Unknown Higher risk of developing nevirapine-associated hypersensitivity HCP5 rs2395029-G Linkage disequilibrium with HLA-B*57:01 Lower viral load and slower progression to AIDS MICA Noncoding SNV near MICA, rs4418214-T May affect HLA class I peptide presentation— linkage with protective HLA-B alleles PSORS1C3 rs3131018-A May affect HLA class I peptide presentation Enriched in HIV-1 controllers ZNRD1 rs9261174-C Possible interference in processing of HIV transcripts; influence ZNRD1 expression Chemokine Receptors CCR5 rs333: 32-bp deletion in the ORF (Δ32) found in persons of European descent Truncated CCR5 protein; reduced co-receptor activity of R5 HIV strain Promoter SNVs, haplotypes (HHA to HHG*2) Altered CCR5 expression, e.g., HHE haplotype correlates with high CCR5 expression Increased expression of the lncRNA RP11-24-11.2, which corresponds to an antisense transcript that overlaps CCR5 (CCR5AS); results in increased CCR5 expression rs1015164 G→A (34 kb downstream from CCR5 and close to CCRL2) CCR2 rs1799864: SNV in ORF (64 V→I) Linkage with polymorphisms in CCR5 promoter 64I-bearing haplotype associated with delayed progression to AIDS CCRL2 rs3204849: SNV in ORF (167 Y→F) SNV in linkage with CCR5 haplotype 167F associated with accelerated progression to AIDS and PCP CXCR6 rs2234358: G→T in the 3’ UTR Trafficking of effector T cells and activation of NK T cells; minor HIV co-receptor CX3CR1 SNVs in ORF: rs3732379 (249 V→I) and rs3732378 (280 T→M) Alleles bearing 249I and 280M reduce receptor expression and binding of fractalkine, the CX3CR1 ligand DARC rs2814778: Promoter SNV (–46T→C) found in persons of African descent –46C/C associated with absent DARC expression (Duffy null), low neutrophil counts, and altered circulating chemokine levels as well as HIV binding to RBCs and trans-infection of HIV-1 Chemokines CCL3L, CCL4L Gene copy number of CCL3L and CCL4L High numbers of CCL3L and CCL4L genecontaining segmental duplications correlated with high CCL3L and CCL4L levels CCL5 Promoter SNVs Altered gene expression Influenced HIV-AIDS susceptibility CCL2 rs1024611: Promoter SNV (–2578 T→G) –2578G allele: increased CCL2 expression and monocyte recruitment

Slower progression to AIDS; higher risk of abacavir-associated hypersensitivity Higher viral load, reduced CD4+ counts, and accelerated disease progression Protection against HIV infection HLA-DRB1*15:02—lower viral load HLA-DRB1*03:01—higher viral load Faster progression to AIDS Decreased viral load set point CHAPTER 208 Enriched in HIV-1 controllers Human Immunodeficiency Virus Disease: AIDS and Related Disorders
Slower disease progression to AIDS Δ32/Δ32: CCR5-null state associated with resistance to acquiring HIV infection Δ32/wild type: slower progression to AIDS; better CD4+ T cell recovery during ART HHE/HHE: increased HIV susceptibility and faster progression to AIDS rs1015164A allele associated with higher viral load Prevalence of rs2234358-T lower in long-term nonprogressors and viremic controllers of African descent 249I and 280M associated with faster AIDS progression in persons of European descent –46C/C: increased risk of acquiring HIV but slower HIV disease progression; Duffy null–associated low neutrophil trait associated with increased HIV risk Gene copy number lower than population median associated with increased HIV-AIDS susceptibility and lower CD4+ T cell recovery during ART –2578G/G associated with increased risk of developing HIV-1–associated dementia and faster AIDS onset (Continued)

TABLE 208-6 Host Genetic Factors Influencing HIV/AIDS Pathogenesis and Therapy Responses GENEa GENETIC VARIATION MECHANISMSb GENETIC ASSOCIATIONSc CXCL12 rs7919208: Promoter SNV (G→A) rs7919208A creates a new transcription factor binding site associated with increased CXCL12 expression Cytokines IL-6 rs1800795: Promoter SNV (–174 G→C) –174G/G associated with

increased IL-6 and CRP levels IL-7RA rs6897932: Coding SNV (244 T→I) 244 I/I associated with increased signal transduction and proliferation in response to IL-7 IL-10 rs1800872: Promoter SNV (–592 C→A) –592A associated with decreased IL-10 levels –592A associated with increased HIV infection risk and AIDS progression rate Drug-Metabolizing Enzyme Gene CYP2B6 Multiple variants (e.g., rs3745274

[516 G→ T], i.e., CYP2B6*6) CYP2B6 variants influence enzyme activity 516T/T associated with higher risk of adverse reactions to efavirenz Innate Immunity Genes MBL Alleles defined by 3 coding SNVs Low plasma concentration and structural variation of MBL protein X allele (promoter SNV –221) Decreased levels of MBL protein Faster progression to AIDS with X/X genotype APOBEC3G rs8177832: ORF SNV (186 H→R) Reduced anti–HIV-1 activity 186R associated with rapid AIDS progression in persons of African descent APOBEC3F Haplotype tagged by rs2076101 in ORF (231 I→V) 231V variant may influence Vif-mediated APOBEC3F degradation TLR7 rs179008: ORF SNV (32A→T) on Chr. X Lower TLR7 mRNA translation efficiency and impaired TLR7-dependent IFN-α production PARD3B rs11884476 near exon 20: C→G Direct interaction with HIV signaling through SMAD family of proteins PART 5 Infectious Diseases IFNL4 rs368234815: Frameshift mutation (TT→ΔG) Polymorphism in IFNL4 gene in linkage with a IFNL3 variant; this haplotype influences IFNL3 levels rs8099917: T→G Unknown rs8099917-G associated with higher susceptibility to KS Others ApoE E4 allele defined by two coding SNVs ApoE is an HIV-1–inducible inhibitor of

HIV-1 replication and infectivity in macrophages ApoL1/MYH9 Several risk haplotypes, including G1 Overexpression of the ApoL1 kidney risk variants may increase kidney cell death RYR3 rs2229116: ORF SNV (A →G) Unknown; potential impact on calcium signaling and homeostasis PROX1 rs17762192-G 36 kb upstream of PROX1 Unknown; presumably due to its impact on PROX1 expression, which is a negative regulator of IFN-γ Gene–Gene Interaction KIR+HLA KIR3DS1 interaction with HLA-Bw4-80Ile Altered NK cell activity required to eliminate

HIV-infected cells KIR2DL3 interaction with HLA-C1 Reduction of inhibitory KIR likely resulting in increased immune activation, impaired killing of latently infected cells, and a higher proviral burden KIR3DL1 I47V interaction with HLA-B*57:01 Variation in an immune NK cell receptor that binds B*57:01, modifying the protective effect of B*57:01 LILRB2+HLA LILRB2 interaction with HLA class I Regulation of dendritic cells by LILRB2-HLA engagement CCL3L1+ CCR5 Low CCL3L1 gene copies + detrimental CCR5 genotypes Low CCL3L1 and high CCR5 expression Increased HIV/AIDS susceptibility and reduced immune reconstitution during ART aRepresentative genes and polymorphisms and bpossible mechanisms are listed. cSome of the associations are population specific and may display cohort-specific effects. Most of the associations were derived from persons of European descent. Abbreviations: APOBEC, apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like; ApoE, apolipoprotein E; ApoL1, apolipoprotein L1; ART, antiretroviral therapy; CCL, CC ligand; CCL3L, CCL3-like; CCR5, CC chemokine receptor 5; CCR5AS, CCR5 antisense RNA; CCRL2, CC chemokine receptor–like 2; CRP, C-reactive protein; CYP2B6, cytochrome P450 family 2 subfamily B member 6; CXCL12, chemokine (C-X-C motif) ligand 12; CXCR6, chemokine (C-X-C motif) receptor 6; CX3CR1, chemokine (C-X3-C motif) receptor 1; DARC, Duffy antigen receptor for chemokines; Del, deletion; HCP5, HLA class I histocompatibility antigen protein P5; HHE, human haplogroup E; HLA, human leukocyte antigen; IFN, interferon; IFNL3, interferon λ3 gene; IFNL4, interferon λ4 gene; IL, interleukin; IL-7RA, interleukin 7 receptor α; KIR, killer cell immunoglobulin-like receptors; KS, Kaposi’s sarcoma; LILRB2, leukocyte immunoglobulin-

like receptor B2; MBL, mannose-binding lectin; MHC, major histocompatibility complex; MICA, MHC class I polypeptide-related sequence A; MYH9, myosin heavy chain 9; NK, natural killer; ORF, open reading frame; PARD3B, par-3 family cell polarity regulator beta; PCP, Pneumocystis jirovecii pneumonia; PROX1, prospero homeobox 1; PSORS1C3, psoriasis susceptibility 1 candidate 3; RYR3, ryanodine receptor 3; SMAD, mothers against decapentaplegic homolog; SNV, single nucleotide variant; rs#, SNV identification number; TLR7, Toll-like receptor 7; TNF-α, tumor necrosis factor α; UTR, untranslated region; VL, viral load; ZNRD1, zinc ribbon domain containing 1; +, present; –, absent. Sources: SK Ahuja, W He. Reviews for additional information; P An et al: Trends Genet 26:119, 2010; J Fellay: Antivir Ther 14:731, 2009; RA Kaslow et al: J Infect Dis 191:S68, 2005; D van Manen et al: Retrovirology 9:70, 2012; MP Martin et al: Immunol Rev 254:245, 2013; S Limou et al: Front Immunol 4:118, 2013; PJ McLaren et al: Curr Opin HIV AIDS 10:110, 2015; PJ McLaren et al: Proc Natl Acad Sci USA 112:14658, 2015; PJ McLaren, M Carrington: Nat Immunol 16:577, 2015; P An et al: PLoS Genet 12:e1005921, 2016; F Pereyra et al: Science 330:1551, 2010; I Bartha et al: PLoS Comput Biol 13:e1005339, 2017; S Kulkarni et al: Nat Immunol 20:824, 2019; S Le Clerc et al: Front Genet 10:799 2019; V Kalidasan et al: Front Microbiol 11:46 2020; SN Gingras et al: Hum Genet 139:865 2020.

(Continued) rs7919208A associated with higher susceptibility to HIV-related non-Hodgkin's lymphoma –174G/G associated with high risk of KS development and variable recovery of CD4+ T cells during ART 244 I/I associated with faster CD4+ T cell recovery during ART Slow progression to AIDS with heterozygosity for coding SNVs 231V associated with lower viral load, slower progression to AIDS and PCP rs179008-T associated with lower viral load and cell-associated HIV-1 DNA in women rs11884476-G associated with slower progression to AIDS rs368234815-ΔG associated with higher prevalence of AIDS-defining illnesses and potentially increased HIV-1 infection risk E4/E4 associated with rapid AIDS progression and HIV-associated dementia Increased risk for HIV-associated nephropathy rs2229116-G associated with subclinical atherosclerosis during ART rs17762192-G associated with reduced rate of HIV disease progression KIR3DS1/HLA-Bw4-80Ile associated with delayed AIDS onset HLA-C1+ KIR2DL+ associated with better immune recovery during ART Increasing copy numbers of 47V associated with lower viral load in persons carrying HLA-B*57 Control of HIV-1

CCR5 promoter rs2856758 rs2734648 rs1799987 rs1799988 rs41469351 rs1800023 rs1800024 rs1015164 rs1799864 rs333 Haplotype A A HHC HHB HHA V V A A G T G G T T A A C C C C wt wt A A V V A A T T G G T T A G C C T C wt wt HHD HHE HHF*1 HHF*2 HHG*1 HHG*2 A G A G A V V I V V A A A G G G G G G G A A A A A C C C C C A A A A A C T T C C C C C C C wt wt wt wt Δ32 HLA-C PSORS1C3 HLA-B MICA HCP5 MICB CCR3 CCR2 CCR5 CCRL2

– Log10 (P value)

Chr. 3p21 CCR5 locus

Chr.

FIGURE 208-26 Schema depicting haplotypes within two regions that contribute significantly to HIV-AIDS susceptibility. Top: Haplotypes (left, CCR5; right, HLA alleles). Bottom: GWAS Manhattan plots schematized. Chr, chromosome. Horizontal dotted line: genome level significance threshold.

greatly advanced our understanding of the genes that influence HIVAIDS pathogenesis and ART-associated immune reconstitution. Of particular interest are polymorphisms in two chromosomal regions, as they are associated with consistent effects on HIV acquisition, viro logic set point, and/or rates of HIV disease progression: the region in chromosome 3 that includes the gene that encodes the HIV co-receptor CC-chemokine receptor 5 (CCR5) and the major histocompatibility locus (MHC) in chromosome 6 (Fig. 208-26). GENETICS OF CCR5: FROM BENCH TO BEDSIDE While the discovery of CCR5 as a major co-receptor for cell entry of HIV-1 was established by in vitro studies, genetic association studies established its seminal role in HIV pathogenesis. Initial in vitro studies revealed that a 32-bp deletion (Δ32) in the coding region of CCR5 contributes to resistance to CCR5 using R5 strains of HIV. The CCR5 Δ32 allele encodes a trun cated protein that is not expressed on the cell surface. Congruently, genotype-phenotype association studies in large cohorts demonstrated that individuals homozygous for the CCR5 Δ32 allele (Δ32/Δ32) lack CCR5 surface expression and are highly resistant to acquiring HIV infection; heterozygosity for the CCR5 Δ32 allele is associated with a lower risk of acquiring HIV. The distribution of the CCR5 Δ32 allele is population specific. Approximately 1% of individuals of European ancestry are homozy gous for the CCR5 Δ32 allele. Depending on the geographic region in Europe, up to 18% of individuals are heterozygous for the CCR5 Δ32 allele. The CCR5 Δ32 allele is rare in other populations. The evolution ary pressure that resulted in the emergence of the CCR5 Δ32 allele in the European population remains unknown and has been speculated to be secondary to an ancestral pandemic, such as the plague. Subsequent studies identified single nucleotide variants (SNVs) in the promoter (regulatory) region of CCR5 that influence gene expres sion levels. Alleles bearing specific cassettes of linked polymorphisms (haplotypes) were identified and designated as human haplogroups A to G*2 (HHA to HHG*2) (Fig. 208-26). The CCR5 Δ32 polymorphism is found on the HHG*2 haplotype. CCR5 haplotypes A–D versus E–G*2 differ by bearing GT versus AC at polymorphic sites rs1799987 and rs1799988 (Fig. 208-26). CCR5-HHA haplotype represents the ances tral haplotype (found in chimpanzees) and is associated with lower CCR5 gene expression, whereas the CCR5-HHE haplotype is associ ated with higher CCR5 expression. Methylation of DNA is a common epigenetic signaling mechanism that cells use to lock genes in the “off”

rs2395029 rs9264942 rs4418214 rs3131018 HLA-C HLA-B

allele allele 63 67 70 97 M M C C C C C B*57:01 B*52:01 B*27:05 G R E E M S V T C T S N G G M V C C R R E E S C T N T C N K G G C C C C A A M M V V V *Cw*08:02 C C T T T B*14:02 R R R R R N N E N N C S S Y F W R R S R T T T T T N N N Q N G G G G T *Cw*07:02 B*07:02 B*35:01 Chr. 6p21 MHC region

CHAPTER 208 position, and polymorphisms in CCR5 haplotypes may mediate their effects by influencing DNA methylation levels in the CCR5 locus. The CCR5-HHE and CCR5-HHA haplotypes are more sensitive and resistant, respectively, to T cell activation–induced demethylation of the CCR5 locus. In worldwide populations, HHE and HHC are prevalent haplotypes, whereas the ancestral HHA haplotype is more common in persons of African ancestry. The associations of CCR5 haplotypes with HIV acquisition and/or HIV disease course are largely consistent with their effects on CCR5 gene expression. For example, homozygosity for the CCR5-HHE haplotype is associated with an increased risk of acquiring HIV, progressing rapidly to AIDS, and reduced immune recovery dur ing ART. The HHA haplotype is associated with slower disease progres sion in African populations and has been speculated to be a basis for why chimpanzees (who all carry the ancestral CCR5-HHA haplotype) naturally infected with SIV resist disease progression. The pairing

of the HHC and CCR5 Δ32-bearing HHG*2 haplotypes (HHC/HHG*2 genotype) is associated with a lower risk of acquiring HIV infection and slower rate of HIV disease progression, whereas the pairing of the HHE haplotype with the HHG*2 haplotype is associated with the opposite effects. The CCR2-64I–bearing HHF*2 haplotype is associated with a slower HIV disease course. Human Immunodeficiency Virus Disease: AIDS and Related Disorders
Consistent with these genetic associations, polymorphisms in genes encoding ligands for CCR5 have also been associated with variable HIV susceptibility and disease progression rates. Examples include copy number variations of CCL3L1 and SNVs in CCL5. The sum of these studies established a pivotal role of CCR5 and its ligands in HIVAIDS pathogenesis and, potentially, immune recovery. The discovery that the CCR5 Δ32/Δ32 genotype is associated with strong resistance to HIV infection, and that uninfected persons bear ing this genotype did not appear to have impaired immunity, led to the development of two kinds of novel therapies. First, it spurred the development of a new class of therapies approved by the U.S. Food and Drug Administration: entry inhibitors (e.g., maraviroc) that block the interaction of CCR5 with the HIV envelope. Second, it led to the evaluation of novel experimental cellular therapies. A person with HIV and acute myelogenous leukemia was given an allogeneic stem cell transplantation from an HLA-compatible person whose cells lacked expression of CCR5 due to the Δ32/Δ32 genotype. There was no evi dence of HIV-1 infection for 13 years in the patient who underwent the transplant; the patient eventually died due to recurrence of leukemia.

This observation provided a proof of concept for an HIV cure and led to the development of additional novel cellular therapies involving autologous transplantation of CD4+ T cells in which the CCR5 gene is inactivated ex vivo using new gene editing procedures. Similar cel lular strategies have had mixed success, mainly due to the latent viral reservoir in various tissues.

DISCOVERY OF HLA CLASS I ALLELES THAT ASSOCIATE WITH VIROLOGIC CONTROL OF HIV INFECTION There is a strong association between variations within the HLA-B gene with protective (e.g., HLA-B*57 and HLA-B*27 alleles) or detrimental (e.g., HLA-B*35 allele) outcomes during HIV infection. Carriage of the HLA-B*57 and/or HLA-B*27 alleles is associated with slower disease progression. The beneficial effects of these alleles may relate in part to their associations with a lower virologic set point as well as to higher cell-mediated immunity in people with HIV. The protective effect of the HLA-B*57 and HLAB*27 alleles on the HIV disease course is underscored by the finding that the prevalence of these alleles is higher among persons with long-term nonprogression and persons who control HIV replication spontaneously (elite controllers). In contrast, the HLA-B*35 allele has been associated with faster progression to AIDS and higher viral load. The prevalence of the HLA-B alleles differs between populations. HLAB*57:01 in Europeans and HLA-B*57:03 in persons of African descent are the protective alleles. In some populations (e.g., Japanese) where the HLA-B*57/HLA-B*27 alleles are absent, HLA-B*51 is associated with a protective phenotype. Possession of the protective HLA-B alleles is associated with broader and stronger CD8+ T cell responses to HIV epitopes. The mechanisms underlying the differential effects of the HLA-B alleles on the course of HIV disease may relate to differences in the ability of antigenpresenting cells to present immunodominant HIV epitopes to T helper or cytotoxic T lymphocytes in the context of MHC-encoded molecules. This may result in differential immune responses that influence viral replication. In this regard, the HLA-B alleles that impact the course of HIV disease differ in their amino acid residues in the HLA-B peptidebinding groove; this difference may play a critical role in virologic control. PART 5 Infectious Diseases The HLA-B−21M allele does

not influence HLA-B gene expression; however, it is in linkage with HLA-B haplotypes that are associated with higher HLA-A and HLA-E expression. Higher HLA-A levels associate with poorer control of HIV as well as higher viral load, reduced CD4+ T cell counts, and accelerated progression to AIDS. HLA-E is the ligand for natural killer (NK) cell NKG2A, an inhibitory receptor. Engage ment of NKG2A with HLA-E inhibits NK cells that would normally be potent eliminators of virally infected cells. Thus, targeting NKG2A might provide a therapeutic avenue for HIV treatment. Investigators have also examined the influence of extended HLA haplotypes (linked alleles) on the course of HIV disease. The extended HLA ancestral haplotype (AH) 8.1 is defined by the presence of HLAA1, HLA-B8, and HLA-DR3 alleles. AH 8.1 is the most common ances tral haplotype in persons of European descent (present in 10%) and is associated with multiple autoimmune diseases in HIV-seronegative persons. These associations of AH 8.1 are thought to be due to a geneti cally determined hyperresponsiveness characterized by high TNF-α production and lack of complement C4A. Strong epidemiologic data indicate that carriage of AH 8.1 in HIV-seropositive persons is associ ated with a rapid decline in the number of CD4+ T cells and faster pro gression to AIDS development. Gene–gene interactions between HLA alleles and other genes (e.g., killer cell immunoglobulin-like receptors) also may influence HIV disease progression rates. POLYMORPHISMS IDENTIFIED BY GWAS THAT ASSOCIATE WITH VIROLOGIC CONTROL AND DISEASE PROGRESSION GWAS have not identified additional genetic variations that associate with the risk of HIV-1 acquisition, presumably due to a paucity of well-characterized risk cohorts in which level of exposure has been quantified. By con trast, large-scale GWAS have identified SNVs, especially in the MHC, that influence HIV viral load, including in a large group of individuals termed HIV controllers (including elite controllers) who spontaneously (without ART) control viral replication. GWAS in people with HIV

-35 kb Indel263 -35 kb Indel263 T C T C – – G G gDNA gDNA HLA-C HLA-C Less silencing Silencing C – T G mRNA mRNA miR-148a binding intact HLA-C expression Viral control HIV outcomes Lower Reduced Worse Higher Increased Better FIGURE 208-27 Linkage disequilibrium between two variants in the HLA-C locus and their influence on binding of miR-148a to the 3′-untranslated region (UTR). Altered binding of miR-148a associates with HLA-C protein expression levels and, in turn, viral control and HIV disease outcomes. Effects associated with T-G (left) and C-del (right) haplotypes are depicted. The C-deletion haplotype prevents binding of miR-148a to 3′-UTR of HLA-C (less silencing). Kb, kilobase. of European ancestry identified four SNVs in genes in the HLA class I loci that associated with virologic control. These SNVs are within or in the vicinity of PSORS1C3, HLA-C, MICA, and HCP5 genes (Fig. 208-26).

As noted in this figure, the individual effects of these alleles are dif ficult to discern because of linkage disequilibrium. The protective effects of the SNVs in HCP5 and MICA may relate to their linkage with known protective HLA-B alleles. The protective HCP5 allele is in linkage disequilibrium with the HLA-B*57:01 allele, and the protective MICA allele tags with the HLA-B*57:01 and HLA-B*27:05 alleles. The protective HLA-C SNV is associated with higher HLA-C expression, which has been associated with viral control and better HIV outcomes. This protective SNV (rs9264942; T→C) resides 35 kb upstream of the HLA-C gene and is in strong linkage disequilibrium with a 3′-UTR indel263 SNV (rs67384697; G→deletion), generating the T-G or C-deletion haplotypes (Fig. 208-27). miR-148a binds to the 3′-UTR region encompassing the rs67384697 SNV and silences HLA-C expres sion. Binding of miR-148a to the 3′-UTR is disrupted on the mRNA transcribed from the C-deletion haplotype; this disruption associates with less silencing of the mRNA and therefore higher HLA-C cell surface expression, which associates with better HIV disease outcomes (Fig. 208-27).

Conversely, binding of miR-148a to the 3′-UTR is intact on the mRNA transcribed from the T-G haplotype; this binding associates with silencing of the mRNA and therefore lower HLA-C cell surface expression associates with worse HIV disease outcomes

(Fig. 208-27). GWAS in persons of African descent have identified an SNV (rs2523608) that tags the HLA-B*57:03 allele that is known to associate with HIV-1 control and a slower disease course. Together, these GWAS data underscore the importance of variations in HLA class I loci in control of viral replication. A recent GWAS suggested that an SNV (rs1015164G→A) approxi mately 34 kb downstream of the CCR5 loci is associated with a higher viral load set point (Fig. 208-26) and lower CD4+ T cell counts in therapy-naïve HIV-seropositive persons. rs1015164 maps to a lncRNA gene in proximity to the CCRL2 gene (Fig. 208-26). The lncRNA is transcribed from the antisense strand of CCR5 and was therefore named CCR5AS. The rs1015164A allele is associated with higher expression of CCR5AS in CD4+ T cells, which in turn was associated with increased levels of CCR5 mRNA. Although the detrimental effect of the rs1015164A allele was suggested to be independent of the det rimental effects of the abovementioned CCR5-HHE haplotype, further investigation is warranted as the rs1015164A allele and CCR5-HHE haplotype are in a high degree of linkage disequilibrium. Most GWAS studies have been performed in European populations, limiting generalizability to other populations. Additionally, GWAS are generally not suitable for identifying rare variants (<1% prevalence). Therefore, next-generation sequencing (NGS) approaches were sug gested to identify these rare variants. However, a recent NGS study suggests that exonic variants with large effect sizes are unlikely to have

a major contribution to host control of HIV infection. Mathematical modeling revealed that variations in host genes may explain about 10% of the observed variability in HIV viral load, whereas viral genetic diversity may explain 29% of the variability. GENETIC ASSOCIATIONS WITH SPECIFIC AIDS AND NON-AIDS CONDITIONS Carotid artery disease Many of the non-AIDS events in HIV-seropositive individuals resemble those attributable to immune senescence and those found in the HIV-seronegative aging population. A functional SNV in the ryanodine receptor 3 (RYR3) gene was found to be associ ated with an increased risk of common carotid intima–media thickness (cIMT), which is a surrogate for subclinical atherosclerosis. Functional studies on RYR3 and its isoforms demonstrate a major role of these receptors in modulating endothelial function and atherogenesis via calcium-signaling pathways, providing a biologically plausible mecha nism by which the SNV in RYR3 may associate with increased cIMT risk. Kidney disease HIV-1–associated nephropathy (HIVAN) is a form of focal sclerosing glomerulonephritis caused by direct infection of kid ney epithelial cells with HIV. HIVAN is more common in persons of African descent. There is evidence that polymorphisms in the MYH9 gene and in the neighboring APOL1 gene are a strong determinant of susceptibility to HIVAN in persons of African descent. The effect of carrying two APOL1 risk alleles explains nearly 35% of HIVAN. Overexpression of the APOL1 kidney risk variants may associate with increased kidney cell death. HIV-associated neurocognitive disorder HIV-associated neurocognitive disorder (HAND) comprises a spectrum of neurocognitive deficits due to HIV infection. Variations in the apolipoprotein E (ApoE) gene have strong associations with Alzheimer’s disease in the HIV-seronegative population. In HIV-seropositive persons, possession of the E4/E4 genotype has been associated with dementia, peripheral neuropathy, and impairment in cognition as well as immediate and delayed verbal memory. Macrophage recruitment and activation play a central role in the development of many of the HAND syndromes. Variations in chemokines that play an influential role in macrophage activation and recruitment, namely CCL2

(MCP-1) and CCL3 (MIP-1α), have been shown to influence the risk of developing HAND. Variations in mitochondrial genes also have been associated with a risk of AIDS and HAND. A GWAS identified a polymorphism in chromosome 14 in the T cell receptor α locus that may influence neurocognitive outcomes. HIV-1–associated pneumocystis pneumonia Human Apobec3 cytidine deaminases are intrinsic resistance factors to HIV-1. However, HIV-1 encodes a viral infectivity factor (Vif) that degrades APOBEC3 pro teins. Association studies suggest a role of genetic variations in the APOBEC3 family in HIV disease. A common haplotype derived from 6 SNVs in the APOBEC3F gene and tagged by a codon-changing vari ant is associated with a significantly lower viral load set point, slower rate of progression to AIDS, and delayed development of Pneumocystis jirovecii pneumonia (PCP). In addition, a coding SNV in the CCRL2 gene is associated with accelerated progression to AIDS and rapid development of PCP. HIV-related non-hodgkin lymphoma (NHL) The relative risk of developing NHL in HIV-seropositive persons is highly elevated compared with the general population. NHL represents approximately 34% of all identi fied cancers in HIV-seropositive persons. A recent GWAS identified a promoter SNV in the CXCL12 gene that was associated with higher susceptibility to develop HIV-related NHL. The effect of this SNV is likely causal as it creates new transcription factor binding sites, impact ing CXCL12 expression. ASSOCIATIONS WITH ART-RELATED ADVERSE EVENTS Abacavir, an effective antiretroviral agent, is associated with significant risk of hypersensitivity reactions (2–9% of cases). Interestingly, while the HLA-B*57:01 allele is associated with a slower HIV disease course, possession of this allele is associated with a higher risk of abacavirassociated hypersensitivity, possibly due to the abacavir-specific acti vation of cytokine-producing CD8+ T cells only in HLA-B*57:01 carriers. Pharmacogenetic screening for the HLA-B*57:01 allele is recommended before initiation of abacavir treatment.

The antiretroviral agent nevirapine is associated with hypersen sitivity reactions in 6–10% of patients, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). rs5010528G, a strong proxy for HLA-C*04:01 carriage, was associated with high risk of SJS and TEN during nevirapine treatment. In addition, efavirenz was among the first antiretroviral agents to be co-formulated into singlepill regimens for mass rollout globally. Several genetic variants in the drug-metabolizing enzyme CYP2B6 have been associated with high efavirenz plasma concentrations and increased risk of adverse neuro psychiatric effects. For example, homozygosity for one such variant, rs3745274 T/T, increases the risk of adverse reactions to efavirenz up to fivefold, and this risk genotype is much more common in Africans (13.7%) than Europeans (5.6%). ■ ■NEUROPATHOGENESIS IN HIV DISEASE While there has been a remarkable decrease in the incidence of the severe forms of HIV encephalopathy among those with access to treat ment in the era of effective ART, people with HIV can still experience milder forms of neurocognitive impairment despite adequate ART. Factors that contribute to the neurocognitive decline include lack of complete control of HIV replication in the brain; production of HIV proteins that may be neurotoxic; low CD4+ T cell nadir; chronic immune activation; comorbidities such as drug abuse, microvascular disease, older age, and diabetes; and the potential for neurotoxicity of certain antiretroviral drugs. HIV has been demonstrated in the brain and CSF of infected individuals with and without neuropsychiatric abnormalities. As opposed to lymphoid tissues, there are no resident lymphocytes in the brain. The main cell types that are infected in the brain in vivo are the perivascular macrophages and the microglial cells, which can sometimes form syncytia resulting in multinucleated giant cells; low-level viral replication is also seen in perivascular astrocytes. It has

been proposed that monocytes that have already been infected in the blood can migrate into the brain, where they then reside as macrophages, or macrophages can be directly infected while residing within the brain. The precise mechanisms whereby HIV enters the brain are unclear; however, they are thought to relate, at least in part, to the ability of virus-infected and immune-activated macrophages to induce adhesion molecules such as E-selectin and vascular cell adhe sion molecule 1 (VCAM-1) on brain endothelium. Other studies have demonstrated that HIV gp120 enhances the expression of intercellular adhesion molecule 1 (ICAM-1) in glial cells and HIV Tat protein can disrupt the tight junctions of the brain endothelial cells to facilitate entry of HIV-infected cells into the CNS. Virus isolates from the brain are preferentially R5 strains as opposed to X4 strains; in this regard, people with HIV who are heterozygous for CCR5-Δ32 appear to be relatively protected against the development of HIV encephalopathy. Once HIV enters the brain due to pressures of the local environment, it evolves to develop distinct sequences in the env, tat, and LTR genes. These unique sequences have been associated with neurocognitive dys function; however, it is unclear if they are causal (see below). CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders

People with HIV may manifest white matter lesions as well as neuro nal loss. The white matter lesions are due to axonal injury and a disrup tion of the blood-brain barrier and not due to demyelination. Given the absence of evidence of HIV infection of neurons, HIV-mediated effects on neurons are thought to involve indirect pathways whereby viral proteins, particularly gp120 and Tat, trigger the release of endogenous neurotoxins from macrophages and to a lesser extent from astrocytes. In addition, it has been demonstrated that both HIV-1 Nef and Tat can induce chemotaxis of leukocytes, including monocytes, into the CNS. Neurotoxins can be released from monocytes as a consequence of infection and/or immune activation. Monocyte-derived neurotoxic factors have been reported to kill neurons via a variety of mechanisms including activation of the N-methyl-d-aspartate (NMDA) receptors and induction of oxidative stress. In addition, HIV gp120 shed by virus-infected monocytes could cause neurotoxicity by antagonizing the function of vasoactive intestinal peptide (VIP), by elevating intracel lular calcium levels, and by decreasing neurotrophic factor levels in the

cerebral cortex. A variety of monocyte-derived cytokines can contribute directly or indirectly to the neurotoxic effects in HIV infection; these include TNF-α, IL-1, IL-6, TGF-β, IFN-γ, platelet-activating factor, and endothelin. Furthermore, among the CC-chemokines, elevated levels of monocyte chemotactic protein 1 (MCP-1 or CCL-2) in the brain and CSF have been shown to correlate best with the presence and degree of HIV encephalopathy in ART-naïve patients. In addition, infection and/ or activation of monocyte-lineage cells can result in increased produc tion of eicosanoids, quinolinic acid, nitric oxide, excitatory amino acids such as l-cysteine and glutamate, arachidonic acid, platelet-activating factor, free radicals, TNF-α, and TGF-β, which may contribute to neu rotoxicity. Astrocytes may play diverse roles in HIV neuropathogenesis. Reactive gliosis or astrocytosis has been demonstrated in the brains of people with HIV, and TNF-α and IL-6 have been shown to induce astrocyte proliferation. In addition, astrocyte-derived IL-6 can induce HIV expression in infected cells in vitro. Furthermore, it has been sug gested that astrocytes may downregulate macrophage-produced neuro toxins. Evidence of neuronal injury can be demonstrated by measuring neurofilament levels in CSF. Treatment with ART leads to improvement in neuropsychiatric manifestations and a decrease in these cytokine levels in CSF, suggesting that they are driven by the virus or by its products. However, even in patients on long-term ART, there may be evidence of persistently activated lymphocytes in the CSF. It is unclear if

these lymphocytes may contribute to neuronal injury in the brain or are critical for controlling the CNS viral reservoir. However, some individuals may develop a subacute encephalitis due to an IRIS reaction (see below). This often occurs weeks or a few months after initiation of ART in individuals with low CD4+ T cell counts. It is thought that the recovery of CD4+ T cells causes a lymphocyte response to the CNS HIV reservoir. The contribution of host genetic factors to development of neuropsychiatric manifestations of HIV infection has not been well studied. However, evidence supports the role of several genetic factors including the E4 allele for apoE in an increased risk of HIV-associated neurocognitive disorders and peripheral neuropathy.

PART 5 Infectious Diseases It has also been suggested that the CNS may serve as a relatively sequestered site for a reservoir of latently infected cells that might be a barrier for the eradication of virus by ART (see “The HIV Reservoir: Obstacles to the Eradication of Virus,” above). ■ ■PATHOGENESIS OF KAPOSI’S SARCOMA There are at least four distinct epidemiologic forms of KS: (1) the clas sic form that occurs in older men of predominantly Mediterranean or eastern European Jewish backgrounds with no recognized contribut ing factors; (2) the equatorial African form that occurs in all ages, also without any recognized precipitating factors; (3) the form associated with organ transplantation and its attendant iatrogenic immunosup pressed state; and (4) the form associated with HIV-1 infection. In the latter two forms, KS is an opportunistic disease; in people with HIV, unlike typical opportunistic infections, its occurrence is not strictly related to the level of depression of CD4+ T cell counts. The pathogen esis of KS is complex; fundamentally, it is an angioproliferative disease that is not a true neoplastic sarcoma, at least not in its early stages. It is a manifestation of excessive proliferation of spindle cells that are believed to be of vascular origin and have features in common with endothelial and smooth-muscle cells. In HIV disease the development of KS is dependent on the interplay of a variety of factors including HIV-1 itself, human herpes virus 8 (HHV-8), immune activation, and cytokine secretion. Numerous epidemiologic and virologic stud ies have clearly linked HHV-8, which is also referred to as Kaposi’s sarcoma–associated herpesvirus (KSHV), to KS not only in people with HIV but also in individuals with the other forms of KS. HHV-8 is a γ-herpesvirus related to EBV and herpesvirus saimiri. It encodes a homologue to human IL-6 and, in addition to KS, has been implicated in the pathogenesis of body cavity lymphoma, multiple myeloma, and monoclonal gammopathy of undetermined significance. Sequences of HHV-8 are found universally in the lesions of KS, and patients with KS are virtually all seropositive for HHV-8. HHV-8 DNA sequences can be found in the B cells of 30–50% of patients with KS and 7% of patients with AIDS without clinically apparent KS.

Between 1% and 2% of eligible blood donors are positive for anti bodies to HHV-8, while the prevalence of HHV-8 seropositivity in men with HIV is 30–35%. The prevalence of HHV-8 seropositivity in women with HIV is ~4%. This finding is reflective of the lower incidence of KS in women. It has been debated whether HHV-8 is the transforming agent in KS; the bulk of the cells in the tumor lesions of KS are not neoplastic cells. However, it has been demonstrated that endothelial cells can be transformed in vitro by HHV-8. In this regard, HHV-8 possesses genes, including homologues of the IL-8 receptor, Bcl-2, and cyclin D, which can potentially transform the host cell. Despite the complexity of the pathogenic events associated with the development of KS in people with HIV, HHV-8 is the etiologic agent of this disease. The initiation and/or propagation of KS requires an activated state and is mediated, at least in part, by cytokines. Mul tiple factors, including TNF-α, IL-1β, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), basic fibroblast growth factor, and oncostatin M, function in an autocrine and paracrine manner to

sustain the growth and chemotaxis of the KS spindle cells. In this regard, KSHV-derived IL-6 has been demonstrated to induce prolifera tion of lymphoma cells and to inhibit the cytostatic effects of IFN-α on KSHV-infected lymphoma cells. IMMUNE RESPONSE TO HIV As detailed above and below, following the initial burst of viremia during primary infection, people with HIV mount robust immune responses that in most cases substantially curtail the levels of plasma viremia and likely contribute to delaying the ultimate development of clinically apparent disease for a median of 10 years in untreated indi viduals. This immune response contains elements of both humoral and cell-mediated immunity involving both adaptive and innate immune responses (Table 208-7; Fig. 208-28). It is directed against multiple antigenic determinants of the HIV virion as well as against viral pro teins expressed on the surface of infected cells. Ironically, those CD4+ T cells with T cell receptors specific for HIV are theoretically those CD4+ T cells most likely to be activated—and thus to serve as early targets for productive HIV infection and the cell death or dysfunction associated with infection. Thus, an early consequence of HIV infection is interference with and decrease of the helper T cell population needed to generate an effective immune response. Although a great deal of investigation has been directed toward delineating and better understanding the components of this immune response, it remains unclear which immunologic effector mechanisms are most important in delaying progression of infection and which, if any, play a role in the pathogenesis of HIV disease. This lack of knowl edge has also hampered the ability to develop an effective vaccine for HIV disease. TABLE 208-7 Elements of the Immune Response to HIV Humoral immunity Neutralizing antibodies Type specific Group specific Broadly neutralizing Antibodies participating in antibody-dependent cellular cytotoxicity (ADCC) Protective Pathogenic (bystander killing) Enhancing antibodies Complement Cell-mediated immunity Helper CD4+ T lymphocytes Class I MHC–restricted cytotoxic CD8+ T lymphocytes CD8+ T cell–mediated inhibition (noncytolytic) ADCC Natural killer cells Abbreviation: MHC, major histocompatibility complex.

Neutralizing antibody Cytotoxic CD8+ T lymphocyte Lysis Class I MHC Activation, proliferation, cytokine and chemokine release TCR Viral antigens Fc receptor ADCC Free gp120 CD4 HIV-infected CD4+ T lymphocyte Bystander killing Uninfected CD4+ T lymphocyte Helper CD4+ T lymphocytes Cytokine release Activation Lysis Class II MHC HIV-infected CD4+ T lymphocyte Natural killer cells FIGURE 208-28 Schematic representation of the different immunologic effector mechanisms thought to be active in the setting of HIV infection. Detailed descriptions are given in the text. ADCC, antibody-dependent cellular cytotoxicity; MHC, major histocompatibility complex; TCR, T cell receptor. ■ ■HUMORAL IMMUNE RESPONSE Antibodies to HIV usually appear within 3–6 weeks and almost invariably within 12 weeks of primary infection (Fig. 208-29); rare exceptions are in individuals who have defects in the ability to produce HIV-specific antibodies. Along with plasma levels of HIV RNA and p24 antigen, detection of these antibodies forms the basis of most diagnostic screening tests for HIV infection. The appearance of HIVbinding antibodies detected by ELISA and Western blot assays occurs prior to the appearance of neutralizing antibodies; the latter generally appear following the initial decreases in plasma viremia and are more closely related to the appearance of HIV-specific CD8+ T lymphocytes. The first antibodies detected are those directed against the immuno dominant region of the envelope gp41, followed by the appearance of antibodies to the structural or gag protein p24 and the gag precursor p55. Antibodies to p24 gag are followed by the appearance of antibod ies to the outer envelope glycoprotein (gp120), the gag protein p17, and the products of the pol gene (p31 and p66). In addition, one may see antibodies to the low-molecular-weight regulatory proteins encoded by the HIV genes vpr, vpu, vif, rev, tat, and nef. On rare occasions, levels of HIV-specific antibodies may decline during treatment of acute HIV

infection; otherwise they remain persistently positive. While antibodies to multiple antigens of HIV are produced, the pre cise functional significance of these different antibodies is unclear. The only viral proteins that elicit neutralizing antibodies are the envelope

Seroconversion, Initial viremia ADCC, CTL Autologous NAbs Broadly reactive NAbs

3–10 Years infected FIGURE 208-29 Relationship between initial HIV viremia and the development of antibodies to HIV. Within 3 to 6 weeks of initial HIV infection, nonneutralizing antibodies to HIV appear. These antibodies are capable of mediating antibodydependent cellular cytotoxicity (ADCC). The decline in plasma viremia generally correlates with the appearance of cytotoxic T lymphocytes (CTL). After approximately 3 months, autologous neutralizing antibodies (NAbs) capable of neutralizing prior circulating strains of HIV appear. After 2 or more years, broadly reactive NAbs appear. (Reproduced with permission from of Annual Reviews, Inc. from The Role of Antibodies in HIV Vaccines, JR Mascola and DC Monteori. 28:413, 2010.) proteins gp120 and gp41. Antibodies directed toward the envelope proteins of HIV have been characterized both as being protective and as possibly contributing to the pathogenesis of HIV disease. Among the protective antibodies are those that function to neutralize HIV directly and prevent the spread of infection to additional cells, as well as those that participate in ADCC. The first neutralizing antibodies are directed against the autologous infecting virus and appear after approximately 12 to 24 weeks of infection. Due to its high rate of mutation the virus is usually able to quickly escape these (and subsequent) neutralizing anti bodies. One important mechanism of immune escape is the addition of N-linked glycosylation sites, forming a glycan shield that interferes with envelope recognition by these initial antibodies. CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders
A number of broad and potent HIV-neutralizing envelope-specific antibodies have been isolated from people with HIV in studies designed to better understand the host response to HIV infection. Approximately 20% of patients develop antibodies capable of neutral izing highly diverse strains. These usually appear 2 or more years fol lowing infection in the face of continual viremia. These studies have revealed at least five major sites within the HIV envelope trimer that are able to elicit broadly neutralizing antibodies. These sites include antibodies directed toward the CD4 binding site (CD4bs) of gp120, those binding glycan-dependent epitopes in the V1/V2 region of gp120, those near the base of the V3 region of gp120, those binding to the gp120/gp41 bridge, and those binding to the membrane-proximal region of gp41 (Fig. 208-30). Several of these antibodies contain unique features including high levels of somatic hypermutation, selec tive germ-line gene usage (especially for CD4bs antibodies), and long CD4 binding site V1V2 glycan V3 glycan Silent face center Subunit interface Membrane proximal external region Fusion peptide FIGURE 208-30 Known targets of broadly neutralizing antibodies against HIV-1. (Courtesy of J Stuckey, GY Chuang.)

heavy chain complementary determining regions (especially CDRH3). Of note, while these antibodies are broadly neutralizing in vitro, their precise in vivo significance is unclear and the patients from whom they were derived demonstrate evidence of ongoing viral replication unless treated with ART.

The other major class of protective antibodies are those that partici pate in ADCC, a form of cell-mediated immunity (Chap. 360) in which NK cells that bear Fc receptors bind specific anti-HIV antibodies that then juxtapose the NK cells to and destroy cells expressing HIV antigens. The levels of anti-envelope antibodies capable of mediating ADCC are highest in the earlier stages of HIV

infection. Antibodies to both gp120 and gp41 have been shown to participate in ADCC-mediated killing of HIV-infected cells. In vitro, IL-2 can augment ADCC-mediated killing. In addition to playing a role in host defense, HIV-specific antibodies have also been implicated in disease pathogenesis. Antibodies directed to gp41, when present in low titer, have been shown in vitro to be capable of facilitating infection of cells through an Fc receptor–mediated mecha nism known as antibody enhancement. Thus, the same regions of the envelope protein of HIV that give rise to antibodies capable of mediat ing ADCC can also elicit the production of antibodies that can facilitate infection of cells in vitro. In addition, it has been postulated that antigp120 antibodies that participate in the ADCC killing of HIV-infected cells might also kill uninfected CD4+ T cells if the uninfected cells had bound free gp120, a phenomenon referred to as bystander killing. One of the most primitive components of the humoral immune system is the complement system (Chap. 360). This element of innate immunity consists of ~30 proteins that are found circulating in blood or associated with cell membranes. While HIV alone is capable of directly activating the complement cascade, the resulting lysis is weak due to the presence of host cell regulatory proteins captured in the virion envelope during budding. It is possible that complement-opsonized HIV virions have increased infectivity in a manner analogous to antibody-mediated enhancement. PART 5 Infectious Diseases ■ ■CELLULAR IMMUNE RESPONSE T cell–mediated immunity plays a major role in host defense against most viral infections (Chap. 360) and is thought to be an important component of the host immune response to HIV. T cell immunity can be divided into two major categories: that mediated by helper/inducer CD4+ T cells and that mediated by cytotoxic/immunoregulatory CD8+ T cells. HIV-specific CD4+ T cells can be detected in the majority of people with HIV via flow cytometry to measure intracellular cytokine produc tion in response to MHC class II tetramers pulsed with HIV peptides or through lymphocyte proliferation assays utilizing HIV antigens such as p24. These cells likely play a critical role in the orchestration of the immune response to HIV by providing help to HIV-specific B cells and CD8+ T cells. They may also be capable of directly killing HIV-infected cells. HIV-specific CD4+ T cells may be preferential targets of HIV infection by HIV-infected antigen-presenting cells during the genera tion of an immune response to HIV (Fig. 208-28). However, they also are likely to undergo clonal expansions in response to HIV antigens and thus survive as a population of cells despite the virus. No clear correlations exist between levels of HIV-specific CD4+ T lymphocytes and plasma HIV RNA levels; however, in the setting of high viral loads, CD4+ T cell responses to HIV antigens appear to shift from one of proliferation and IL-2 production to one of IFN-γ production. Thus, while a reverse correlation exists between the level of p24-specific proliferation and levels of plasma HIV viremia, the nature of the causal relationship between these parameters is unclear. MHC class I–restricted, HIV-specific CD8+ T cells have been identified in the peripheral blood of patients with HIV-1 infection. These cells include CTLs that produce perforins and granzyme, and T cells that can be induced by HIV antigens to express an array of cytokines such as IFN-γ, IL-2, MIP-1β, and TNF-α. Multiple HIV antigens, including Gag, Env, Pol, Tat, Rev, and Nef, can elicit CD8+ T cell responses. CTLs have been identified in the peripheral blood of patients within weeks of HIV infection and prior to the appearance of plasma virus. The selective pressure they exert on the evolution of the population of circulating viruses reflects their potential role in

control of HIV infection. These CD8+ T lymphocytes, through their HIV-specific antigen receptors, bind to and cause the lytic destruction of target cells bearing autologous MHC class I molecules presenting HIV antigens. Two types of CTL activity can be demonstrated in the peripheral blood or lymph node mononuclear cells of people with HIV. The first type directly lyses appropriate target cells in culture without prior in vitro stimulation (spontaneous CTL activity). The other type of CTL

activity reflects the precursor frequency of CTLs (CTLp); this type of CTL activity can be demonstrated by stimulation of CD8+ T cells in vitro with a mitogen such as phytohemagglutinin or anti-CD3 antibody to expand the population prior to detection. In addition to CTLs, CD8+ T cells capable of being induced by HIV antigens to express cytokines such as IFN-γ also appear in the setting of HIV-1 infection. It is not clear whether these are the same or differ ent effector pools compared with those cells mediating cytotoxicity; in addition, the relative roles of each in host defense against HIV are not fully understood. It does appear that these CD8+ T cells are driven to in vivo expansion by HIV antigen. There is a direct correlation between levels of CD8+ T cells capable of producing IFN-γ in response to HIV antigens and plasma levels of HIV-1 RNA. Thus, while these cells are clearly induced by HIV-1 infection, in most instances they are not able to effectively control infection. One exception may be a subset of patients who control viral replication in the absence of antiretroviral drugs and are referred to as elite nonprogressors (see “Long-Term Sur vivors, Long-Term Nonprogressors, and Elite Controllers,” above). The peripheral blood of these patients contains a population of CD8+ T cells that undergo substantial in vitro proliferation in response to HIV antigens and express perforin and granzyme. At least three other forms of cell-mediated immunity to HIV have been described: non-cytolytic CD8+ T cell–mediated suppression of HIV replication, ADCC, and NK cell activity. Non-cytolytic CD8+ T cell–mediated suppression of HIV replication refers to the ability of CD8+ T cells from a patient with HIV to inhibit the replication of HIV in tissue culture without killing infected targets. There is no requirement for HLA compatibility between the CD8+ T cells and the HIV-infected cells. This effector mechanism is thus nonspecific and appears to be mediated by soluble factor(s) including the CCchemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4). These CC-chemokines are potent suppressors of HIV replication and operate at least in part via blockade of the HIV co-receptor (CCR5) for R5 (macrophage-tropic) strains of HIV-1 (see above). ADCC, as described above in relation to humoral immunity, involves the killing of HIV-expressing cells by NK cells armed with specific antibodies directed against HIV antigens. Finally, NK cells alone have been shown to be capable of killing HIV-infected target cells in tissue culture. This primitive cytotoxic mechanism of host defense is directed toward non specific surveillance for neoplastic transformation and viral infection through recognition of altered class I MHC molecules. DIAGNOSIS AND LABORATORY MONITORING OF HIV INFECTION The establishment of HIV as the causative agent of AIDS and related syndromes early in 1984 was followed by the rapid development of sen sitive screening tests for HIV infection. By March 1985, blood donors in the United States were routinely screened for antibodies to HIV. In 1996, blood banks in the United States added the p24 antigen capture assay to the screening process to help identify the rare, infected individuals who were donating blood in the time (up to 3 months) between infection and the development of antibodies. In 2002, the ability to detect early infection with HIV was further enhanced by the licensure of nucleic acid testing (NAT) as a routine part of blood donor screening. These refinements decreased the interval between infection and detection (window period) from 22 days for antibody testing to 16 days with p24 antigen testing and subsequently to 12 days with NAT. The development of sensitive assays for monitoring levels of plasma viremia ushered in a new era of being able to monitor the progression of HIV disease more closely. Utilization of these tests, coupled with the measurement of levels of CD4+ T lymphocytes in peripheral blood, is an important compo nent of the management of persons with HIV infection.

■ ■DIAGNOSIS OF HIV INFECTION The CDC has recommended that screening for HIV infection be performed as a matter of routine health care. The diagnosis of HIV infection depends on the

demonstration of antibodies to HIV and/or the direct detection of HIV or one of its components. As noted above, antibodies to HIV generally appear in the circulation 3–12 weeks following infection. In addition to laboratory-based screening tests, several home tests are available. The standard blood screening tests for HIV infection are based on the detection of antibodies to HIV and/or the p24 antigen (see below) of HIV. A common laboratory-based platform is the ELISA, also referred to as an enzyme immunoassay (EIA). This solid-phase assay is an extremely good screening test with a sensitivity of >99.5%. Most diagnostic laboratories use commercial kits that contain antigens from both HIV-1 and HIV-2 and thus can detect antibodies to either. These kits use both natural and recombinant antigens and are continu ously updated to increase their sensitivity to newly discovered species, such as group O viruses (Fig. 208-1). The fourth-generation EIA tests combine detection of antibodies to HIV-1 or HIV-2 with detection of the p24 antigen of HIV. EIA tests are generally scored as positive (highly reactive), negative (nonreactive), or indeterminate (partially reactive). While the EIA is an extremely sensitive test, it is not optimal with regard to specificity. This is particularly true in studies of low-risk individuals, such as volunteer blood donors. In this latter population, as few as 10% of EIA-positive individuals are subsequently confirmed to have HIV infection. Among the factors associated with false-positive EIA tests are antibodies to class II antigens (such as may be seen follow ing pregnancy, blood transfusion, or transplantation), autoantibodies, hepatic disease, recent influenza vaccination, acute viral infections, and administration of an HIV vaccine. For these reasons, anyone suspected of having HIV infection based on a positive or inconclusive fourth-generation EIA result should have the result confirmed with a more specific assay such as an HIV-1– or HIV-2–specific antibody immunoassay or a plasma HIV RNA level. One can estimate whether an individual has a recent infection with HIV-1 by comparing the results on a standard EIA test that will score positive for all infected individuals with the results on an assay modified to be less sensitive (“detuned assay”) that will score positive for individuals with estab lished HIV infection and negative for individuals with recent infection. In rare instances, an individual with HIV treated early in the course of infection may revert to a negative EIA. This does not indicate clearing of infection; rather, it signifies levels of ongoing exposure to virus or viral proteins insufficient to maintain a measurable antibody response. When these individuals have discontinued therapy, viruses and anti bodies have reappeared. CDC recommendations indicate that a positive fourth-generation assay confirmed by a second HIV-1– or HIV-2–specific immunoassay or a plasma HIV RNA level is adequate for diagnosis. The Western blot, which had previously been used for a confirmatory test, is no longer used for this purpose. A guideline for the use of these serologic tests in attempting to make a diagnosis of HIV infection is depicted in Fig. 208-31.

In patients in whom HIV infection is suspected, the appropriate initial test is a fourth-generation HIV-1/2 antigen anti body immunoassay. If the result is negative, unless there is strong reason to suspect early HIV infection (as in a patient exposed within the previous 3 months), the diag nosis is ruled out and retesting should be performed only as clinically indicated. If the immunoassay is indeterminate or positive, the test should be repeated. If the repeat is negative on two occasions, one can assume that the initial positive reading was due to a + – HIV-1 HIV-2 HIV-1 antibodies detected + – Reactive test result Nonreactive test result FIGURE 208-31 CDC algorithm for making a diagnosis of HIV infection using tests for antibody, antigen, and RNA. NAT, nucleic acid test. (Adapted from stacks.cdc.gov/view/cdc/23446.)

technical error in the performance of the assay and that the patient is negative. If the repeat is indeterminate or positive, one should proceed to an HIV-1/HIV-2 antibody differentiation immunoassay such as the Bio-Rad Geenius. If testing is positive for HIV-1 and/or HIV-2 one may make a diagnosis of HIV-1 and/or HIV-2 infection. If the HIV-1/ HIV-2 antibody testing is negative or indeterminate one should pro ceed to HIV-1 RNA testing with a nucleic acid test (NAT; see below). If the NAT is positive, in the presence of a negative antibody test, one can make a diagnosis of acute HIV-1 infection. If the NAT test is negative for HIV-1 one should consider additional NAT testing for HIV-2. One can conclude a false-positive fourth-generation test in the setting of repeated negative or indeterminate HIV-2/HIV-2 antibody tests in the setting of negative NAT tests.

In addition to these standard laboratory-based assays for detecting antibodies to HIV, a series of point-of-care tests can provide results in 1 to 60 minutes. While the sensitivity and specificity of these tests are generally quite high, it is generally recommended that any positive results be confirmed with standard laboratory testing. Currently in the United States there is one FDA-approved rapid test kit available for use at home (OraQuick). It provides results in approximately 20 minutes. There are several other tests for which the sample is obtained at home and mailed to the lab. A positive result with any of these tests should be followed with confirmatory laboratory testing by a health care professional. A variety of laboratory tests are available for the direct detection of HIV or its components (Table 208-8). These tests may be of consider able help in making a diagnosis of HIV infection when the antibody determination assays are indeterminate. In addition, the tests detecting levels of HIV RNA can be used to determine prognosis and to assess the response to antiretroviral therapies. The simplest, least expensive, and most rarely used of the direct detection tests is the p24 antigen cap ture assay. This is an EIA-type assay in which the solid phase consists of antibodies to the p24 antigen of HIV. It detects the viral protein p24 in the blood of people with HIV where it exists either as free antigen or complexed to anti-p24 antibodies. It is currently part of the fourthgeneration HIV-1/2 antigen antibody immunoassay test recommended for initial screening. Overall, ~30% of individuals with untreated HIV infection have detectable levels of free p24 antigen. This increases to ~50% when samples are treated with a weak acid to dissociate antigen– antibody complexes. Throughout the course of HIV infection, an equi librium exists between p24 antigen and anti-p24 antibodies. During the first few weeks of infection, before an immune response develops, there is a brisk rise in p24 antigen levels. After the development of anti-p24 antibodies, these levels decline. Late in the course of infection, when CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders
HIV-1/2 ANTIGEN/ANTIBODY COMBINATION IMMUNOASSAY + – Negative for HIV-1 and HIV-2 antibodies and p24Ag HIV-1/HIV-2 antibody differentiation immunoassay + + HIV-1 HIV-2 – + HIV-1 HIV-2 – – HIV-1 or indeterminate HIV-2 HIV-2 antibodies detected HIV antibodies detected HIV-1 NAT + – HIV-1 NAT Negative for HIV-1 HIV-1 NAT Acute HIV-1 infection

TABLE 208-8 Characteristics of Tests for Direct Detection of HIV TEST TECHNIQUE SENSITIVITYa COST/TESTb Immune complex–dissociated p24 antigen capture assay Measurement of levels of HIV-1 core (p24) protein in an EIA-based format following dissociation of antigen–antibody complexes by weak acid treatment HIV RNA by PCR Target amplification of HIV-1 RNA via reverse transcription followed by PCR Reliable to 20 copies/mL of HIV RNA $75–150 HIV RNA by bDNA Measurement of levels of particle-associated HIV RNA in a nucleic acid capture assay employing signal amplification HIV RNA by TMA Target amplification of HIV-1 RNA via reverse transcription followed by T7 RNA polymerase HIV RNA by NASBA Isothermal nucleic acid amplification with

internal controls Reliable to 80 copies/mL of HIV RNA $75–150 aSensitivity figures refer to those approved by the U.S. Food and Drug Administration. bPrices may be lower in large-volume settings. Abbreviations: bDNA, branched DNA; cDNA, complementary DNA; EIA, enzyme immunoassay; NASBA, nucleic acid sequence–based amplification; PCR, polymerase chain reaction; TMA, transcription-mediated amplification. circulating levels of virus are high, p24 antigen levels also increase, particularly when detected by techniques involving dissociation of antigen-antibody complexes. The p24 antigen capture assay has its greatest use as a screening test for HIV infection in patients suspected of having the acute HIV syndrome (see below), as high levels of p24 antigen are present prior to the development of antibodies. Its use as a stand-alone test for routine blood donor screening for HIV infection has been replaced by the use of “fourth-generation” assays that com bine antigen and antibody testing or NAT. The ability to measure and monitor levels of HIV RNA in the plasma of patients with HIV infection has been of extraordinary value in fur thering our understanding of the pathogenesis of HIV infection, in monitoring the response to ART, and in providing a diagnostic tool in settings where measurements of anti-HIV antibodies may be mislead ing, such as in acute infection and neonatal infection. In addition to the commercially available tests for measuring HIV RNA, DNA PCR assays also are employed by research laboratories for making a diagnosis of HIV infection by amplifying HIV proviral DNA from peripheral blood mononuclear cells. The commercially available RNA detection tests have a sensitivity of 20–50 copies of HIV RNA per milliliter of plasma. Research laboratory–based RNA assays can detect as few as one HIV RNA copy per milliliter, while the DNA PCR tests can detect proviral DNA at a frequency of one copy per 10,000–100,000 cells. Thus, these tests are extremely sensitive. One frequent consequence of a high degree of sensitivity is some loss of specificity, and false-positive results have been reported with each of these techniques. For this reason, a positive EIA with a positive HIV RNA assay can be considered the “gold standard” for a diagnosis of HIV infection, and the interpretation of other test results must be done with this in mind. PART 5 Infectious Diseases In the RT-PCR technique, following DNAse treatment, a cDNA copy is made of the HIV RNA species present in plasma typically using tRNALys3 as a primary primer. This is the same host cell primer used during the reverse transcription stage of the viral life cycle (Fig. 208-32). Because HIV is an RNA virus, this will result in the production of DNA copies of the HIV genome in amounts proportional to the amount of HIV RNA present in plasma. This cDNA is then amplified and charac terized using standard PCR techniques. In addition to being diagnostic and prognostic tools, RT-PCR and DNA-PCR also are useful for ampli fying defined areas of the HIV genome for sequence analysis and have become an important technique for studies of sequence diversity and microbial resistance to antiretroviral agents. In patients with a positive or indeterminate EIA test and an indeterminate Western blot, and in patients in whom serologic testing may be unreliable (such as patients with hypogammaglobulinemia or advanced HIV disease), these tests for quantitating HIV RNA in plasma or detecting proviral DNA in periph eral blood mononuclear cells are valuable tools for making a diagnosis of HIV infection; however, they should be used for diagnosis only when standard serologic testing has failed to provide a definitive result. ■ ■LABORATORY MONITORING OF PATIENTS

WITH HIV INFECTION The integration of clinical and laboratory data is essential to optimal management of patients with HIV infection. The close relationship

Positive in 50% of patients; detects down to 15 pg/mL of p24 protein $1–2 Reliable to 50 copies/mL of HIV RNA $75–150 Reliable to 100 copies/mL of HIV RNA $225 between clinical manifestations of

HIV infection and CD4+ T cell count has made measurement of CD4+ T cell numbers a routine part of the initial evaluation of people with HIV. The discovery of HIV as the cause of AIDS led to the development of sensitive tests that allow one to monitor the levels of HIV in the blood. Determinations of peripheral blood CD4+ T cell counts and measurements of the plasma levels of HIV RNA provide a powerful set of tools for determining prognosis and monitoring response to therapy. CD4+ T Cell Counts The CD4+ T cell count is the laboratory test generally accepted as the best indicator of the immediate state of immunologic competence of the patient with HIV infection. This mea surement has been shown to correlate very well with the level of immu nologic competence. Patients with CD4+ T cell counts <200/μL are at high risk of disease from P. jirovecii, while patients with CD4+ T cell counts <50/μL are also at high risk of disease from CMV, mycobacteria of the M. avium complex (MAC), and/or T. gondii (Fig. 208-32). Once the CD4+ T cell count is <200/μL, patients should be placed on a regimen for P. jirovecii prophylaxis. Once the count is <50/μL, primary prophylaxis for MAC infection is indicated unless the patient is imme diately started on ART. As with any laboratory measurement, one may wish to obtain two determinations prior to any significant changes in patient management based on CD4+ T cell count alone. Patients with HIV infection should have CD4+ T cell measurements performed at the time of diagnosis and every 3–6 months for the first 2 years there after. More frequent measurements should be made if a declining trend is noted. For patients who have been on ART for at least 2 years with HIV RNA levels persistently <50 copies/mL and CD4 counts 300– 500/μL, monitoring may be decreased to every year. For those with CD4 counts >500/μL, the monitoring of the CD4 count is felt by many to be optional. There are a handful of clinical situations in which the CD4+

T cell count may be misleading. Patients with HTLV-1/HIV co-infection may have elevated CD4+ T cell counts that do not accurately reflect their degree of immune competence. In patients with hypersplenism or those who have undergone splenectomy, and in patients receiving medi cations that suppress the bone marrow such as IFN-α, the CD4+ T cell percentage may be a more reliable indication of immune function than the CD4+ T cell count. A CD4+ T cell percentage of 15 is comparable to a CD4+ T cell count of 200/μL. HIV RNA Determinations Facilitated by highly sensitive tech niques for the precise quantitation of small amounts of nucleic acids, the measurement of serum or plasma levels of HIV RNA has become an essential component in the monitoring of patients with HIV infec tion. As discussed in “Diagnosis of HIV Infection,” above, the most used technique is the RT-PCR assay. This assay generates data in the form of number of copies of HIV RNA per milliliter of serum or plasma, and commercial assays can reliably detect as few as 20 cop ies of HIV RNA per milliliter of plasma. Research-based assays can detect down to one copy per milliliter. While it is common practice to describe levels of HIV RNA below these cut-offs as “undetectable,” this is a term that should be avoided as it is imprecise and leaves the false impression that the level of virus is 0. By utilizing more sensitive,

CD4 (cells/μL3) * *

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HSV HZos Crp KS Cry Can PCP NHL DEM PML WS Tox CMV PCP2 MAC Opportunistic illness FIGURE 208-32 Relationship between CD4+ T cell counts and the development of opportunistic diseases. Boxplot of the median (line inside the box), first quartile (bottom of the box), third quartile (top of

the box), and mean (asterisk) CD4+ lymphocyte count at the time of the development of opportunistic disease. Can, candidal esophagitis; CMV, cytomegalovirus infection; Crp, cryptosporidiosis; Cry, cryptococcal meningitis; DEM, AIDS dementia complex; HSV, herpes simplex virus infection; HZos, herpes zoster; KS, Kaposi's sarcoma; MAC, Mycobacterium avium complex bacteremia; NHL, nonHodgkin's lymphoma; PCP, primary Pneumocystis jirovecii pneumonia; PCP2, secondary P. jirovecii pneumonia; PML, progressive multifocal leukoencephalopathy; Tox, Toxoplasma gondii encephalitis; WS, wasting syndrome. (From Annals of Internal Medicine, RD Moore, RE Chaisson: Natural History of Opportunistic Disease in an HIV-Infected Urban Clinical Cohort. 124(7):633-642, 1996. Copyright © 1996 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.) nested PCR techniques and by studying tissue levels of virus as well as plasma levels, HIV RNA can be detected in virtually every patient with HIV infection. There are notable exceptions to this that involve patients who underwent cytoreductive therapy followed by transplant from CCR5Δ32 donors. Measurements of changes in HIV RNA levels over time have been of great value in delineating the relationship between levels of virus and rates of disease progression (Fig. 208-22), the rates of viral turnover, the relationship between immune system activation and viral replication, and the time to development of drug resistance. HIV RNA measure ments are greatly influenced by the state of activation of the immune system and may fluctuate greatly in the setting of secondary infections or immunization. For these reasons, decisions based on HIV RNA levels should never be made on a single determination. Measurements of plasma HIV RNA levels should be made at the time of HIV diagno sis. At the time of diagnosis, ART should be initiated, and HIV RNA levels monitored approximately every 4 weeks until the effectiveness of the therapeutic regimen is determined by the development of a new steady-state level of HIV RNA. In most instances of effective antiretro viral therapy, the plasma level of HIV RNA will drop to <50 copies/mL within 6 months of the initiation of treatment. During therapy, levels of HIV RNA should be monitored every 3–6 months to evaluate the continuing effectiveness of therapy. HIV Resistance Testing The availability of multiple antiretroviral drugs as treatment options has generated a great deal of interest in the potential for measuring the sensitivity of an individual's HIV viral quasispecies to different antiretroviral agents. HIV resistance testing can be done through either genotypic or phenotypic measurements. In the genotypic assays, sequence analyses of the HIV genomes obtained from patients are compared with sequences of viruses with known antiretroviral resistance profiles. In the phenotypic assays, the in vivo growth of patient-derived viral isolates or genetically constructed pseu doviruses is compared with the growth of reference strains of the virus in the presence or absence of different antiretroviral drugs. These tests are quite good at identifying those antiretroviral agents that have been utilized in the past and suggesting agents that may be of future value in a given patient. Resistance testing is recommended at the time of ini tial diagnosis and, if therapy is not initiated at that time, at the time of initiation of ART. Drug resistance testing is also indicated in the setting of virologic failure and should be performed while the patient is still

on the failing regimen because of the propensity for the pool of HIV quasi species to rapidly revert to wild-type in the absence of the selective pressures of ART. In the hands of experts, resis tance testing enhances the short-term ability to decrease viral load by ~0.5 log compared with changing drugs merely based on drug history. In addi tion to the use of resistance testing to help in the selection of new drugs in patients with virologic failure, it may also be of value in selecting an ini tial regimen for treatment of therapynaïve individuals. This is particularly true in geographic areas with a high level of background resistance. The patient needs to have an HIV-1 RNA level above

500–1000 copies/mL for an accurate resistance determination. Resistance assays lose their consis tency at lower levels of plasma viremia.

Co-Receptor Tropism Assays

Following the licensure of maravi roc as the first CCR5 antagonist for the treatment of HIV infection (see below), it became necessary to be able to determine whether a patient's virus was likely to respond to this treatment. Patients tend to have CCR5-tropic virus early in the course of infection, with a trend toward CXCR4 viruses later in disease. The antiretroviral agent maraviroc is effective only against CCR5-tropic viruses. Because the genotypic determinants of cellular tropism are poorly defined, a phenotypic assay is necessary to determine this prop erty of HIV. The Trofile assay (Monogram Biosciences) is available to make this determination. This assay clones the envelope regions of the patient's virus into an indicator virus that is then used to infect target cells expressing either CCR5 or CXCR4 as their co-receptor. The assay takes weeks to perform and is expensive. Another, less costly option is to obtain a genotypic assay of the V3 region of HIV-1 and then employ a computer algorithm to predict viral tropism from the sequence. While this approach is less expensive than the classic phenotypic assay, there are fewer data to validate its predictive value. CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders
Other Tests A variety of other laboratory tests have been studied as potential markers of HIV disease activity. Among these are quantitative culture of replication-competent HIV from plasma, peripheral blood mononuclear cells, or resting memory CD4+ T cells; circulating levels of β2-microglobulin, soluble IL-2 receptor, IgA, acid-labile endogenous IFN, or TNF-α; and the presence or absence of activation markers such as CD38, HLA-DR, and PD-1 on CD4+ or CD8+ T cells. Nonspecific serologic markers of inflammation and/or coagulation such as IL-6, d-dimer, and sCD14 have been shown to have a high correlation with all-cause mortality (Table 208-9). While these measurements have value as markers of disease activity and help to increase our under standing of the pathogenesis of HIV disease, they do not currently play a major role in the monitoring of patients with HIV infection. TABLE 208-9 Association between High-Sensitivity CRP, Il-6, and d-Dimer with All-Cause Mortality in Patients with HIV Infection UNADJUSTED ADJUSTED ODDS RATIO (FOURTH/FIRST) P ODDS RATIO (FOURTH/FIRST) P MARKER Hs-CRP 2.0 .05 2.8 .03 IL-6 8.3 <.0001 11.8 <.0001 d-dimer 12.4 <.0001 26.5 <.0001 Abbreviations: Hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6. Source: From LH Kuller et al: PLoS Med 5:e203, 2008.

CLINICAL MANIFESTATIONS The clinical consequences of HIV infection encompass a spectrum ranging from an acute syndrome associated with primary infection to a prolonged asymptomatic state to advanced disease. It is best to regard HIV disease as beginning at the time of primary infection and progressing through vari ous stages. As mentioned above, active virus replication and progressive immunologic impairment occur throughout the course of HIV infec tion in most patients. Except for the rare, true, "elite" virus controllers or long-term nonprogressors (see "Long-Term Survivors, Long-Term Nonprogressors, and Elite Controllers," above), HIV disease in untreated patients inexorably progresses even during the clinically latent stage. Since the mid-1990s, ART has had a major impact on preventing and reversing the progression of disease over extended periods of time in a substantial proportion of adequately treated patients. Today, a person diagnosed with HIV infection and treated with ART has a close to normal life expectancy.

■ ■ACUTE HIV INFECTION It is estimated that 50–70% of individuals with HIV infection experi ence an acute clinical syndrome ~3–6 weeks after primary infection (Fig. 208-33). Varying degrees of clinical severity have been reported, and although it has been suggested that symptomatic seroconversion leading to the seeking of medical attention indicates an increased risk for an accelerated course of disease, there does not appear to be a cor relation between the level of the initial burst of viremia in acute HIV infection and the subsequent course of disease. The typical clinical findings in the acute HIV syndrome are listed in Table 208-10; they occur along with a burst of plasma viremia. It has been reported that several symptoms of the acute HIV syndrome (fever, skin rash, pharyngitis, and myalgia) occur less frequently in those infected by injection drug use compared with those infected by sexual contact. The syndrome is typical of an acute viral syndrome and has been lik ened to acute infectious mononucleosis. Symptoms usually persist for one to several weeks and gradually subside as an immune response to HIV develops and the levels of plasma viremia decrease. Opportunistic infections have been reported during this stage of infection, reflecting the immunodeficiency that results from reduced numbers of CD4+ T cells and likely also from the dysfunction of CD4+ T cells owing to viral protein and endogenous cytokine-induced perturbations of cells (Table 208-5) associated with the extremely high levels of plasma viremia. The Fiebig staging system has been used to describe the different stages of acute HIV infection, ranging from stage 1 (HIV RNA positive alone) to stage VI (HIV RNA and full Western blot positive). A number of immunologic abnormalities accompany the acute HIV syndrome, including multiphasic perturbations of the numbers of circulating lymphocyte subsets. The numbers of total lymphocytes and T cell subsets (CD4+ and CD8+) are initially reduced. An inversion of the CD4+/CD8+ T cell ratio occurs later because of a rise in the number PART 5 Infectious Diseases Primary Infection 3–6 weeks Plasma viremia (wide dissemination of virus) Acute syndrome Retrafficking of lymphocytes 1 week–3 months Immune response to HIV Curtailment of plasma viremia Establishment of chronic, persistent infection in lymphoid tissue 1–2 weeks Clinical latency FIGURE 208-33 The acute HIV syndrome. See text for detailed description. (From

G Pantaleo, C Graziosi, AS Fauci: The Immunopathogenesis of Human Immunodeficiency Virus Infection. N Engl J Med 328:327, 1993. Copyright © 1993 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

TABLE 208-10 Clinical Findings in the Acute HIV Syndrome General Neurologic Fever Meningitis Pharyngitis Encephalitis Lymphadenopathy Peripheral neuropathy Headache/retroorbital pain Myelopathy Arthralgias/myalgias Dermatologic Lethargy/malaise Erythematous maculopapular rash Anorexia/weight loss Mucocutaneous ulceration Nausea/vomiting/diarrhea Source: Reproduced with permission from B Tindall, DA Cooper: Primary HIV infection: Host responses and intervention strategies. AIDS 5:1, 1991. of CD8+ T cells. In fact, there may be a selective and transient expan sion of CD8+ T cell subsets, as determined by T cell receptor analysis (see above). The total circulating CD8+ T cell count may remain elevated or return to normal; however, CD4+ T cell levels usually remain somewhat depressed, although there may be a slight rebound toward normal. Lymphadenopathy occurs in ~70% of individuals with primary HIV infection. Most patients recover spontaneously from this syndrome, and many are left with only a mildly depressed CD4+ T cell count that remains stable for a variable period before beginning its pro gressive decline; in some individuals, the CD4+ T cell count returns to the normal range. Approximately 10% of patients manifest a fulminant course of immunologic and clinical deterioration after primary infec tion, even after the disappearance of initial symptoms. In most patients, primary infection with or without the

acute syndrome is followed by a prolonged period of clinical latency or smoldering low disease activity. ■ ■THE ASYMPTOMATIC STAGE—CLINICAL LATENCY Although the length of time from initial infection to the development of clinical disease varies greatly, the median time for untreated patients is ~10 years. As emphasized above, HIV disease with active virus replica tion is ongoing and progressive during this asymptomatic period. The rate of disease progression is directly correlated with HIV RNA levels. Patients with high levels of HIV RNA in plasma progress to symptomatic disease faster than patients with low levels of HIV RNA (Fig. 208-22). Some patients referred to as long-term nonprogressors show little if any decline in CD4+ T cell counts over extended periods of time. These patients generally have extremely low levels of HIV RNA; a subset, referred to as elite nonprogressors, exhibits HIV RNA levels <50 copies/ mL. Certain other patients remain entirely asymptomatic even though their CD4+ T cell counts show a steady progressive decline to extremely low levels. In these patients, the appearance of an opportunistic disease may be the first manifestation of HIV infection. During the asymptom atic period of HIV infection, the average rate of CD4+ T cell decline is ~50/μL per year in an untreated patient. When the CD4+ T cell count falls to <200/μL, the resulting state of immunodeficiency is severe enough to place the patient at high risk for opportunistic infections and neoplasms and, hence, for clinically apparent disease. ■ ■SYMPTOMATIC DISEASE Symptoms of HIV disease can appear at any time during the course of HIV infection. Generally, the spectrum of illnesses that one observes changes as the CD4+ T cell count declines. The more severe and lifethreatening complications of HIV infection occur in patients with CD4+ T cell counts <200/μL. A diagnosis of AIDS is made in any individual age 6 years and older with HIV infection and a CD4+ T cell count <200/μL (stage 3, Table 208-2) and in anyone with HIV infec tion who develops one of the HIV-associated diseases considered to be indicative of a severe defect in cell-mediated immunity (Table 208-1). While the causative agents of the secondary infections are characteristically opportunistic organisms such as P. jirovecii, atypical mycobacteria, CMV, and other organisms that do not ordinarily cause disease in the absence of a compromised immune system, they also include several common bacterial and mycobacterial pathogens. Following the wide spread use of ART and implementation of guidelines for the preven tion of opportunistic infections (Table 208-11), the incidence of these

TABLE 208-11 NIH/CDC/IDSA 2024 Guidelines for the Prevention of Opportunistic Infections in Persons Infected with HIV PATHOGEN INDICATIONS FIRST CHOICE(S) ALTERNATIVES Pneumocystis jirovecii CD4+ T cell count <100–200/μL if HIV RNA level above detection limits or CD4+ T cell count <100 /μL regardless of HIV RNA level or Oropharyngeal candidiasis or Prior bout of PCP May stop prophylaxis if CD4+ T cell count

> 200/μL for ≥3 months Mycobacterium tuberculosis Important to double check drug–drug interactions with ART regimen Isoniazid sensitive Skin test >5 mm or Positive IFN-γ release assay or Prior positive test without treatment or Close contact with case of active pulmonary TB Same with high probability of exposure to drugresistant TB Drug resistant Consult local public health authorities Mycobacterium avium complex CD4+ T cell count <50/μL unless ART immediately initiated—or if not able to achieve viral suppression or Prior documented disseminated disease May stop prophylaxis once fully suppressive ART in place Toxoplasma gondii T. gondii IgG antibody positive and CD4+ T cell

> count <100/µL or Prior toxoplasmic encephalitis and CD4+ T cell count <200/µL May stop prophylaxis if CD4+ T cell count

> 200/µL and HIV RNA suppressed for ≥3 months Varicella zoster virus Significant exposure to chickenpox or shingles in a patient with no history of immunization or prior exposure to either

Trimethoprim-sulfamethoxazole (TMP-SMX), 1 DS tablet qd PO or TMP-SMX, 1 SS tablet qd PO Dapsone 50 mg bid PO or 100 mg/d PO or Dapsone 50 mg/d PO + Pyrimethamine 50 mg/week PO + Leucovorin 25 mg/week PO or (Dapsone 200 mg PO + Pyrimethamine 75 mg PO + Leucovorin 25 mg weekly PO) or Aerosolized pentamidine, 300 mg via Respirgard II nebulizer every month or Atovaquone 1500 mg/d PO or TMP-SMX 1 DS tablet 3?/week PO Isoniazid 15 mg/kg PO once weekly

(900 mg maximum) plus rifapentine

(600 mg for 25.1-32 kg; 750 mg for

32.1-49.9 kg; 900 mg ≥ 50.0 kg Pyridoxine 50 mg PO weekly for

12 weeks or Isoniazid 300 mg PO daily + rifampin

600 mg PO daily + pyridoxine 25–50 mg PO daily for 3 months Isoniazid 300 mg PO daily + pyridoxine 25–50 mg PO daily for 6–9 months Rifampin 600 mg PO daily for 4 months Isoniazid 300 mg PO daily + rifapentine (<35 kg: 300 mg; 35–45 kg: 450 mg; >45 kg: 600 mg) PO daily + pyridoxine 25–50 mg PO daily for 4 weeks (only for persons on an efavirenz-based ART) CHAPTER 208 Azithromycin 1200 mg weekly PO or

600 mg twice weekly PO or Clarithromycin 500 mg twice daily PO Rifabutin (dose adjusted based on cART regimen) Human Immunodeficiency Virus Disease: AIDS and Related Disorders
TMP-SMX 1 DS tablet PO daily or Sulfadiazine 2000–4000 mg in 2–4 divided doses daily PO + Pyrimethamine 25–50 mg/d PO + Leucovorin 10–25 mg/d PO TMP-SMX 1 DS 3 times weekly PO or TMP-SMX, 1 SS PO daily or Dapsone 50 mg/d PO + Pyrimethamine 50 mg weekly PO + Leucovorin 25 mg weekly PO or (Dapsone 200 mg PO + Pyrimethamine 75 mg PO + Leucovorin 25 mg PO) weekly or Atovaquone 1500 mg PO daily ± (Pyrimethamine 75 mg PO + Leucovorin 10 mg PO) daily or (Clindamycin 600 mg q8h PO + Pyrimethamine 25 mg/d PO + Leucovorin 10mg/d PO) daily Varicella zoster immune globulin, IM, within 10 d of exposure (800-843-7477) Acyclovir 800 mg PO 5 times a day for 5–7 days or Valacyclovir 1 g PO tid for 5–7 days (Continued)

TABLE 208-11 NIH/CDC/IDSA 2024 Guidelines for the Prevention of Opportunistic Infections in Persons Infected with HIV PATHOGEN INDICATIONS FIRST CHOICE(S) ALTERNATIVES Cryptococcus neoformans Prior documented disease—primary prophylaxis not recommended in United States May stop secondary prophylaxis 1 year after initiation of therapy if CD4+ T cell count >100/µL, no evidence of active fungal infection, and HIV RNA levels suppressed for >3 months Histoplasma

capsulatum Prior documented disease or CD4+ T cell count <150 µL and high risk (endemic area or occupational exposure) May stop prophylaxis after 1 year if CD4+ T cell count >150/µL and patient on effective ART for ≥6 months Coccidioides immitis Prior documented disease or positive serology and CD4+ T cell count <250/µL if from a disease endemic area. (For this indication prophylaxis can be stopped if CD4+ T cell count ≥250 for 6 months.) Talaromyces (formerly Penicillium) marneffei Prior documented disease Patients with CD4+ T cell counts <100 who live or stay in northern Thailand, Southern China, or Vietnam May stop secondary prophylaxis in patients on ART with CD4+ T cell count >100/µL for ≥6 months Salmonella species Prior recurrent bacteremia—primary prophylaxis not generally recommended Bartonella Prior infection Doxycycline 200 mg/d PO May stop after 3–4 months of therapy and with a CD4+ T cell count >200/µL for >3 months and effective ART for at least 6 months PART 5 Infectious Diseases Cytomegalovirus Prior end-organ disease—primary prophylaxis not recommended May stop secondary prophylaxis if CD4+ T cell count >100/µL for 6 months and no evidence of active CMV disease Restart if CD4+ T cells <100/µL Immunizations Generally Recommended Hepatitis B virus All susceptible (anti-HBc– and anti-HBs– negative) patients Hepatitis A virus All susceptible (anti-HAV–negative) patients Hepatitis A vaccine: 2 doses Influenza virus All patients annually Inactivated trivalent influenza virus vaccine 1 dose yearly COVID-19 Annually or per updated CDC recommendations (www.cdc.gov/covid/vaccines/ immunocompromised-people.html) Streptococcus pneumoniae All patients, preferably before CD4+ T cell count ≤200/µL Reimmunize persons initially immunized at a CD4+ T cell count <100/µL whose CD4+ T cell count then increases to >200/µL Human papillomavirus All patients 13–26 years of age HPV vaccine; 3 doses Mpox All patients with HIV who have potential for mpox exposure Meningococcal disease All patients with HIV infection >18 years Two doses of quadrivalent meningococcal conjugate vaccine Zoster Age <18 years Two-dose series of recombinant zoster vaccine (Shingrix) IM 2–6 months apart

(Continued) Fluconazole 200 mg/d PO Itraconazole 200 mg/d PO Itraconazole 200 mg bid PO Fluconazole 400 mg/d PO Fluconazole 400 mg PO daily Itraconazole 200 mg/d PO Fluconazole 400 mg PO once weekly Based on sensitivity of initial infection or Azithromycin 1200 mg weekly PO or Clarithromycin 500 mg bid PO Valganciclovir 900 mg once daily PO Hepatitis B vaccine: 3 doses Pneumococcal conjugated vaccine (15 or 20) 0.5 mL IM; if 15-valent is used, follow in 8 weeks or more by pneumococcal polysaccharide vaccine (23) Mpox vaccine (MVA-BN); 2 doses (Continued)

TABLE 208-11 NIH/CDC/IDSA 2024 Guidelines for the Prevention of Opportunistic Infections in Persons Infected with HIV PATHOGEN INDICATIONS FIRST CHOICE(S) ALTERNATIVES Recommended for Prevention of Severe or Frequent Recurrences Herpes simplex Frequent/severe recurrences Valacyclovir 500 mg twice daily PO Candida (mucocutaneous) Frequent/severe recurrences—primary prophylaxis not recommended Abbreviations: ART, antiretroviral therapy; bid, twice daily; cART, combination antiretroviral therapy; DS, double-strength; IFN-γ, interferon γ; IM, intramuscular; PCP, Pneumocystis jirovecii pneumonia; PO, by mouth; qd, daily; SS, single-strength; TB, tuberculosis; tid, three times a day. secondary infections has decreased dramatically (Fig. 208-34). Overall, the clinical spectrum of HIV disease is constantly changing as patients live longer and new and better approaches to treatment and prophylaxis are developed. In addition to the classic, original AIDSdefining illnesses, patients with HIV infection also have an increase in several serious non-AIDS illnesses, including non-AIDS-related cancers and cardiovascular, renal, and hepatic disease. Non-AIDS events (Table 208-4) now dominate the disease burden for patients

Incidence/100 person-years No. of opportunistic infections

Pneumocystis pneumonia

Disseminated Mycobacterium avium complex Esophageal candidiasis

Cytomegalovirus retinitis Kaposi’s sarcoma

Cytomegalovirus disease

Cryptococcosis Toxoplasmosis

A Year of observation

per 100 person-years

B

FIGURE 208-34 A. Decrease in the incidence of opportunistic infections and Kaposi’s sarcoma in people with HIV with CD4+ T cell counts <100/µL from 1992 through 1998. (Reproduced with permission from JE Kaplan et al: Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. Clin Infect Dis 30:S5-14, 2000.) B. Quarterly incidence rates of cytomegalovirus (CMV), Pneumocystis jirovecii pneumonia (PCP), and Mycobacterium avium complex (MAC) from 1995 to 2001. (Reproduced with permission from Palella FJ Jr et al; HIV Outpatient Study Investigators. Durability and predictors of success of highly active antiretroviral therapy for ambulatory patients with HIV. AIDS 16:1617, 2002.)

(Continued) or Acyclovir 400 mg twice daily PO or Famciclovir 500 mg twice daily PO Fluconazole 100–200 mg daily PO Posaconazole oral suspension 400 mg daily PO or Itraconazole 200 mg oral suspension daily or Posaconazole tablet 300 mg PO daily with HIV infection successfully treated with ART. In developed coun tries, AIDS-related illnesses are responsible for only ~25% of deaths in patients with HIV infection. A similar percentage of deaths are due to non-AIDS-defining malignancies. Cardiovascular disease and liver disease each account for approximately 15% of deaths with 3% of deaths due to suicide The physician providing care to a patient with HIV infection must be well versed in general internal medicine as well as HIV-related opportunistic diseases. In general, it should be stressed that a key element of treatment of symptomatic complications of HIV disease, whether they are primary or secondary, is achieving good control of HIV replication with the use of ART and instituting primary and secondary prophylaxis for opportunistic infections as indicated. CHAPTER 208 Diseases of the Respiratory System Acute bronchitis and sinusitis are prevalent during all stages of HIV infection. The most severe cases tend to occur in patients with lower CD4+ T cell counts. Sinusitis presents as fever, nasal congestion, and headache. The diag nosis is made by CT or MRI. The maxillary sinuses are most commonly involved; however, disease is also frequently seen in the ethmoid, sphenoid, and frontal sinuses. While some patients may improve without antibiotic therapy, radiographic improvement is quicker and more pronounced in patients who have received antimicrobial ther apy. It is postulated that this high incidence of sinusitis results from an increased frequency of infection with encapsulated organisms such as

H. influenzae and S. pneumoniae. In patients with low CD4+ T cell counts one may see mucormycosis infections of the sinuses. In contrast to the course of this infection in other patient popula tions, mucormycosis of the sinuses in patients with HIV infection may progress more slowly. In this setting aggressive, frequent local debridement in addition to local and systemic amphotericin B may result in effective treatment. Human Immunodeficiency Virus Disease: AIDS and Related Disorders
CMV PCP MAC Pulmonary disease is one of the most frequent complications of HIV infection. The most common manifestation of pulmonary disease is pneumonia. Three of the 10 most common AIDS-defining illnesses are recurrent bacterial pneumonia, tuberculosis, and pneumonia due to the unicellular fungus P. jirovecii. Other major causes of pulmonary infiltrates include other mycobacterial infections, other fungal infec tions, nonspecific interstitial pneumonitis, KS, and lymphoma. Bacterial pneumonia is seen with an increased frequency in patients with HIV infection, with 0.8–2.0 cases per 100 person-years. Patients with HIV infection are particularly prone to infections with encapsulated organisms. S. pneumoniae (Chap. 153) and H. influenzae (Chap. 162) are responsible for most cases of bacterial pneumonia in patients with AIDS. This may be a consequence of altered B cell function and/or defects in neutrophil function that may be secondary to HIV disease (see above). Pneumonias due to S. aureus (Chap. 152) and P. aeru ginosa (Chap. 170) also are reported to occur with an increased fre quency in patients with HIV infection. S. pneumoniae (pneumococcal) infection may be the earliest serious infection to occur in patients with

HIV disease. This can present as pneumonia, sinusitis, and/or bacte remia. Patients with untreated HIV infection have a 6-fold increase in the incidence of pneumococcal pneumonia and a 100-fold increase in the incidence of pneumococcal bacteremia. Pneumococcal disease may be seen in patients with relatively intact immune systems. In one study, the baseline CD4+ T cell count at the time of a first episode of pneumo coccal pneumonia was ~300/μL. Of interest is the fact that the inflam matory response to pneumococcal infection appears proportional to the CD4+ T cell count. Due to this high risk of pneumococcal disease, immunization with the conjugated pneumococcal vaccine followed by booster immunization with the 23-valent pneumococcal polysac charide vaccine is one of the generally recommended prophylactic measures for patients with HIV infection. This is likely most effective if given while the CD4+ T cell count is >200/μL and, if given to patients with lower CD4+ T cell counts, should be repeated once the count has been above 200 for 6 months. Although clear guidelines do not exist, it also makes sense to repeat immunization every 5 years. The incidence of bacterial pneumonia is cut in half when patients quit smoking.

Pneumocystis pneumonia (PCP; Chap. 227) is caused by the fungus P. jirovecii and was once the hallmark of AIDS. It has dramatically declined in incidence following the development of effective prophy lactic regimens and the widespread use of ART. It is, however, still the single most common cause of pneumonia in patients with HIV infec tion in the United States and can be identified as a likely etiologic agent in 25% of cases of pneumonia in patients with HIV infection, with an incidence of about 1 case per 100 person-years. Approximately 30% of cases of HIV-associated PCP occur in patients who are unaware of their HIV status. The risk of PCP is greatest among those who have experienced a previous bout of PCP and those who have CD4+ T cell counts of <200/μL. Overall, 79% of patients with PCP have CD4+ T cell counts <100/μL and 95% of patients have CD4+ T cell counts <200/μL. Recurrent fever, night sweats, thrush, and unexplained weight loss also are associated with an increased incidence of PCP. For these reasons, it is strongly recommended that

all patients with CD4+ T cell counts <200/µL (or a CD4 percentage <15) receive some form of PCP prophylaxis. The incidence of PCP is approaching zero in patients with known HIV infection receiving appropriate ART and prophylaxis. In the United States, primary PCP is now occurring at a median CD4+ T cell count of 36/µL, while secondary PCP is occurring at a median CD4+ T cell count of 10/µL. PART 5 Infectious Diseases Patients with PCP generally present with fever and a cough that is usually nonproductive or productive of only scant amounts of white sputum. They may complain of a characteristic retrosternal chest pain that is worse on inspiration and is described as sharp or burning. HIV-associated PCP may have an indolent course characterized by weeks of vague symptoms and should be included in the differential diagnosis of fever, pulmonary complaints, or unexplained weight loss in any patient with HIV infection and <200 CD4+ T cells/µL. The most common finding on chest x-ray is either a normal film, if the disease is suspected early, or a faint bilateral interstitial infiltrate. The classic finding of a dense perihilar infiltrate is unusual in patients with AIDS. In patients with PCP who have been receiving aerosolized pentamidine for prophylaxis, one may see an x-ray picture of upper lobe cavi tary disease, reminiscent of TB. Other less common findings on chest x-ray include lobar infiltrates and pleural effusions. Thin-section CT may demonstrate a patchy ground-glass appearance. Routine laboratory evaluation is usually of little help in the differential diagnosis of PCP. A mild leukocytosis is common, although this may not be obvious in patients with prior neutropenia. Elevation of lactate dehydrogenase is common. Arterial blood-gases may indicate hypoxemia with a decline in Pao2 and an increase in the arterial-alveolar (a–a) gradient. Arterial blood-gas measurements not only aid in making the diagnosis of PCP but also provide important information for staging the severity of the disease and directing treatment (see below). A definitive diagnosis of PCP requires demonstration of the organism in samples obtained from induced sputum, bronchoalveolar lavage, transbronchial biopsy, or open-lung biopsy. PCR has been used to detect specific DNA sequences for P. jirovecii in clinical specimens where histologic exami nations have failed to make a diagnosis.

In addition to pneumonia, other clinical problems have been reported in people with HIV as a result of infection with P. jirovecii. Otic involvement may be seen as a primary infection, presenting as a polypoid mass involving the external auditory canal. In patients receiv ing aerosolized pentamidine for prophylaxis against PCP, one may see a variety of extrapulmonary manifestations of P. jirovecii. These include ophthalmic lesions of the choroid, a necrotizing vasculitis that resembles Buerger disease, bone marrow hypoplasia, and intestinal obstruction. Other organs that have been involved include lymph nodes, spleen, liver, kidney, pancreas, pericardium, heart, thyroid, and adrenals. Organ infection may be associated with cystic lesions that may appear calcified on CT or ultrasound. The standard treatment for PCP or disseminated pneumocystosis is trimethoprim-sulfamethoxazole (TMP-SMX). A high (20–85%) inci dence of side effects, particularly skin rash and bone marrow suppres sion, is seen with TMP-SMX in patients with HIV infection. Alternative treatments for mild to moderate PCP include dapsone/trimethoprim, clindamycin/primaquine, and atovaquone. IV pentamidine is the treatment of choice for severe disease in the patient unable to tolerate TMP-SMX. For patients with a Pao2 <70 mmHg or with an a–a gradient

> “ 35 mmHg, adjunct glucocorticoid therapy should be used in addition to specific antimicrobials. Overall, treatment should be continued for 21 days and followed by secondary prophylaxis. Prophylaxis for PCP is indicated for any individual with

HIV who has experienced a prior bout of PCP, any patient with a CD4+ T cell count of <200/μL or a CD4 percentage <15, any patient with unexplained fever for >2 weeks, and any patient with a recent history of oropharyngeal candidiasis. The preferred regimen for prophylaxis is TMP-SMX, one double-strength tablet daily. This regimen also provides protection against toxoplasmo sis and some bacterial respiratory pathogens. For patients who cannot tolerate TMP-SMX, alternatives for prophylaxis include dapsone plus pyrimethamine plus leucovorin, aerosolized pentamidine administered by the Respirgard II nebulizer, and atovaquone. Primary or secondary prophylaxis for PCP can be discontinued in those patients treated with ART who maintain good suppression of HIV (<50 copies/mL) and CD4+ T cell counts >200/μL for at least 3 months. M. tuberculosis, once thought to be on its way to extinction in the United States, experienced a resurgence associated with the HIV epi demic (Chap. 183). Worldwide, approximately one-third of all AIDSrelated deaths are associated with TB, and TB is the primary cause of death for 10–15% of patients with HIV infection. In the United States ~5% of untreated AIDS patients have active TB. Patients with HIV infection are more likely to have active TB by a factor of 100 when compared with an HIV-negative population. For an asymptomatic HIV-negative person with a positive purified protein derivative (PPD) skin test, the risk of reactivation TB is around 1% per year. For the patient with untreated HIV infection, a positive PPD skin test, and no signs or symptoms of TB, the rate of reactivation TB is 7–10% per year. Untreated TB can accelerate the course of HIV infection. Levels of plasma HIV RNA increase in the setting of active TB and decline in the setting of successful TB treatment. Active TB is most common in patients 25–44 years of age, in African Americans and Hispanics, in patients in New York City and Miami, and in patients in developing countries. In these demographic groups, 20–70% of the new cases of active TB are in patients with HIV infection. The epidemic of TB embedded in the epidemic of HIV infection probably represents the greatest health risk to the general public and the health care profession associated with the HIV epidemic. In contrast to infection with atypical mycobacteria such as MAC, active TB often develops relatively early in the course of HIV infection and may be an early clinical sign of HIV disease. In one study, the median CD4+ T cell count at presentation of TB was 326/μL. The clinical manifestations of TB in people with HIV are quite varied and generally show different patterns as a function of the CD4+ T cell count. In patients with relatively high CD4+ T cell counts, the typical pattern of pulmonary reactivation occurs: patients present with fever, cough, dyspnea on exertion, weight loss, night sweats, and a chest x-ray revealing cavitary apical disease of the upper lobes. In patients with lower CD4+ T cell counts, disseminated disease is more common.

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CHAPTER 208 In these patients the chest x-ray may reveal diffuse or lower-lobe bilat eral reticulonodular infiltrates consistent with miliary spread, pleural effusions, and hilar and/or mediastinal adenopathy. Infection may be present in bone, brain, meninges, GI tract, lymph nodes (particularly cervical lymph nodes), and viscera. Some patients with advanced HIV infection and active TB may have no symptoms of illness, and thus screening for TB should be part of the initial evaluation of every patient with HIV infection. Approximately 60–80% of people with HIV and TB have pulmonary disease, and 30–40% have extrapulmonary disease. Respiratory isolation and a negative-pressure room should be used for patients in whom a diagnosis of pulmonary TB is being considered. This approach is critical to limit nosocomial and community spread of infection. Culture of the organism from an involved site provides a definitive diagnosis. Blood cultures are positive in 15% of patients. This figure is higher in patients with lower CD4+ T cell counts. In the setting of fulminant disease, one cannot rely on the accuracy of a negative PPD skin test to rule out a diagnosis of TB. In addition, IFN-γ release assays may be difficult to interpret due to high backgrounds as a consequence of HIV-associated immune activation. TB is one of the conditions associated with HIV infection for which cure is possible with appropriate therapy. Therapy for TB is generally the same in the patient with HIV as in the HIV-negative patient (Chap. 183). Due to the possibility of multidrug-resistant or extensively drug-resistant TB, drug susceptibility testing should be performed to guide therapy. Due to pharmacokinetic interactions, adjusted doses of rifabutin and/or changes in ART are required when treating TB in the setting of HIV infection. Treatment is most effective in programs that involve directly observed therapy. Initiation of ART and/or anti-TB therapy may be associated with clinical deterioration due to immune reconstitution inflammatory syndrome (IRIS) reactions. These are most common in patients initiating both treatments at the same time, may occur as early as 1 week after initiation of ART therapy, and are seen more fre quently in patients with advanced HIV disease. For these reasons it is recommended that initiation of ART be delayed in antiretroviral-naïve patients with CD4 counts ≥50 cells/μL until 2–8 weeks following the initiation of treatment for TB. For patients with CD4 counts <50 cells/μL the benefits of more immediate ART outweigh the risks of IRIS, and ART should be started as soon as possible in those patients. Effective prevention of active TB can be a reality if the health care professional is aggressive in looking for evidence of latent or active TB by making sure that all patients with HIV infection receive a PPD skin test or evaluation with an IFN-γ release assay. Anergy testing is not of value in this setting. Since these tests rely on the host mounting an immune response to M. tuberculosis, patients with CD4+ T cell counts <200 cells/μL should be retested if their CD4+ T cell counts rise to persistently above 200. Patients at risk of continued exposure to TB should be tested annually. People with HIV with a skin-test reaction of

> 5 mm, those with a positive IFN-γ release assay, or those who are close household contacts of persons with active TB should receive treatment with 12 weeks of once-weekly isoniazid and rifapentin. Atypical mycobacterial infections also are seen with an increased frequency in patients with HIV infection. Infections with at least 12 different mycobacteria have been reported, including M. bovis and representatives of all four Runyon groups. The most common atypical mycobacterial infection is with M. avium or M. intracellulare species—the Mycobacterium avium complex (MAC). Infections with MAC are seen mainly in patients in the United States and are rare in Africa. It has been suggested that

prior infection with M. tuberculosis decreases the risk of MAC infection. MAC infections probably arise from organ isms that are ubiquitous in the environment, including both soil and water. There is little evidence for person-to-person transmission of MAC infection. The presumed portals of entry are the respiratory and GI tracts. MAC infection is a late complication of HIV infection, occurring predominantly in patients with CD4+ T cell counts of <50/μL. The average CD4+ T cell count at the time of diagnosis is 10/μL. The most common presentation is disseminated disease with fever, weight loss, and night sweats. At least 85% of patients with MAC infection are mycobacteremic, and large numbers of organisms can often be demonstrated on bone marrow biopsy. The chest x-ray is abnormal in ~25% of patients, with the most common pattern being that of a bilateral, lower-lobe infiltrate suggestive of miliary spread. Alveolar or nodular infiltrates and hilar and/or mediastinal adenopathy also can occur. Other clinical findings include endobronchial lesions, abdomi nal pain, diarrhea, and lymphadenopathy. Anemia and elevated liver alkaline phosphatase are common. The diagnosis is made by the cul ture of blood or involved tissue. The finding of two consecutive sputum samples positive for MAC is highly suggestive of pulmonary infection. Cultures may take 2 weeks to turn positive. Therapy consists of a mac rolide, usually clarithromycin, with ethambutol. Some physicians elect to add a third drug from among rifabutin, ciprofloxacin, or amikacin in patients with extensive disease. Therapy is continued until resolution of clinical signs and symptoms, negative cultures, and CD4+ T cell counts 100/μL for 3–6 months in the setting of ART. Primary prophylaxis for MAC is indicated in patients with HIV infection and CD4+ T cell counts <50/μL not immediately starting ART (Table 208-11). This may be discontinued in patients in whom ART induces a sustained suppres sion of viral replication regardless of the change in CD4+ T cell count. Rhodococcus equi is a gram-positive, pleomorphic, acid-fast, nonspore-forming bacillus that can cause pulmonary and/or disseminated infection in patients with advanced HIV infection. Fever and cough are the most common presenting signs. Radiographically one may see cavitary lesions and consolidation. Blood cultures are often positive. Treatment is based on antimicrobial sensitivity testing. Fungal infections of the lung, in addition to PCP, can be seen in patients with AIDS. Patients with pulmonary cryptococcal disease present with fever, cough, dyspnea, and, in some cases, hemoptysis. A focal or diffuse interstitial infiltrate is seen on chest x-ray in >90% of patients. In addition, one may see lobar disease, cavitary disease, pleural effusions, and hilar or mediastinal adenopathy. More than half of patients are fungemic, and 90% of patients have concomitant CNS infection. Coccidioides immitis is a mold that is endemic in the south west United States. It can cause a reactivation pulmonary syndrome in patients with HIV infection. Most patients with this condition will have CD4+ T cell counts <250/μL. Patients present with fever, weight loss, cough, and extensive, diffuse reticulonodular infiltrates on chest x-ray. One may also see nodules, cavities, pleural effusions, and hilar adenop athy. While serologic testing is of value in the

> immunocompetent host, serologies are negative in 25% of patients with HIV and coccidioidal infection. Invasive aspergillosis is not an AIDS-defining illness and is generally not seen in patients with AIDS in the absence of neutropenia or administration of glucocorticoids. When it does occur, Aspergillus infection may have an unusual presentation in the respiratory tract of patients with AIDS, where it gives the appearance of a pseudomem branous tracheobronchitis. Primary pulmonary infection of the lung may be seen with histoplasmosis. The most common pulmonary mani festation of histoplasmosis, however, is in the setting of disseminated disease, presumably due to reactivation. In this setting respiratory symptoms are usually minimal, with cough and dyspnea occurring in 10–30% of patients. The chest x-ray is abnormal in ~50% of patients, showing either a diffuse interstitial infiltrate or diffuse small nodules, and the urine will often be positive for Histoplasma antigen. Two forms of idiopathic interstitial pneumonia have been identified in patients with HIV infection: lymphoid interstitial pneumonitis (LIP) and nonspecific interstitial pneumonitis (NIP). LIP, a common finding in children, is seen in about 1% of adult patients with untreated HIV infection. This disorder is characterized by a benign infiltrate of the lung and is thought to be part of the polyclonal activation of lympho cytes seen in the context of HIV and EBV infections. Transbronchial biopsy is diagnostic in 50% of the cases, with an open-lung biopsy required for diagnosis in the remainder of cases. This condition is gen erally self-limited, and no specific treatment is necessary. Severe cases have been managed with brief courses of glucocorticoids. Although rarely a clinical problem since the use of ART, evidence of NIP may be seen in up to half of all patients with untreated HIV infection. Histologically, interstitial infiltrates of lymphocytes and plasma cells in a perivascular and peribronchial distribution are present. When symptomatic, patients present with fever and nonproductive cough occasionally accompanied by mild chest discomfort. Chest x-ray is

usually normal or may reveal a faint interstitial pattern. Like LIP, NIP is a self-limited process for which no therapy is indicated other than appropriate management of the underlying HIV infection. HIVrelated pulmonary arterial hypertension (HIV-PAH) is seen in ~0.5% of people with HIV. Patients may present with an array of symptoms including shortness of breath, fatigue, syncope, chest pain, and signs of right-sided heart failure. Chest x-ray reveals dilated pulmonary vessels and right-sided cardiomegaly with right ventricular hypertrophy seen on electrocardiogram. ART does not appear to be of clear benefit, and the prognosis is quite poor with a median survival in the range of 2 years.

Neoplastic diseases of the lung including KS and lymphoma are dis cussed below in the section on neoplastic diseases. Diseases of the Cardiovascular System Heart disease is a rela tively common postmortem finding in people with HIV (25–75% in autopsy series). The most common form of heart disease is coronary heart disease. In one large series the overall rate of myocardial infarc tion (MI) was 3.5/1000 patient-years, 28% of these events were fatal, and MI was responsible for 7% of all deaths in the cohort. In patients with HIV infection, cardiovascular disease may be associated with

classic risk factors such as smoking, a direct consequence of HIV infection and the accompanying immune activation, or a complication of ART. In general, patients with HIV infection have higher levels of triglycerides, lower levels of high-density lipoprotein cholesterol, and a higher prevalence of smoking than cohorts of individuals without HIV infection. The finding that the rate of cardiovascular disease events was lower in patients on antiretroviral therapy than in those randomized to undergo a treatment interruption identified a clear association between HIV replication and risk of cardiovascular disease. In one study, a baseline CD4+ T cell count of <500/μL was found to be an independent risk factor for cardiovascular disease comparable in magnitude to that attributable to smoking. While the precise pathogenesis of this associa tion remains unclear, it is likely related to the immune activation and increased propensity for coagulation seen because of HIV replication. Exposure to HIV protease inhibitors and certain reverse transcriptase inhibitors has been associated with increases in total cholesterol and/ or risk of MI. Any increases in the risk of death from MI resulting from the use of certain antiretrovirals must be balanced against the marked increases in overall survival brought about by these drugs. PART 5 Infectious Diseases Another form of heart disease associated with HIV infection is a dilated cardiomyopathy associated with congestive heart failure (CHF) referred to as HIV-associated cardiomyopathy. This generally occurs as a late complication of HIV infection and, histologically, displays elements of myocarditis. For this reason, some have advocated it be treated with IV immunoglobulin (IVIg). HIV can be directly demon strated in cardiac tissue in this setting, and there is debate over whether HIV plays a direct role in this condition. Patients present with typical findings of CHF including edema and shortness of breath. Patients with HIV infection may also develop cardiomyopathy as side effects of IFN-α or nucleoside analogue therapy. These are reversible once therapy is stopped. KS, cryptococcosis, Chagas' disease, and toxoplas mosis can involve the myocardium, leading to cardiomyopathy. In one series, most patients with HIV infection and a treatable myocarditis were found to have myocarditis associated with toxoplasmosis. Most of these patients also had evidence of CNS toxoplasmosis. Thus, MRI or double-dose contrast CT scan of the brain should be included in the workup of any patient with advanced HIV infection and cardiomyopathy. A variety of other cardiovascular problems are found in patients with HIV infection. Pericardial effusions may be seen in the setting of advanced HIV infection. Predisposing factors include TB, CHF, mycobacterial infection, cryptococcal infection, pulmonary infection, lymphoma, and KS. While pericarditis is quite rare, in one series 5% of patients with HIV disease had pericardial effusions considered to be moderate or severe. Tamponade and death have occurred in asso ciation with pericardial KS, presumably owing to acute hemorrhage. Nonbacterial thrombotic endocarditis has been reported and should be considered in patients with unexplained embolic phenomena. IV

pentamidine, when given rapidly, can result in hypotension as a conse quence of cardiovascular collapse. Diseases of the Oropharynx and Gastrointestinal System

Oropharyngeal and GI diseases are common features of HIV infection. They are most frequently due to secondary infections. In addition, oral and GI lesions may occur with KS and lymphoma. Oral lesions, including thrush, hairy leukoplakia, and aphthous ulcers (Fig. 208-35), are particularly common in patients with untreated HIV infection. Thrush, due to Candida infection, and oral hairy leuko plakia, associated with EBV, are usually indicative of fairly advanced immunologic decline; they generally occur in patients with CD4+ T cell counts of <300/μL. In one study, 59% of patients with oral can didiasis went on to develop AIDS in the next year. Thrush appears as a white, cheesy

exudate, often on an erythematous mucosa in the poste rior oropharynx. While most commonly seen on the soft palate, early lesions are often found along the gingival vestibule. The diagnosis is made by direct examination of a scraping for pseudohyphal elements. Culturing is of no diagnostic value, as patients with HIV infection may have a positive throat culture for Candida in the absence of thrush. Oral hairy leukoplakia presents as white, frondlike lesions, generally along the lateral borders of the tongue and sometimes on the adjacent buccal mucosa (Fig. 208-35). Despite its name, oral hairy leukoplakia is not considered a premalignant condition. Lesions are associated with florid replication of EBV. While usually more disconcerting as a sign of HIV-associated immunodeficiency than a clinical problem in need of treatment, severe cases of oral hairy leukoplakia have been reported to respond to topical podophyllin or systemic therapy with anti-herpesvirus agents. Aphthous ulcers of the posterior oropharynx also are seen with regularity in patients with untreated HIV infection (Fig. 208-35). These lesions are of unknown etiology and can be quite painful and interfere with swallowing. Topical anesthetics provide immediate symptomatic relief of short duration. The fact that tha lidomide is an effective treatment for this condition suggests that the pathogenesis may involve the action of tissue-destructive cytokines. Palatal, glossal, or gingival ulcers may also result from cryptococcal disease or histoplasmosis. Esophagitis (Fig. 208-36) may present with odynophagia and retrosternal pain. Upper endoscopy is generally required to make an accurate diagnosis. Esophagitis may be due to Candida, CMV, or HSV. While CMV tends to be associated with a single large ulcer, HSV infec tion is more often associated with multiple small ulcers. The esophagus may also be the site of KS and lymphoma. Like the oral mucosa, the esophageal mucosa may have large, painful ulcers of unclear etiology that may respond to thalidomide. While achlorhydria is a common problem in patients with HIV infection, other gastric problems are generally rare. Among the neoplastic conditions involving the stomach are KS and lymphoma. Infections of the small and large intestine leading to diarrhea, abdominal pain, and occasionally fever are among the most significant GI problems in people with HIV. They include infections with bacteria, protozoa, and viruses. Bacteria may be responsible for infections of the GI tract in patients with HIV infection. Infections with enteric pathogens such as Salmo nella, Shigella, and Campylobacter are more common in men who have sex with men and are often more severe and more apt to relapse in patients with HIV infection. Patients with untreated HIV have approxi mately a 20-fold increased risk of infection with S. typhimurium. They may present with a variety of nonspecific symptoms including fever, anorexia, fatigue, and malaise of several weeks' duration. Diarrhea is common but may be absent. Diagnosis is made by culture of blood and stool. Long-term therapy with ciprofloxacin is the recommended treatment. HIV-infected patients also have an increased incidence of S. typhi infection in areas of the world where typhoid is a problem. Shigella spp., particularly S. flexneri, can cause severe intestinal dis ease in people with HIV. Up to 50% of patients with GI disease will develop bacteremia. Campylobacter infections occur with an increased frequency in patients with HIV infection. While C. jejuni is the strain most frequently isolated, infections with many other strains have been

A C FIGURE 208-35 Various oral lesions in people with HIV. A. Thrush. B. Hairy leukoplakia. C. Aphthous ulcer. D. Kaposi's sarcoma. FIGURE 208-36 Barium swallow of a patient with Candida esophagitis. The flow of barium along the mucosal surface is grossly irregular.

 reported. Patients usually present with crampy abdominal pain, fever, and bloody diarrhea. Infection may also present as proctitis. Stool examination reveals the presence of fecal leukocytes.

Systemic infec tion can occur, with up to 10% of infected patients exhibiting bacte remia. Most strains are sensitive to erythromycin. Abdominal pain and diarrhea may be seen with MAC infection, and patients with HIV infection may have persistent diarrhea due to enteroaggregative E. coli. Fungal infections including histoplasmosis, coccidioidomycosis, and penicilliosis have all been identified as a cause of fever and diar rhea in patients with HIV infection. Peritonitis has been seen with C. immitis. Cryptosporidia, microsporidia, and Isospora belli (Chap. 236) are the most common opportunistic protozoa that infect the GI tract and cause diarrhea in patients with HIV. Cryptosporidial infection may present in a variety of ways, ranging from a self-limited or intermittent diarrheal illness in patients in the early stages of HIV infection to a severe, life-threatening diarrhea in severely immunodeficient individu als. In patients with untreated HIV infection and CD4+ T cell counts of <300/μL, the incidence of cryptosporidiosis is ~1% per year. In 75% of cases the diarrhea is accompanied by crampy abdominal pain, and 25% of patients have nausea and/or vomiting. Cryptosporidia may also cause biliary tract disease in the patient with HIV, leading to cho lecystitis with or without accompanying cholangitis and pancreatitis secondary to papillary stenosis. The diagnosis of cryptosporidial diar rhea is made by stool examination or biopsy of the small intestine. The

diarrhea is noninflammatory, and the characteristic finding is the pres ence of oocysts that stain with acid-fast dyes. Therapy is predominantly supportive and marked improvements have been reported in the set ting of effective ART. Treatment with up to 2000 mg/d of nitazoxanide (NTZ) is associated with improvement in symptoms or a decrease in shedding of organisms in about half of patients. Its overall role in the management of this condition remains unclear. Patients can minimize their risk of developing cryptosporidiosis by avoiding contact with human and animal feces, by not drinking untreated water from lakes or rivers, and by not eating raw shellfish.

Microsporidia are small, unicellular, obligate intracellular parasites that reside in the cytoplasm of enteric cells (Chap. 236). The main spe cies causing disease in humans is Enterocytozoon bieneusi. The clinical manifestations are similar to those described for cryptosporidia and include abdominal pain, malabsorption, diarrhea, and cholangitis. The small size of the organism may make it difficult to detect; however, with the use of chromotrope-based stains, organisms can be identified in stool samples by light microscopy. Definitive diagnosis generally depends on electron-microscopic examination of a stool specimen, intestinal aspirate, or intestinal biopsy specimen. In contrast to crypto sporidia, microsporidia have been noted in a variety of extraintestinal locations, including the eye, brain, sinuses, muscle, and liver, and they have been associated with conjunctivitis and hepatitis. The most effec tive way to deal with microsporidia in a patient with HIV infection is to restore the immune system by treating the HIV infection with ART. Albendazole, 400 mg bid, has been reported to be of benefit in some patients. I. belli is a coccidian parasite (Chap. 236) most commonly found as a cause of diarrhea in patients from tropical and subtropical regions. Its cysts appear in the stool as large, acid-fast structures that can be differentiated from those of cryptosporidia based on size, shape, and number of sporocysts. The clinical syndromes of Isospora infection are identical to those caused by cryptosporidia. The important distinction is that infection with Isospora is generally easy to treat with TMP-SMX. While relapses are common, a thrice-weekly regimen of TMP-SMX appears adequate to prevent recurrence. PART 5 Infectious Diseases CMV colitis (Chap. 200) was once seen as a consequence of advanced immunodeficiency in 5–10% of patients with AIDS. It is much less common with the advent of ART. CMV colitis presents as diarrhea, abdominal pain, weight loss, and anorexia. The diarrhea is usually nonbloody, and the

diagnosis is achieved through endoscopy and biopsy. Multiple mucosal ulcerations are seen at endoscopy, and biopsies reveal characteristic intranuclear and cytoplasmic inclusion bodies. Secondary bacteremias may result as a consequence of thinning of the bowel wall. Treatment is with either valganciclovir/ganciclovir or foscarnet for 3–6 weeks. Relapses are common, and maintenance therapy is typically necessary in patients whose HIV infection is poorly controlled. Patients with CMV disease of the GI tract should be care fully monitored for evidence of CMV retinitis. In addition to disease caused by specific secondary infections, patients with HIV infection may also experience a chronic diarrheal syndrome for which no etiologic agent other than HIV can be identi fied. This entity is referred to as AIDS enteropathy or HIV enteropathy. It is most likely a direct result of HIV infection in the GI tract and improves with ART. Histologic examination of the small bowel in these patients reveals low-grade mucosal atrophy with a decrease in mitotic figures, suggesting a hyporegenerative state. Patients often have decreased or absent small-bowel lactase and malabsorption with accompanying weight loss. The initial evaluation of a patient with HIV infection and diarrhea should include a set of stool examinations, including culture, examina tion for ova and parasites, and examination for Clostridium difficile toxin. Approximately 50% of the time this workup will demonstrate infection with pathogenic bacteria, mycobacteria, or protozoa. If the initial stool examinations are negative, additional evaluation, including upper and/or lower endoscopy with biopsy, will yield a diagnosis of microsporidial or mycobacterial infection of the small intestine ~30% of the time. In patients for whom this diagnostic evaluation is nonre vealing, a presumptive diagnosis of HIV enteropathy can be made if the

History and physical Stool culture for enteric pathogens Stool for ova and parasites × 3 Stool for Clostridium difficile toxin Diagnosis No diagnosis Treat No suspicion of colitis Suspicion of colitis Upper endoscopy and biopsy Diagnosis Colonoscopy and biopsy Treat No diagnosis HIV-Associated Enteropathy FIGURE 208-37 Algorithm for the evaluation of diarrhea in a patient with HIV infection. HIV-associated enteropathy is a diagnosis of exclusion and can be made only after other, generally treatable, forms of diarrheal illness have been ruled out. diarrhea has persisted for >1 month. An algorithm for the evaluation of diarrhea in patients with HIV infection is given in Fig. 208-37. Rectal lesions are common in patients with HIV, particularly the perirectal ulcers and erosions due to the reactivation of HSV (Fig. 208-38). These lesions may appear quite atypical, as denuded skin without vesicles. They typically respond well to treatment with valacyclovir, famciclovir, or foscarnet. Other rectal lesions encountered in patients with HIV infection include condylomata acuminata, KS, and intraepi thelial neoplasia (see below). Hepatobiliary Diseases Diseases of the hepatobiliary system are a major problem in patients with HIV infection. It has been estimated that approximately 15% of the deaths of patients with HIV infection FIGURE 208-38 Severe, erosive perirectal herpes simplex in a patient with AIDS.

are related to liver disease. While this is predominantly a reflection of the problems encountered in the setting of co-infection with hepatitis B or C, it is also a reflection of the hepatic injury, ranging from hepatic steatosis to hypersensitivity reactions to immune reconstitution, that can be seen in the context of ART. The prevalence of co-infection with HIV and hepatitis viruses varies by geographic region. In the United States, ~90% of people with HIV have evidence of infection with HBV; 6–14% have chronic HBV infec tion; 5–50% of patients are co-infected with HCV; and co-infections with hepatitis D, E, and/or G viruses are common. Among IV drug users with HIV infection, rates of HCV infection range from 70 to 95%. HIV infection has a significant impact on the course of hepatitis virus infection. It is associated with approximately a 3-fold increase in the

development of persistent hepatitis B surface antigenemia. Patients infected with both HBV and HIV have decreased evidence of inflam matory liver disease. The presumption that this is due to the immuno suppressive effects of HIV infection is supported by the observations that this situation can be reversed, and one may see the development of more severe hepatitis following the initiation of effective ART. In studies of the impact of HIV on HBV infection, 4- to 10-fold increases in liver-related mortality rates have been noted in patients with HIV and active HBV infection compared to rates in patients with either infection alone. There is, however, only a slight increase in overall mor tality rate in people with HIV who are also hepatitis B surface antigen (HBsAg)–positive. IFN-α is less successful as treatment for HBV in patients with HIV co-infection. Lamivudine, emtricitabine, adefovir/ tenofovir/entecavir, and telbivudine alone or in combination are use ful in the treatment of hepatitis B in patients with HIV infection. It is important to remember that all the above-mentioned drugs also have activity against HIV and should not be used alone in patients with HIV infection, to avoid the emergence of quasispecies of HIV resistant to these drugs. For this reason, the treatment of hepatitis B infection in a patient with HIV infection should always be done in the setting of ART, and alterations in ART need to take into account that the current regi men is also treating HBV. HCV infection is more severe in the patient with HIV infection; it does not appear to affect overall mortality rates in people with HIV when other variables such as age, baseline CD4+

T cell count, and use of ART are taken into account. In the setting of HIV and HCV co-infection, levels of HCV are approximately 10-fold higher than in the HIV-negative patient with HCV infection. There is a 50% higher overall mortality rate with a five-fold increased risk of death due to liver disease in patients chronically infected with both HCV and HIV. Use of directly acting agents for the treatment of HCV leads to cure rates approaching 100%, even in patients with HIV coinfection. Successful treatment of HCV in patients with HIV decreases mortality. Hepatitis A virus infection is not seen with an increased frequency in patients with HIV infection. It is recommended that all patients with HIV infection who have not experienced natural infec tion be immunized with hepatitis A and/or hepatitis B vaccines. Infec tion with hepatitis G virus, also known as GB virus C, is seen in ~50% of patients with HIV infection. For reasons that are currently unclear, there are data to suggest that patients with HIV infection co-infected with this virus have a decreased rate of progression to AIDS. A variety of other infections also may involve the liver. Granuloma tous hepatitis may be seen as a consequence of mycobacterial or fungal infections, particularly MAC infection. Hepatic masses may be seen in the context of TB, peliosis hepatis, or fungal infection. Among the fungal opportunistic infections, C. immitis and Histoplasma capsula tum (Chap. 218) are those most likely to involve the liver. Biliary tract disease in the form of papillary stenosis or sclerosing cholangitis has been reported in the context of cryptosporidiosis, CMV infection, and KS. When no diagnosis can be made, the term AIDS cholangiopathy is used. Hemophagocytic lymphohistiocytosis of the liver has been seen in the setting of Hodgkin’s disease and may occur prior to diagnosis of the underlying neoplasm. Many of the drugs used to treat HIV infection are metabolized by the liver and can cause liver injury. Fatal hepatic reactions have been reported with a wide array of antiretrovirals including nucleoside ana logues, nonnucleoside analogues, and protease inhibitors. Nucleoside

analogues work by inhibiting DNA synthesis. This can result in toxicity to mitochondria, which can lead to disturbances in oxidative metabo lism. This may manifest as hepatic steatosis and, in severe cases, lactic acidosis and fulminant liver failure. It is important to be aware of this condition

and to watch for it in patients with HIV infection receiving nucleoside analogues. It is reversible if diagnosed early and the offend ing agent(s) discontinued. Nevirapine has been associated with at times fatal fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure. Indinavir may cause mild to moderate elevations in serum bilirubin in 10–15% of patients in a syndrome similar to Gilbert's syn drome. A similar pattern of hepatic injury may be seen with atazanavir. In the patient receiving ART with an unexplained increase in hepatic transaminases, strong consideration should be given to drug toxicity.

Pancreatic injury is most commonly a consequence of drug toxicity, notably that secondary to pentamidine or dideoxynucleosides. While up to half of patients in some series have biochemical evidence of pancreatic injury, <5% of patients show any clinical evidence of pan creatitis that is not linked to a drug toxicity. Diseases of the Kidney and Genitourinary Tract Diseases of the kidney or genitourinary tract may be a direct consequence of HIV infection, due to an opportunistic infection or neoplasm, or related to drug toxicity. Overall, microalbuminuria is seen in ~20% of untreated patients with HIV; significant proteinuria is seen in closer to 2%. The presence of microalbuminuria has been associated with an increase in all-cause mortality. HIV-associated nephropathy (HIVAN) was first described in IDUs and was initially thought to be IDU nephropathy in patients with HIV infection; it is now recognized as a true direct com plication of HIV infection. Although most patients with this condition have CD4+ T cell counts <200/μL, HIV-associated nephropathy can be an early manifestation of HIV infection and is also seen in children. More than 90% of reported cases have been in African-American or Hispanic individuals; the disease is not only more prevalent in these populations but also more severe and at one point was the third leading cause of end-stage renal failure among African Americans age 20–64 years in the United States. Proteinuria is the hallmark of this disorder. Edema and hypertension are rare. Ultrasound examination reveals enlarged, hyperechogenic kidneys. A definitive diagnosis is obtained through renal biopsy. Histologically, focal segmental glomerulosclero sis is present in 80%, and mesangial proliferation in 10–15% of cases. Prior to effective antiretroviral therapy, this disease was characterized by relatively rapid progression to end-stage renal disease. Patients with HIV-associated nephropathy should be treated for their HIV infection. Treatment with angiotensin-converting enzyme (ACE) inhibitors and/ or prednisone, 60 mg/d, have been reported to be of benefit in some cases. The incidence of this disease in patients receiving adequate ART has not been well defined; however, the impression is that it has decreased in frequency and severity. It is the leading cause of end-stage renal disease in patients with HIV infection. CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders
Among the drugs commonly associated with renal damage in patients with HIV disease are pentamidine, amphotericin, adefovir, cidofovir, tenofovir, and foscarnet. Switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) may lead to a decrease in renal injury from TDF. TMP-SMX may compete for tubular secre tion with creatinine and cause an increase in the serum creatinine level. The pharmacokinetic booster cobicistat, a component of several fixeddrug ART formulations, inhibits renal tubular secretion of creatinine leading to increased serum creatinine levels without a true decline in glomerular filtration rate. Sulfadiazine may crystallize in the kidney and result in an easily reversible form of renal shutdown, while indi navir or atazanavir may form renal calculi. Adequate hydration is the mainstay of treatment and prevention for these latter two conditions. Genitourinary tract infections are seen with a high frequency in patients with HIV infection; they present with skin lesions, dysuria, hematuria, and/or pyuria and are managed in the same fashion as in patients without HIV infection. Infections with HSV are

covered below (“Dermatologic Diseases”). Infections with T. pallidum, the etio logic agent of syphilis, play an important role in the HIV epidemic. In HIV-negative individuals, genital syphilitic ulcers as well as the ulcers

PART 5 Infectious Diseases A B C FIGURE 208-39 Characteristics of lipodystrophy. A. Truncal obesity and buffalo hump. B. Facial wasting. C. Accumulation of intraabdominal fat on CT scan. of chancroid are major predisposing factors for heterosexual transmission of HIV infection. While most people with HIV and syphilis have a typical presentation of the latter, a variety of formerly rare clinical problems may be encountered in the setting of dual infection. Among them are lues maligna, an ulcerating lesion of the skin due to a necrotizing vasculitis and associated with unexplained fever; nephrotic syndrome; and neurosyphilis. The most common presentation of syphilis in the patient with HIV is that of condylomata lata, a form of second ary syphilis. Neurosyphilis may be asymptomatic or may present as acute meningitis, neuroretinitis, deafness, or stroke. The rate of neurosyphilis may be as high as 1% in patients with HIV infection, and one should consider a lumbar puncture to look for neurosyphilis in all patients with HIV infec tion and secondary syphilis. As a consequence of the immunologic abnormalities seen in the setting of HIV infection, diagnosis of syphilis through standard serologic testing may be challenging. On the one hand, a significant number of patients have false-positive Venereal Disease Research Laboratory (VDRL) tests due to polyclonal B cell activation. On the other hand, the development of a new positive VDRL may be delayed in patients with new infec tions, and the anti–fluorescent treponemal antibody (anti-FTA) test may be negative in the setting of immunodeficiency. Thus, dark-field examination of appropriate specimens should be performed in any patient in whom syphilis is suspected, even if the patient has a negative VDRL. Similarly, any patient with a positive serum VDRL test, neurologic findings, and an abnormal spinal fluid examination should be considered to have neurosyphilis and treated accordingly, regardless of the CSF VDRL result. In any setting, patients treated for syphilis need to be carefully monitored to ensure adequate therapy. Approximately one-third of patients with HIV infection will experience a Jarisch-Herxheimer reaction upon initiation of therapy for syphilis. Vulvovaginal candidiasis is a common problem in women with HIV infection. Symptoms include pruritus, discomfort, dyspareunia, and dysuria. Vulvar infection may present as a morbilliform rash that may extend to the thighs. Vaginal infection is usually associated with a white discharge, and plaques may be seen along an erythematous vaginal wall. Diagnosis is made by microscopic examination of the discharge for pseudohyphal ele ments in a 10% potassium hydroxide solution. Mild disease can be treated with topical therapy. More serious disease can be treated with fluconazole. Other causes of vaginitis include Trichomonas and mixed bacteria. Diseases of the Endocrine System and Metabolic Disorders A variety of endocrine and metabolic disorders are seen in the context of HIV infection. These may be a direct consequence of HIV infec tion, secondary to opportunistic infections or neoplasms, or related to medication side effects. Between 33% and 75% of patients with HIV infection receiving thymidine analogues or protease inhibitors as a component of ART develop a syndrome often referred to as lipodystro phy, consisting of elevations in plasma triglycerides, total cholesterol, and apolipoprotein B, as well as hyperinsulinemia and hyperglycemia. Many of the patients have been noted to have a characteristic set of body habitus changes associated with fat redistribution, consisting of truncal obesity coupled with peripheral wasting (Fig. 208-39). Trun cal obesity is apparent as an increase in abdominal girth related to increases in mesenteric fat, a dorsocervical fat pad (“buffalo hump”) reminiscent of patients with Cushing’s syndrome, and enlargement of the breasts. The peripheral wasting, or lipoatrophy, is particularly noticeable in the face and buttocks

and by the prominence of the veins in the legs. These changes may develop at any time ranging from ~6 weeks to several years following the initiation of ART. Approximately 20% of the patients with HIV-associated lipodystrophy meet the criteria for the metabolic syndrome as defined by the International Diabetes Federation or the U.S. National Cholesterol Education Program (NCEP) Adult Treatment Panel III. The lipodystrophy syndrome has been reported in association with regimens containing a variety of different drugs, and while initially reported in the setting of protease inhibitor therapy, it appears that similar changes can also be induced by protease-sparing regimens. It has been suggested that the lipoatrophy changes are par ticularly severe in patients receiving the thymidine analogues stavudine and zidovudine. Current treatment guidelines avoid these drugs and recommend drugs with fewer of these side effects. NCEP guidelines should be followed in the management of these lipid abnormalities (Chap. 419), with a further recommendation that moderate-intensity statin therapy be given to all individuals with HIV infection between the ages of 40 and 75 years unless their 10-year risk of cardiovascular disease is <5%. In all patients, consideration should be given to chang ing the components of ART with avoidance of thymidine analogues (azidothymidine and stavudine) and offending protease inhibitors. Due to concerns regarding drug interactions, the most utilized lipidlowering agents in this setting are gemfibrozil and atorvastatin. Lactic acidosis is associated with certain ART medications. This is most often seen with the nucleoside analogue reverse transcriptase inhibitors and can be fatal.

Patients with advanced HIV disease may develop hyponatremia due to the syndrome of inappropriate antidiuretic hormone (vasopressin) secre tion (SIADH) because of increased free-water intake and decreased free-water excretion. SIADH is usually seen in conjunction with pulmonary or CNS disease. Low serum sodium may also be due to adrenal insufficiency; a concomitant high serum potassium should alert one to this possibility. Hyperkalemia may be secondary to adrenal insufficiency, HIV nephropathy; or medications, particularly trim ethoprim and pentamidine. Hypokalemia may be seen in the setting of tenofovir or amphotericin therapy. Adrenal gland disease may be due to mycobacterial infections, CMV disease, cryptococcal disease, histoplasmosis, or ketoconazole toxicity. Iatrogenic Cushing’s syn drome with suppression of the hypothalamic-pituitary-adrenal axis may be seen with the use of local glucocorticoids (injected or inhaled) in patients receiving ritonavir or cobicistat. This is due to inhibition of the hepatic enzyme CYP3A4 by ritonavir leading to prolongation of the glucocorticoid half-life. Thyroid function may be altered in 10–15% of patients with HIV infection. Both hypo- and hyperthyroidism may be seen. The pre dominant abnormality is subclinical hypothyroidism. In the setting of ART, up to 10% of patients have been noted to have elevated thyroidstimulating hormone levels, suggesting that this may be a manifesta tion of immune reconstitution. Immune-reconstitution Graves’ disease may occur as a late (9–48 months) complication of ART. In advanced HIV disease, infection of the thyroid gland may occur with opportunis tic pathogens, including P. jirovecii, CMV, mycobacteria, Toxoplasma gondii, and Cryptococcus neoformans. These infections are generally associated with a nontender, diffuse enlargement of the thyroid gland. Thyroid function is usually normal. Diagnosis is made by fine-needle aspirate or open biopsy. Depending on the severity of disease, HIV infection is associated with hypogonadism in 20–50% of men and is lowest in the setting of ART. While this is generally a complication of underlying illness, tes ticular dysfunction may also be a side effect of ganciclovir therapy. In some surveys, up to two-thirds of patients report decreased libido and one-third complain of erectile dysfunction. Androgen-replacement therapy should be considered in patients with symptomatic hypogo nadism. HIV infection does not seem to have a significant effect

on the menstrual cycle outside the setting of advanced disease. Immunologic and Rheumatologic Diseases Immunologic and rheumatologic disorders are common in patients with HIV infection and range from excessive immediate-type hypersensitivity reactions (Chap. 363) to an increase in the incidence of reactive arthritis (Chap. 386) to conditions characterized by a diffuse infiltrative lymphocytosis. The occurrence of these phenomena is an appar ent paradox in the setting of the profound immunodeficiency and immunosuppression that characterizes HIV infection and reflects the complex nature of the immune system and its regulatory mechanisms. Drug allergies are the most significant allergic reactions occurring in patients with HIV and appear to become more common as the disease progresses. They occur in up to 65% of patients who receive therapy with TMP-SMX for PCP. In general, these drug reactions are characterized by erythematous, morbilliform eruptions that are pru ritic, tend to coalesce, and are often associated with fever. Nonetheless, ~33% of patients can be maintained on the offending therapy, and thus these reactions are not an immediate indication to stop the drug. Ana phylaxis is extremely rare in patients with HIV infection, and patients who have a cutaneous reaction during a single course of therapy can still be considered candidates for future treatment or prophylaxis with the same agent. The one exception to this is the nucleoside analogue abacavir, where fatal hypersensitivity reactions have been reported with rechallenge. This hypersensitivity is strongly associated with the HLA-B5701 haplotype, and a hypersensitivity reaction to abacavir is an absolute contraindication to future therapy. For other agents, including TMP-SMX, desensitization regimens are moderately suc cessful. While the mechanisms underlying these allergic-type reactions remain unknown, patients with HIV infection have been noted to have elevated IgE levels that increase as the CD4+ T cell count declines. The

numerous examples of patients with multiple drug reactions suggest that a common pathway is involved.

HIV infection shares many similarities with a variety of autoim mune diseases, including a substantial polyclonal B cell activation that is associated with a high incidence of antiphospholipid antibodies, such as anticardiolipin antibodies, VDRL antibodies, and lupus-like antico agulants. In addition, people with HIV have an increased incidence of antinuclear antibodies. Despite these serologic findings, there is no evidence that people with HIV have an increase in two of the more common autoimmune diseases, i.e., systemic lupus erythematosus and rheumatoid arthritis. In fact, it has been observed that these diseases may be somewhat ameliorated by the concomitant presence of HIV infection, suggesting that an intact CD4+ T cell limb of the immune response plays an integral role in the pathogenesis of these conditions. Similarly, there are anecdotal reports of patients with common vari able immunodeficiency (Chap. 362), characterized by hypogamma globulinemia, who have had a normalization of Ig levels following the development of HIV infection, suggesting a possible role for overactive CD4+ T cell immunity in certain forms of that syndrome. The one autoimmune disease that may occur with an increased frequency in patients with HIV infection is a variant of primary Sjögren’s syndrome (Chap. 373) in which patients with HIV infection develop a syndrome consisting of parotid gland enlargement, dry eyes, and dry mouth. This condition is associated with lymphocytic infiltrates of the salivary gland and lung. One also can see peripheral neuropathy, polymyositis, renal tubular acidosis, and hepatitis. In contrast to Sjögren’s syndrome, in which the lymphocytic infiltrates are composed predominantly of CD4+ T cells, in patients with HIV infection the infiltrates are com posed predominantly of CD8+ T cells. In addition, while patients with Sjögren’s syndrome are mainly women who have autoantibodies to Ro

and La and who frequently have HLA-DR3 or B8 MHC haplotypes, people with HIV who have this syndrome are usually African-American men who do not have anti-Ro or anti-La and who most often have the HLA-DR5 haplotype. This syndrome appears to be less common with the increased use of effective ART. The term diffuse infiltrative lymphocytosis syndrome (DILS) is used to describe this entity and to distinguish it from Sjögren's syndrome. CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders

Approximately one-third of people with HIV experience arthralgias; furthermore, 5–10% are diagnosed as having some form of reactive arthritis, such as Reiter's syndrome or psoriatic arthritis as well as undifferentiated spondyloarthropathy (Chap. 374). These syndromes occur with increasing frequency as the competency of the immune system declines. This association may be related to an increase in the number of infections with organisms that may trigger a reactive arthri tis with progressive immunodeficiency or to a loss of important regula tory T cells. Reactive arthritides in people with HIV generally respond well to standard treatment; however, therapy with methotrexate has been associated with an increase in the incidence of opportunistic infections and should be used with caution and only in severe cases. People with HIV also experience a variety of joint problems without obvious cause that are referred to generically as HIV- or AIDS-associated arthropathy. This syndrome is characterized by subacute oligoarticular arthritis developing over a period of 1–6 weeks and lasting 6 weeks to 6 months. It generally involves the large joints, predominantly the knees and ankles, and is nonerosive with only a mild inflammatory response. X-rays are nonrevealing. Nonsteroidal anti-inflammatory drugs are only marginally helpful; however, relief has been noted with the use of intraarticular glucocorticoids. A second form of arthritis also thought to be secondary to HIV infection is called painful articular syndrome. This condition, reported as occurring in up to 10% of AIDS patients, presents as an acute, severe, sharp pain in the affected joint. It affects primarily the knees, elbows, and shoulders; lasts 2–24 h; and may be severe enough to require narcotic analgesics. The cause of this arthropathy is unclear; however, it is thought to result from a direct effect of HIV on the joint. This condition is reminiscent of the fact that other lentiviruses, in particular the caprine arthritis-encephalitis virus, are capable of directly causing arthritis. A variety of other immunologic or rheumatologic diseases have been reported in people with HIV, either de novo or in association

with opportunistic infections or drugs. Using the criteria of widespread musculoskeletal pain of at least 3 months' duration and the presence of at least 11 of 18 possible tender points by digital palpation, 11% of a cohort of people with HIV containing 55% IDUs were diagnosed as having fibromyalgia (Chap. 385). While the incidence of frank arthri tis was less in this population than in other studied populations that consisted predominantly of men who have sex with men, these data support the concept that there are musculoskeletal problems that occur as a direct result of HIV infection. CNS angiitis and polymyositis also have been reported in people with HIV. Septic arthritis is surprisingly rare, especially given the increased incidence of staphylococcal bactere mias seen in this population. When septic arthritis has been reported, it has usually been due to Staphylococcus aureus, systemic fungal infec tion with C. neoformans, Sporothrix schenckii, or H. capsulatum or to systemic mycobacterial infection with M. tuberculosis, M. haemophilum, M. avium, or M. kansasii.

Patients with HIV infection treated with ART have been found to have an increased incidence of osteonecrosis or avascular necrosis of the hip and shoulders. In a study of asymptomatic patients, 4.4% were found to have evidence of osteonecrosis on MRI. While precise causeand-effect relationships have been difficult to establish, this complica tion has been associated with the use of

lipid-lowering agents, systemic glucocorticoids, and testosterone; bodybuilding exercise; alcohol con sumption; and the presence of anticardiolipin antibodies. Osteoporosis has been reported in 7% of women with HIV infection, with 41% of women demonstrating some degree of osteopenia. Several studies have documented decreases in bone mineral density of 2–6% in the first 2 years following the initiation of ART. This may be particularly apparent with tenofovir-containing regimens. PART 5 Infectious Diseases Immune Reconstitution Inflammatory Syndrome (IRIS)

Following the initiation of effective ART, a paradoxical worsening of pre-existing, untreated, or partially treated opportunistic infections may be noted. One may also see exacerbations of pre-existing autoim mune conditions or the development of new autoimmune conditions following the initiation of antiretrovirals (Table 208-12). IRIS related to a known pre-existing infection or neoplasm is referred to as para doxical IRIS, while IRIS associated with a previously undiagnosed con dition is referred to as unmasking IRIS. The term immune reconstitution disease (IRD) is sometimes used to distinguish IRIS manifestations related to opportunistic diseases from IRIS manifestations related to autoimmune diseases. IRD is particularly common in patients with underlying untreated mycobacterial or fungal infections. Some form of IRIS is seen in 10–30% of patients following the initiation of ART, depending on the clinical setting, and is most common in patients starting therapy with CD4+ T cell counts <50 cells/μL who have a precipitous drop in HIV RNA levels following the initiation of ART. Signs and symptoms may appear anywhere from 2 weeks to 2 years after the initiation of ART and can include localized lymphadenitis, prolonged fever, pulmonary infiltrates, hepatitis, increased intracra nial pressure, uveitis, sarcoidosis, and Graves' disease. The clinical course can be protracted, and severe cases can be fatal. The underlying mechanism appears to be related to a phenomenon similar to type IV hypersensitivity reactions and reflects the immediate improvements in immune function that occur as levels of HIV RNA drop and the TABLE 208-12 Characteristics of Immune Reconstitution Inflammatory Syndrome (IRIS) Paradoxical worsening of an existing clinical condition or abrupt appearance of a new clinical finding (unmasking) is seen following the initiation of antiretroviral therapy Occurs weeks to months following the initiation of antiretroviral therapy Is most common in patients starting therapy with a CD4+ T cell count <50/μL who experience a precipitous drop in viral load Is frequently seen in the setting of tuberculosis, particularly when ART is started soon after initiation of anti-TB therapy Can be fatal Abbreviations: ART, antiretroviral therapy; TB, tuberculosis.

TABLE 208-13 Causes of Bone Marrow Suppression in Patients with HIV Infection DISEASES MEDICATIONS HIV infection Mycobacterial infections Fungal infections B19 parvovirus infection Lymphoma Zidovudine Dapsone Trimethoprim-sulfamethoxazole Pyrimethamine 5-flucytosine Ganciclovir Interferon α Trimetrexate Foscarnet immunosuppressive effects of HIV infection are controlled. In severe cases, the use of immunosuppressive drugs such as glucocorticoids may be required to blunt the inflammatory component of these reac tions while specific antimicrobial therapy takes effect. Diseases of the Hematopoietic System Disorders of the hema topoietic system including lymphadenopathy, anemia, leukopenia, and/or thrombocytopenia are common throughout the course of HIV infection and may be the direct result of HIV, manifestations of second ary infections and neoplasms, or side effects of therapy (Table 208-13). Direct histologic examination and culture of lymph node or bone marrow tissue are often diagnostic. A significant percentage of bone marrow aspirates from patients with HIV infection have been reported to contain lymphoid aggregates, the precise significance of which is unknown. Initiation of ART will lead to reversal of most hematologic complications that are the direct result of HIV infection. Some

patients, otherwise asymptomatic, may develop persistent generalized lymphadenopathy as an early clinical manifestation of HIV infection. This condition is defined as the presence of enlarged lymph nodes (>1 cm) in two or more extrainguinal sites for >3 months without an obvious cause. The lymphadenopathy in this setting is due to marked follicular hyperplasia in the node in response to HIV infec tion. The nodes are generally discrete and freely movable. This feature of HIV disease may be seen at any point in the spectrum of immune dysfunction and is not associated with an increased likelihood of devel oping AIDS. Paradoxically, a loss in lymphadenopathy or a decrease in lymph node size outside the setting of ART may be a prognostic marker of disease progression. In patients with CD4+ T cell counts >200/μL, the differential diagnosis of lymphadenopathy includes TB, KS, Castle man's disease, and lymphoma. In patients with more advanced disease, lymphadenopathy may also be due to atypical mycobacterial infection, toxoplasmosis, systemic fungal infection, or bacillary angiomatosis. While indicated in patients with CD4+ T cell counts <200/μL, lymph node biopsy is not indicated in patients with early-stage disease unless there are signs and symptoms of systemic illness, such as fever and weight loss, or unless the nodes begin to enlarge, become fixed, or coalesce. Monoclonal gammopathy of unknown significance (MGUS) (Chap. 116), defined as the presence of a serum monoclonal IgG, IgA, or IgM in the absence of a clear cause, has been reported in 3% of patients with HIV infection. The overall clinical significance of this finding in patients with HIV infection is unclear, although it has been associated with other viral infections, non-Hodgkin's lymphoma, and plasma cell malignancy. Anemia is the most common hematologic abnormality in patients with HIV and, in the absence of a specific treatable cause, is indepen dently associated with a poor prognosis. While generally mild, anemia can be quite severe and require chronic blood transfusions. Among the specific reversible causes of anemia in the setting of HIV infection are drug toxicity, systemic fungal and mycobacterial infections, nutritional deficiencies, and parvovirus B19 infections. The antiretroviral zid ovudine may block erythroid maturation prior to its effects on other marrow elements. A characteristic feature of zidovudine therapy is an elevated mean corpuscular volume (MCV). Another drug used in

patients with HIV infection that has a selective effect on the erythroid series is dapsone. This drug can cause a serious hemolytic anemia in patients who are deficient in glucose-6-phosphate dehydrogenase and can create a functional anemia in others through induction of methemoglobinemia. Folate levels are usually normal in people with HIV; however, vitamin B12 levels may be depressed as a consequence of achlorhydria or malabsorption. True autoimmune hemolytic anemia is rare, although ~20% of patients with HIV infection may have a positive direct antiglobulin test as a consequence of polyclonal B cell activation. Infection with parvovirus B19 also may cause anemia. It is important to recognize this possibility given the fact that it responds well to treat ment with IVIg. Erythropoietin levels in patients with HIV infection and anemia are generally lower than expected given the degree of anemia. Treatment with erythropoietin may result in an increase in hemoglobin levels. An exception to this is a subset of patients with zidovudine-associated anemia in whom erythropoietin levels may be quite high. During the course of HIV infection, neutropenia may be seen in approximately half of patients. In most instances it is mild; however, it can be severe and can put patients at risk of spontaneous bacterial infec tions. This is most frequently seen in patients with severely advanced HIV disease and in patients receiving potentially myelosuppressive therapies. In the setting of neutropenia, diseases not commonly seen in patients with HIV, such as aspergillosis or mucormycosis, may occur. Both granulocyte colony-stimulating factor (G-CSF) and GM-CSF increase neutrophil counts in patients with HIV infection regardless of the cause of the neutropenia. Earlier concerns about the potential

of these agents to also increase levels of HIV were not confirmed in controlled clinical trials. Thrombocytopenia may be an early consequence of HIV infection. Approximately 3% of patients with untreated HIV infection and CD4+ T cell counts ≥400/μL have platelet counts <150,000/μL. For untreated patients with CD4+ T cell counts <400/μL, this incidence increases to 10%. Thrombocytopenia is more common in patients with hepatitis C co-infection, cirrhosis, and/or ongoing high-level HIV replication. Thrombocytopenia is rarely a serious clinical problem in patients with HIV infection and generally responds well to successful ART. Clini cally, it resembles the thrombocytopenia seen in patients with idio pathic thrombocytopenic purpura (Chap. 120). Immune complexes containing anti-gp120 antibodies and anti-anti-gp120 antibodies have been noted in the circulation and on the surface of platelets in patients with HIV infection. Patients with HIV infection have also been noted to have a platelet-specific antibody directed toward a 25-kDa compo nent of the surface of the platelet. Other data suggest that the thrombo cytopenia in patients with HIV infection may be due to a direct effect of HIV on megakaryocytes. Whatever the cause, it is very clear that the most effective medical approach to this problem has been the use of ART. For patients with platelet counts <20,000/μL, a more aggressive approach combining IVIg or anti-Rh Ig for an immediate response and ART for a more lasting response is appropriate. Rituximab has been used with some success in otherwise refractory cases. Splenectomy is a rarely needed option and is reserved for patients refractory to medical management. Because of the risk of serious infection with encapsulated organisms, all patients with HIV infection about to undergo splenec tomy should be immunized with vaccines to prevent disease from

S. pneumoniae, N. meningitidis, and H. influenzae type b. It should be noted that, in addition to causing an increase in the platelet count, removal of the spleen will result in an increase in the peripheral blood lymphocyte count, making CD4+ T cell counts unreliable markers of immunocompetence. In this setting, the clinician should rely on the CD4+ T cell percentage for making diagnostic decisions with respect to the likelihood of opportunistic infections. A CD4+ T cell percentage of 15 is approximately equivalent to a CD4+ T cell count of 200/μL.

In patients with early HIV infection, thrombocytopenia has also been reported as a consequence of classic thrombotic thrombocytopenic purpura (Chap. 120). This clinical syndrome, consisting of fever, thrombocytopenia, hemolytic anemia, and neurologic and renal dys function, is a rare complication of early HIV infection. As in other set tings, the appropriate management is the use of salicylates and plasma

exchange. Other causes of thrombocytopenia include lymphoma, mycobacterial infections, and fungal infections.

The incidence of venous thromboembolic disease such as deepvein thrombosis or pulmonary embolus is approximately 1% per year in patients with HIV infection. This is approximately 10 times higher than that seen in an age-matched population. Factors associ ated with an increased risk of clinical thrombosis include age >45, history of an opportunistic infection, lower CD4 count, and estrogen use. Abnormalities of the coagulation cascade, including decreased protein S activity, increases in factor VIII, anticardiolipin antibodies, PAR-1 expression on T cells, or lupus-like anticoagulant, have been reported in more than 50% of patients with HIV infection. The clini cal significance of this increased propensity toward thromboembolic disease is likely reflected in the observation that elevations in d-dimer are strongly associated with all-cause mortality in patients

with HIV infection (Table 208-9). Dermatologic Diseases Dermatologic problems occur in >90% of patients with HIV infection. From the macular, roseola-like rash seen with the acute seroconversion syndrome to extensive end-stage KS, cutaneous manifestations of HIV disease can be seen throughout the course of HIV infection. Among the more common nonneoplas tic problems are seborrheic dermatitis, folliculitis, and opportunistic infections. Extrapulmonary pneumocystosis may cause a necrotizing vasculitis. Neoplastic conditions are covered in a separate section below. Seborrheic dermatitis occurs in 3% of the general population and in up to 50% of patients with HIV infection. Seborrheic dermatitis increases in prevalence and severity as the CD4+ T cell count declines. In patients with HIV, seborrheic dermatitis may be aggravated by concomitant infection with Pityrosporum, a yeastlike fungus; use of topical antifungal agents has been recommended in cases refractory to standard topical treatment. CHAPTER 208 Folliculitis is among the most prevalent dermatologic disorders in patients with HIV infection and is seen in ~20% of patients. It is more common in patients with CD4+ T cell counts <200 cells/μL. Pruritic papular eruption is one of the most common pruritic rashes in patients with HIV infection. It appears as multiple papules on the face, trunk, and extensor surfaces and may improve with ART. Eosinophilic pustular folliculitis is a rare form of folliculitis that is seen with increased fre quency in patients with HIV infection. It presents as multiple, urticarial perifollicular papules that may coalesce into plaque-like lesions. Skin biopsy reveals an eosinophilic infiltrate of the hair follicle, which in certain cases has been associated with the presence of a mite. Patients typically have an elevated serum IgE level and may respond to treat ment with topical anthelmintics. Pruritus is a common symptom in patients with HIV infection and can lead to prurigo nodularis. Patients with HIV infection have also been reported to develop a severe form of Norwegian scabies with hyperkeratotic psoriasiform lesions.

Both psoriasis and ichthyosis, although they are not reported to be increased in frequency, may be particularly severe when they occur in patients with HIV infection. Pre-existing psoriasis may become guttate in appearance and more refractory to treatment in the setting of HIV infection. Reactivation herpes zoster (shingles) is seen in 10–20% of patients with HIV infection. This reactivation syndrome of varicella-zoster virus indicates a modest decline in immune function and may be the first indication of clinical immunodeficiency. In one series, patients who developed shingles did so an average of 5 years after HIV infec tion. In a cohort of patients with HIV infection and localized zoster, the subsequent rate of the development of AIDS was 1% per month. In that study, AIDS was more likely to develop if the outbreak of zoster was associated with severe pain, extensive skin involvement, or involve ment of cranial or cervical dermatomes. The clinical manifestations of reactivation zoster in patients with HIV, although indicative of immu nologic compromise, are not as severe as those seen in other immu nodeficient conditions. Thus, while lesions may extend over several dermatomes, involve the spinal cord, and/or be associated with frank cutaneous dissemination, visceral involvement has not been reported. In contrast to patients without a known underlying immunodeficiency

state, patients with HIV infection tend to have recurrences of shingles with a relapse rate of ~20%. Valacyclovir, famciclovir, or acyclovir is the treatment of choice. IV acyclovir can be used in severe cases, and foscarnet may be of value in patients with acyclovir-resistant virus.

Infection with herpes simplex virus in people with HIV is associated with recurrent orolabial, genital, and perianal lesions as part of recur rent reactivation syndromes (Chap. 197). As HIV disease progresses and the CD4+ T cell count declines, these infections become more frequent and severe.

Lesions often appear as beefy red, are exquisitely painful, and tend to occur high in the gluteal cleft (Fig. 208-38). Peri rectal HSV may be associated with proctitis and anal fissures. HSV should be high in the differential diagnosis of any patient with HIV who has a poorly healing, painful perirectal lesion. In addition to recurrent mucosal ulcers, recurrent HSV infection in the form of her petic whitlow can be a problem in patients with HIV infection, present ing with painful vesicles or extensive cutaneous erosion. Valacyclovir, famciclovir, or acyclovir is the treatment of choice in these settings. It is noteworthy that even subclinical reactivation of herpes simplex may be associated with increases in plasma HIV RNA levels. Diffuse skin eruptions due to Molluscum contagiosum may be seen in patients with advanced HIV infection. These flesh-colored, umbilicated lesions resemble those of Talaromyces (formerly Penicil lium) marnefei or Cryptococcosis. They tend to regress with effective ART and can also be treated with local therapy. Similarly, condyloma acuminatum lesions may be more severe and more widely distributed in patients with low CD4+ T cell counts. Imiquimod cream may be helpful in some cases. Atypical mycobacterial infections may present as erythematous cutaneous nodules, as may fungal infections, Bartonella, Acanthamoeba, and KS. Cutaneous infections with Aspergillus have been noted at the site of IV catheter placement. PART 5 Infectious Diseases The skin of patients with HIV infection is often a target organ for drug reactions (Chap. 63). Although most skin reactions are mild and not necessarily an indication to discontinue therapy, some patients may have particularly severe cutaneous reactions to drugs, including eryth roderma, Stevens-Johnson syndrome, and toxic epidermal necrolysis. This is particularly true for sulfa drugs, nonnucleoside reverse tran scriptase inhibitors, abacavir, amprenavir, darunavir, fosamprenavir, and tipranavir. Similarly, patients with HIV infection are often quite photosensitive and burn easily following exposure to sunlight or as a side effect of radiation therapy (Chap. 64). HIV infection and its treatment may be accompanied by cosmetic changes of the skin that are not of great clinical importance but may be troubling to patients. Yellowing of the nails and straightening of the hair, particularly in African-American patients, have been reported as a consequence of HIV infection. Zidovudine therapy has been associ ated with elongation of the eyelashes and the development of a bluish discoloration to the nails, again more common in African-American patients. Therapy with clofazimine may cause a yellow-orange discol oration of the skin and urine. Neurologic Diseases Clinical disease of the nervous system accounts for a significant degree of morbidity in a high percentage of patients with HIV infection (Table 208-14). The neurologic problems that occur in people with HIV may be either primary to the patho genic processes of HIV infection or secondary to opportunistic infec tions or neoplasms. Among the more frequent opportunistic diseases that involve the CNS are toxoplasmosis, cryptococcosis, progressive multifocal leukoencephalopathy, and primary CNS lymphoma. Other less common problems include mycobacterial infections; syphilis; and infection with CMV, herpes zoster, HTLV-1, Trypanosoma cruzi, or Acanthamoeba. Overall, secondary diseases of the CNS have been reported to occur in approximately one-third of patients with AIDS. These data antedate the widespread use of ART, and this frequency is considerably lower in patients with suppressed viral replication. Primary processes related to HIV infection of the nervous system are reminiscent of those seen with other lentiviruses, such as the maedivisna virus of sheep. Neurologic problems directly attributable to HIV occur through out the course of infection and may be inflammatory, demyelinating,

TABLE 208-14 Neurologic Diseases in Patients with HIV Infection HIV-1 infection Aseptic meningitis HIV-associated neurocognitive disorders Opportunistic infections Toxoplasmosis Cryptococcosis Progressive multifocal (HAND), including HIV encephalopathy/AIDS dementia complex Myelopathy

Vacuolar myelopathy Pure sensory ataxia Paresthesia/dysesthesia Peripheral neuropathy Acute inflammatory demyelinating leukoencephalopathy Cytomegalovirus Syphilis Mycobacterium tuberculosis HTLV-1 infection Amebiasis Neoplasms Primary CNS lymphoma Kaposi’s sarcoma polyneuropathy (Guillain-Barré syndrome) Chronic inflammatory demyelinating polyneuropathy (CIDP) Mononeuritis multiplex Distal symmetric polyneuropathy Myopathy or degenerative in nature. The term HIV-associated neurocognitive disorders (HAND) is used to describe a spectrum of disorders that range from asymptomatic neurocognitive impairment (ANI) to minor neurocognitive disorder (MND) to clinically severe dementia. The most severe form, HIV-associated dementia (HAD), also referred to as the AIDS dementia complex, or HIV encephalopathy, is considered an AIDS-defining illness. Many HIV-infected patients have some neurologic problem during the course of their disease. Even in the setting of suppressive ART, approximately 50% of people with HIV can be shown to have mild to moderate neurocognitive impairment using sensitive neuropsychiatric testing. As noted in the section on pathogenesis, damage to the CNS may be a direct result of viral infec tion of the CNS macrophages or glial cells or may be secondary to the release of neurotoxins and potentially toxic cytokines such as IL-1β, TNF-α, IL-6, and TGF-β. It has been reported that people with HIV who have the E4 allele for apoE are at increased risk for AIDS encephalopathy and peripheral neuropathy. Virtually all patients with HIV infection have some degree of nervous system involvement with the virus. This is evidenced by the fact that CSF findings are abnormal in ~90% of untreated patients, even during the asymptomatic phase of HIV infection. CSF abnormalities include pleocytosis (50–65% of patients), detection of viral RNA (~75%), elevated CSF protein (35%), and evidence of intrathecal synthesis of anti-HIV antibodies (90%). It is important to point out that evidence of infection of the CNS with HIV does not imply impairment of cognitive function. The neurologic function of a person with HIV should be considered normal unless clinical signs and symptoms suggest otherwise. Aseptic meningitis may occur at any time in the course of HIV infection; however, it is rare following the development of AIDS. This suggests that clinical aseptic meningitis in the context of HIV infection is an immune-mediated disease. In the setting of acute primary infec tion, patients may experience a syndrome of headache, photophobia, and meningismus. Rarely, an acute encephalopathy due to encephalitis may occur. Cranial nerve involvement may be seen, predominantly cranial nerve VII but occasionally V and/or VIII. CSF findings include a lymphocytic pleocytosis, elevated protein level, and normal glucose level. This syndrome, which cannot be clinically differentiated from other viral meningitides (Chap. 143), usually resolves spontaneously within 2–4 weeks; however, in some patients, signs and symptoms may become chronic. Fungal meningitis is the leading infectious cause of meningitis in patients with AIDS (Chaps. 143 and 144). While the vast majority of these are due to C. neoformans, up to 12% may be due to C. gattii. Cryptococcal meningitis is the initial AIDS-defining illness in ~2% of patients and generally occurs in patients with CD4+ T cell counts <100/μL. Cryptococcal meningitis is particularly common in untreated patients with AIDS in Africa, occurring in ~5% of patients. Most patients present with a picture of subacute meningoencephalitis with

fever, nausea, vomiting, altered mental status, headache, and meningeal signs. The incidence of seizures and focal neurologic deficits is low. The CSF profile may be normal or may show only modest elevations in WBC or protein levels and decreases in glucose. The opening pres sure in the CSF is usually elevated. In addition to meningitis, patients may develop cryptococcomas and cranial nerve involvement. Approxi mately one-third of patients also have pulmonary disease. Uncommon manifestations of cryptococcal infection include skin lesions that resemble molluscum contagiosum, lymphadenopathy, palatal and glos sal ulcers, arthritis, gastroenteritis, myocarditis,

and prostatitis. The prostate gland may serve as a reservoir for smoldering cryptococcal infection. The diagnosis of cryptococcal meningitis is made by iden tification of organisms in spinal fluid with India ink examination or by the detection of cryptococcal antigen. Blood cultures for fungus are often positive. A biopsy may be needed to make a diagnosis of CNS cryptococcoma and to distinguish inadequately treated infection from immune reconstitution syndrome. Initial treatment is with IV amphotericin B 0.7 mg/kg daily, or liposomal amphotericin 3–4 mg/kg

daily, with flucytosine 25 mg/kg qid for at least 2 weeks if possible. Decreases in renal function in association with amphotericin can lead to increases in flucytosine levels and subsequent bone marrow suppres sion. Therapy continues with amphotericin alone until the CSF culture turns negative followed by fluconazole 800 mg/d PO for 8 weeks, and then fluconazole 200 mg/d until the CD4+ T cell count has increased to >200 cells/μL for 6 months in response to ART. Repeated lumbar puncture may be required to manage increased intracranial pressure. Symptoms may recur with initiation of ART as an immune reconstitu tion syndrome (see above). For this reason, it is recommended that patients receive 4–6 weeks of antifungal therapy prior to initiation of ART. Other fungi that may cause meningitis in patients with HIV infection are C. immitis and H. capsulatum. Meningoencephalitis has also been reported due to Acanthamoeba or Naegleria. HIV-associated dementia consists of a constellation of signs and symptoms of CNS disease. While this is generally a late complication of HIV infection that progresses slowly over months, it can be seen in patients with CD4+ T cell counts >350 cells/μL. A major feature of this entity is the development of dementia, defined as a decline in cogni tive ability from a previous level. It may present as impaired ability to concentrate, increased forgetfulness, difficulty reading, or increased difficulty performing complex tasks. Initially these symptoms may be indistinguishable from findings of situational depression or fatigue. In contrast to “cortical” dementia (such as Alzheimer’s disease), aphasia, apraxia, and agnosia are uncommon, leading some investigators to classify HIV encephalopathy as a “subcortical dementia” character ized by defects in short-term memory and executive function (see below). In addition to dementia, patients with HIV encephalopathy may also have motor and behavioral abnormalities. Among the motor problems are unsteady gait, poor balance, tremor, and difficulty with rapid alternating movements. Increased tone and deep tendon reflexes may be found in patients with spinal cord involvement. Late stages may be complicated by bowel and/or bladder incontinence. Behavioral problems include apathy, irritability, and lack of initiative, with pro gression to a vegetative state in some instances. Some patients develop a state of agitation or mild mania. These changes usually occur without significant changes in level of alertness. This contrasts with the find ing of somnolence in patients with dementia due to toxic/metabolic encephalopathies. HIV-associated dementia is the initial AIDS-defining illness in ~3% of patients with HIV infection and thus only rarely precedes clinical evidence of immunodeficiency. Clinically significant encephalopathy eventually develops in ~25% of untreated patients with AIDS. As immunologic function declines, the risk and severity of HIV-associated dementia increases. Autopsy series suggest that 80–90% of patients with HIV infection have histologic evidence of CNS involvement. Several classification schemes have been developed for grading HIV encephalopathy; a commonly used clinical staging system is outlined in Table 208-15. The precise cause of HIV-associated dementia remains unclear, although the condition is thought to be a result of a combination of

TABLE 208-15 Clinical Staging of HAND According to Frascati Criteria NEUROCOGNITIVE STATUSa FUNCTIONAL STATUSb STAGE Asymptomatic 1 SD below mean in 2 cognitive domains No

impairments in activities of daily living Mild neurocognitive disorder 1 SD below mean in 2 cognitive domains Impairments in activities of daily living HIV-associated dementia 2 SD below mean in 2 cognitive domains Notable impairments in activities of daily living aNeurocognitive testing should include assessment of at least 5 domains, including attention/information processing, language, abstraction/executive function, complex perceptual motor skills, memory (including learning and recall), simple motor skills, or sensory perceptual skills. Appropriate norms must be available to establish the number of domains in which performance is below 1 SD. bFunctional status is typically assessed by self-reporting but might be corroborated by a collateral source. No agreed measures exist for HIV-associated neurocognitive disorder criteria. Note that, for diagnosis of HIV-associated neurocognitive disorder, other causes of dementia must be ruled out and potential confounding effects of substance use or psychiatric illness should be considered. Source: Adapted from A Antinori et al: Neurology 69:1789, 2007. direct effects of HIV on the CNS and associated immune activation. HIV has been found in the brains of patients with HIV encephalopathy by Southern blot, in situ hybridization, PCR, and electron microscopy. Multinucleated giant cells, macrophages, and microglial cells appear to be the main cell types harboring virus in the CNS. Histologically, the major changes are seen in the subcortical areas of the brain and include pallor and gliosis, multinucleated giant cell encephalitis, and vacuolar myelopathy. Less commonly, diffuse or focal spongiform changes occur in the white matter. Areas of the brain involved in motor function, language, and judgment are most severely affected. CHAPTER 208 There are no specific criteria for a diagnosis of HIV-associated dementia, and this syndrome must be differentiated from other dis eases that affect the CNS of patients with HIV (Table 208-14). The diagnosis of dementia depends on demonstrating a decline in cogni tive function. This can be accomplished objectively with the use of a Mini-Mental State Examination (MMSE) in patients for whom prior scores are available. For this reason, it is advisable for all patients with a diagnosis of HIV infection to have a baseline MMSE. However, changes in MMSE scores may be absent in patients with mild HIV encepha lopathy. Imaging studies of the CNS, by either MRI or CT, often demonstrate evidence of cerebral atrophy (Fig. 208-40). MRI may also reveal small areas of increased density on T2-weighted images. Lumbar puncture is an important element of the evaluation of patients with Human Immunodeficiency Virus Disease: AIDS and Related Disorders
FIGURE 208-40 AIDS dementia complex. Postcontrast CT scan through the lateral ventricles of a 47-year-old man with AIDS, altered mental status, and dementia. The lateral and third ventricles and the cerebral sulci are abnormally prominent. Mild white matter hypodensity is seen adjacent to the frontal horns of the lateral ventricles.

PART 5 Infectious Diseases HIV infection and neurologic abnormalities. It is generally most help ful in ruling out or making a diagnosis of opportunistic infections. In HIV encephalopathy, patients may have the nonspecific findings of an increase in CSF cells and protein level. While HIV RNA can often be detected in the spinal fluid and HIV can be cultured from the CSF, this finding is not specific for HIV encephalopathy. There appears to be no correlation between the presence of HIV in the CSF and the presence of HIV encephalopathy. Elevated levels of monocyte chemoattractant protein-1 (MCP-1), β2-microglobulin, neopterin, and quinolinic acid (a metabolite of tryptophan reported to cause CNS injury) have been noted in the CSF of patients with HIV encephalopathy. These findings suggest that these factors as well as inflammatory cytokines may be involved in the pathogenesis of this syndrome. Combination antiretroviral therapy is of benefit in patients with HIV-associated dementia. Improvement in neuropsychiatric test scores has been noted for both adult and pediatric patients treated with anti retrovirals. The rapid improvement in cognitive function noted with the

initiation of ART suggests that at least some component of this problem is quickly reversible, again supporting at least a partial role of soluble mediators in the pathogenesis. It should also be noted that these patients have an increased sensitivity to the side effects of neuroleptic drugs. The use of these drugs for symptomatic treatment is associated with an increased risk of extrapyramidal side effects; therefore, patients with HIV encephalopathy who receive these agents must be monitored carefully. It is felt by many physicians that the decrease in the preva lence of severe cases of HAND brought about by ART has resulted in an increase in the prevalence of milder forms of this disorder. Seizures may be a consequence of opportunistic infections, neo plasms, or HIV encephalopathy (Table 208-16). The seizure threshold is often lower than normal in patients with advanced HIV infection due in part to the frequent presence of electrolyte abnormalities. Seizures are seen in 15–40% of patients with cerebral toxoplasmosis, 15–35% of patients with primary CNS lymphoma, 8% of patients with cryptococcal meningitis, and 7–50% of patients with HIV encepha lopathy. Seizures may also be seen in patients with CNS tuberculosis, aseptic meningitis, and progressive multifocal leukoencephalopathy. Seizures may be the presenting clinical symptom of HIV disease. In one study of 100 patients with HIV infection presenting with a first seizure, cerebral mass lesions were the most common cause, responsible for 32 of the 100 new-onset seizures. Of these 32 cases, 28 were due to toxoplasmosis and 4 to lymphoma. HIV encephalopathy accounted for an additional 24 new-onset seizures. Cryptococcal meningitis was the third most common diagnosis, responsible for 13 of the 100 seizures. In 23 cases, no cause could be found, and it is possible that these cases represent a subcategory of HIV encephalopathy. Of these 23 cases, 16 (70%) had 2 or more seizures, suggesting that anticonvulsant therapy is indicated in all patients with HIV infection and seizures unless a rap idly correctable cause is found. Due to a variety of drug–drug interac tions between antiseizure medications and antiretrovirals, drug levels need to be monitored carefully. Patients with HIV infection may present with focal neurologic defi cits from a variety of causes. The most common causes are toxoplasmo sis, progressive multifocal leukoencephalopathy, and CNS lymphoma. Other causes include cryptococcal infections (discussed above; also Chap. 221), stroke, and reactivation of Chagas' disease. FIGURE 208-41 Central nervous system toxoplasmosis. A coronal postcontrast T1-weighted MRI scan demonstrates a peripheral enhancing lesion in the left frontal lobe, associated with an eccentric nodular area of enhancement (arrow); this so-called eccentric target sign is typical of toxoplasmosis. Toxoplasmosis (Chap. 235) has been one of the most common causes of secondary CNS infections in patients with AIDS, but its inci dence is decreasing in the era of ART. It is most common in patients from the Caribbean and from France, where the seroprevalence of T. gondii is around 50%. This figure is closer to 15% in the United States. Toxoplasmosis is generally a late complication of HIV infection and usually occurs in patients with CD4+ T cell counts <200/μL. Cerebral toxoplasmosis is thought to represent a reactivation of latent tissue cysts. It is 10 times more common in patients with antibodies to the organism than in patients who are seronegative. Patients diagnosed with HIV infection should be screened for IgG antibodies to T. gondii during the time of their initial workup. Those who are seronegative should be counseled about ways to minimize the risk of primary infec tion including avoiding the consumption of undercooked meat and careful hand washing after contact with soil or changing the cat litter box. The most common clinical presentation of cerebral toxoplasmosis in patients with HIV infection is fever, headache, and focal neurologic deficits. Patients may present with seizure, hemiparesis, or aphasia as a manifestation of these focal deficits or with a picture more influenced by the accompanying cerebral edema and characterized by confusion, dementia, and lethargy, which can progress to coma. The diagnosis is usually suspected on the basis of MRI findings of multiple lesions in multiple locations, although in some cases only a single lesion is

seen. Pathologically, these lesions generally exhibit inflammation and central necrosis and, as a result, demonstrate ring enhancement on contrast MRI (Fig. 208-41) or, if MRI is unavailable or contraindicated, on double-dose contrast CT. There is usually evidence of surrounding edema. In addition to toxoplasmosis, the differential diagnosis of single or multiple enhancing mass lesions in the patient with HIV includes primary CNS lymphoma and, less commonly, TB or fungal or bacterial abscesses. The definitive diagnostic procedure is brain biopsy. How ever, given the morbidity rate that can accompany this procedure, it is usually reserved for the patient who has failed 2–4 weeks of empiric therapy for toxoplasmosis. If the patient is seronegative for T. gondii, the likelihood that a mass lesion is due to toxoplasmosis is <10%. In that setting, one may choose to be more aggressive and perform a brain biopsy sooner. Standard treatment is sulfadiazine and pyrimethamine with leucovorin as needed for a minimum of 4–6 weeks. Alternative therapeutic regimens include clindamycin in combination with pyri methamine; atovaquone plus pyrimethamine; and azithromycin plus pyrimethamine plus rifabutin. Relapses are common, and it is recom mended that patients with a history of prior toxoplasmic encephalitis receive maintenance therapy with sulfadiazine, pyrimethamine, and leucovorin as long as their CD4+ T cell counts remain <200 cells/μL. Patients with CD4+ T cell counts <100/μL and IgG antibody to Toxoplasma should receive primary prophylaxis for toxoplasmosis. TABLE 208-16 Causes of Seizures in Patients with HIV Infection DISEASE OVERALL CONTRIBUTION TO FIRST SEIZURE, % FRACTION OF PATIENTS WHO HAVE SEIZURES, % HIV encephalopathy 24–47 7–50 Cerebral toxoplasmosis

15–40 Cryptococcal meningitis

Primary central nervous system lymphoma

15–30 Progressive multifocal leukoencephalopathy

Source: From DM Holtzman et al: Am J Med 87:173, 1989.

Fortunately, the same daily regimen of a single double-strength tab let of TMP-SMX used for P. jirovecii prophylaxis provides adequate primary protection against toxoplasmosis. Secondary prophylaxis/ maintenance therapy for toxoplasmosis may be discontinued in the setting of effective ART and increases in CD4+ T cell counts to >200/μL for 6 months. JC virus, a human polyomavirus that is the etiologic agent of pro gressive multifocal leukoencephalopathy (PML), is an important oppor tunistic pathogen in patients with AIDS (Chap. 142). While ~80% of the general adult population has antibodies to JC virus, indicative of prior infection, <10% of healthy adults show any evidence of ongo ing viral replication. PML is the only known clinical manifestation of JC virus infection. It is a late manifestation of AIDS and is seen in ~1–4% of patients with AIDS. The lesions of PML begin as small foci of demyelination in subcortical white matter that eventually coalesce. The cerebral hemispheres, cerebellum, and brainstem may all be involved. Patients typically have a protracted course with multifocal neurologic deficits, with or without changes in mental status. Approximately 20% of patients experience seizures. Ataxia, hemiparesis, visual field defects, aphasia, and sensory defects may occur. Headache, fever, nausea, and vomiting are rarely seen. Their presence should suggest another diagnosis. MRI typically reveals multiple, nonenhancing white matter lesions that may coalesce and have a predilection for the occipital and parietal lobes. The lesions show signal hyperintensity on T2-weighted images and diminished signal on T1-weighted images. The measure ment of JC virus DNA levels in CSF has a diagnostic sensitivity of

76% and a specificity of close to 100%. Prior to the availability of ART, most patients with PML died within 3–6 months of the onset of symptoms. Paradoxical worsening of PML has been seen with initiation of ART as an immune reconstitution syndrome. There is no specific treat ment for PML; however, a median survival of 2 years and survival of

> 15 years have been reported in patients with PML treated with ART for their HIV disease. Despite having a significant impact on survival, only ~50% of patients with HIV infection and PML show neurologic improvement with ART. Studies with other antiviral agents such as cidofovir have failed to show clear benefit. Factors influencing a favor able prognosis for PML in the setting of HIV infection include a CD4+ T cell count >100/μL at baseline and the ability to maintain an HIV viral load of <500 copies/mL. Baseline HIV-1 viral load does not have independent predictive value of survival. PML is one of the few oppor tunistic infections that continues to occur with some frequency despite the widespread use of ART. Reactivation American trypanosomiasis may present as acute menin goencephalitis with focal neurologic signs, fever, headache, vomiting, and seizures. Accompanying cardiac disease in the form of arrhythmias or heart failure should increase the index of suspicion. The presence of antibodies to T. cruzi supports the diagnosis. In South America, reactivation of Chagas' disease is considered to be an AIDS-defining condition and may be the initial AIDS-defining condition. Most cases occur in patients with CD4+ T cell counts <200 cells/μL. Lesions appear radiographically as single or multiple hypodense areas, typically with ring enhancement and edema. They are found predominantly in the subcortical areas, a feature that differentiates them from the deeper lesions of toxoplasmosis. T. cruzi amastigotes, or trypanosomes, can be identified from biopsy specimens or CSF. Other CSF findings include elevated protein and a mild (<100 cells/μL) lymphocytic pleocytosis. Organisms can also be identified by direct examination of the blood. Treatment consists of benzimidazole (2.5 mg/kg bid) or nifurtimox (2 mg/kg qid) for at least 60 days, followed by maintenance therapy for the duration of immunodeficiency with either drug at a dose of 5 mg/kg three times a week. As is the case with cerebral toxoplasmosis, successful therapy with antiretrovirals may allow discontinuation of maintenance therapy for Chagas' disease. Stroke may occur in patients with HIV infection. In contrast to the other causes of focal neurologic deficits in patients with HIV infec tion, the symptoms of a stroke are sudden in onset. Patients with HIV infection have an increased prevalence of many classic risk factors associated with stroke, including smoking and diabetes. It has been reported that HIV infection itself can lead to an increase in carotid

artery stiffness. The relative increase in risk for stroke as a consequence of HIV infection is more pronounced in women and in individuals between the ages of 18 and 29. Among the secondary infectious dis eases in patients with HIV infection that may be associated with stroke are vasculitis due to cerebral varicella zoster or neurosyphilis and septic embolism in association with fungal infection. Other elements of the differential diagnosis of stroke in the patient with HIV infection

include atherosclerotic cerebral vascular disease, thrombotic thrombo cytopenic purpura, and cocaine or amphetamine use.

Primary CNS lymphoma is discussed below in the section on neo plastic diseases. Spinal cord disease, or myelopathy, is present in ~20% of patients with AIDS, often as part of HIV-associated neurocognitive disorder. In fact, 90% of the patients with HIV-associated myelopathy have some evidence of dementia, suggesting that similar pathologic processes may be responsible for both conditions. Three main types of spinal cord disease are seen in patients with AIDS. The first of these is a vacuolar myelopathy, as mentioned above. This condition is pathologically simi lar to subacute combined degeneration of the cord, such as that occur ring with pernicious anemia. Although vitamin B12 deficiency can be seen in patients with AIDS as a primary complication of HIV infection, it does not appear to be responsible for most cases of myelopathy seen in patients with HIV infection. However, it should be included in the differential diagnosis. Vacuolar myelopathy is characterized by a sub acute onset and often presents with gait disturbances, predominantly ataxia and spasticity; it may progress to include bladder and bowel dysfunction. Physical findings include evidence of increased deep ten don reflexes and extensor plantar responses. The second form of spinal cord disease involves the dorsal columns and presents as a pure sensory ataxia. The third form is also sensory in nature and presents with par esthesias and dysesthesias of the lower extremities. In contrast to the cognitive problems seen in patients with HIV encephalopathy, these spinal cord syndromes do not respond well to antiretroviral drugs, and therapy is mainly supportive. CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders One important disease of the spinal cord that also involves the peripheral nerves is a myelopathy and polyradiculopathy seen in asso ciation with CMV infection. This entity is generally seen late in the course of HIV infection and is fulminant in onset, with lower extremity and sacral paresthesias, difficulty in walking, areflexia, ascending sen sory loss, and urinary retention. The clinical course is rapidly progres sive over a period of weeks. CSF examination reveals a predominantly neutrophilic pleocytosis, and CMV DNA can be detected by CSF PCR. Intravenous therapy with ganciclovir or foscarnet can lead to rapid improvement, and prompt initiation of therapy is important in minimizing the degree of permanent neurologic damage. Combination therapy with both drugs should be considered in patients who have been previously treated for CMV disease. Other diseases involving the spinal cord in patients with HIV infection include HTLV-1-associated myelopathy (HAM) (Chap. 207), neurosyphilis (Chap. 187), infection with herpes simplex (Chap. 197) or varicella-zoster (Chap. 198), TB (Chap. 183), and lymphoma (Chap. 113). Peripheral neuropathies are common in patients with HIV infection. They occur at all stages of illness and take a variety of forms. Early in the course of HIV infection, an acute inflammatory demyelinat ing polyneuropathy resembling Guillain-Barré syndrome may occur (Chap. 458). In other patients, a progressive or relapsing-remitting inflammatory neuropathy resembling chronic inflammatory demy elinating polyneuropathy (CIDP) has been noted. Patients commonly present with progressive weakness, areflexia, and minimal sensory changes. CSF examination often reveals a mononuclear pleocytosis, and peripheral nerve biopsy demonstrates a perivascular infiltrate sug gesting an autoimmune etiology. Plasma exchange or IVIg has been tried with variable success. Because of the immunosuppressive effects of glucocorticoids, they should be reserved for severe cases of CIDP refractory to other measures. Another autoimmune peripheral neurop athy seen in patients with AIDS is mononeuritis multiplex (Chap. 457) due to a necrotizing arteritis of peripheral nerves. The most common peripheral neuropathy in patients with HIV infection is a distal sensory polyneuropathy (DSPN) also referred to as painful sensory neuropathy

(HIV-SN), predominantly sensory neuropathy, or distal symmetric peripheral neuropathy. This condition may be a direct consequence of HIV infection or a side effect of ART with dideoxynucleosides. It is more common in taller individuals, older individuals, and those with lower CD4 counts. Two-thirds of patients with AIDS may be shown by electrophysiologic studies to have some evidence of peripheral nerve disease. Presenting symptoms are usually painful burning sensations in the feet and lower extremities. Findings on examination include a stocking-type sensory loss to pinprick, temperature, and touch sensa tion and a loss of ankle reflexes. Motor changes are mild and are usu ally limited to weakness of the intrinsic foot muscles. Response of this condition to antiretrovirals has been variable, perhaps because antiret rovirals are responsible for the problem in some instances. When due to dideoxynucleoside therapy, patients with lower extremity peripheral neuropathy may complain of a sensation that they are walking on ice. Other entities in the differential diagnosis of peripheral neuropathy include diabetes mellitus, vitamin B12 deficiency, and side effects from metronidazole or dapsone. For distal symmetric polyneuropathy that fails to resolve following the discontinuation of dideoxynucleosides, therapy is symptomatic; gabapentin, carbamazepine, tricyclics, or analgesics may be effective for dysesthesias. Treatment-naïve patients may respond to ART.

Myopathy may complicate the course of HIV infection; causes include HIV infection itself, zidovudine, and the generalized wasting syndrome (discussed below). HIV-associated myopathy may range in severity from an asymptomatic elevation in creatine kinase levels to a subacute syndrome characterized by proximal muscle weakness and myalgias. Quite pronounced elevations in creatine kinase may occur in asymptomatic patients, particularly after exercise. The clinical sig nificance of this as an isolated laboratory finding is unclear. A variety of both inflammatory and noninflammatory pathologic processes have been noted in patients with more severe myopathy, including myofiber necrosis with inflammatory cells, nemaline rod bodies, cytoplasmic bodies, and mitochondrial abnormalities. Profound muscle wasting, often with muscle pain, may be seen after prolonged zidovudine ther apy. This toxic side effect of the drug is dose-dependent and is related to its ability to interfere with the function of mitochondrial polymer ases. It is reversible following discontinuation of the drug. Red ragged fibers are a histologic hallmark of zidovudine-induced myopathy. PART 5 Infectious Diseases Ophthalmologic Diseases Ophthalmologic problems occur in ~50% of patients with advanced HIV infection. The most common abnormal findings on funduscopic examination are cotton-wool spots. These are hard white spots that appear on the surface of the retina and often have an irregular edge. They represent areas of retinal ischemia secondary to microvascular disease. At times they are associated with small areas of hemorrhage and thus can be difficult to distinguish from CMV retinitis. In contrast to CMV retinitis, however, these lesions are not associated with visual loss and tend to remain stable or improve over time. One of the most devastating consequences of HIV infection is CMV retinitis. Patients at high risk of CMV retinitis (CD4+ T cell count <100/μL) should undergo an ophthalmologic examination every 3–6 months. The majority of cases of CMV retinitis occur in patients with a CD4+ T cell count <50/μL. Prior to the availability of ART, this CMV reactivation syndrome was seen in 25–30% of patients with AIDS. In the ART era this has dropped to close to 2%. CMV retinitis usually presents as a painless, progressive loss of vision. Patients may also complain of blurred vision, “floaters,” and scintillations. The dis ease is usually bilateral, although typically it affects one eye more than the other. The diagnosis is made on clinical grounds by an experienced ophthalmologist. The characteristic retinal appearance is that of peri vascular hemorrhage and exudate. In situations where the diagnosis is in doubt due to an atypical presentation or an unexpected lack of response

to therapy, vitreous or aqueous humor sampling with molecu lar diagnostic techniques may be of value. CMV infection of the retina results in a necrotic inflammatory process, and the visual loss that develops is irreversible. CMV retinitis may be complicated by rheg matogenous retinal detachment as a consequence of retinal atrophy

in areas of prior inflammation. Therapy for CMV retinitis consists of oral valganciclovir, IV ganciclovir, or IV foscarnet, with cidofovir as an alternative. Combination therapy with ganciclovir and foscarnet has been shown to be slightly more effective than either ganciclovir or foscarnet alone in the patient with relapsed CMV retinitis. A 3-week induction course is followed by maintenance therapy with oral valgan ciclovir. If CMV disease is limited to the eye, intravitreal injections of ganciclovir or foscarnet may be considered. Intravitreal injections of cidofovir are generally avoided due to the increased risk of uveitis and hypotony. Maintenance therapy is continued until the CD4+ T cell count remains >100 µL for >6 months. The majority of patients with HIV infection and CMV disease develop some degree of uveitis with the initiation of ART. The etiology of this is unknown; however, it has been suggested that this may be due to the generation of an enhanced immune response to CMV as an IRIS (see above). In some instances, this has required the use of topical glucocorticoids. Both HSV and varicella zoster virus can cause a rapidly progressing, bilateral, necrotizing retinitis referred to as the acute retinal necrosis syndrome, or progressive outer retinal necrosis (PORN). This syndrome, in contrast to CMV retinitis, is associated with pain, keratitis, and iritis. It is often associated with orolabial HSV or trigeminal zoster. Ophthalmologic examination reveals widespread pale gray peripheral lesions. This condition is often complicated by retinal detachment. It is important to recognize and treat this condition with IV ganciclovir or IV acyclovir (if definitely due to HSV) as quickly as possible to mini mize the loss of vision. Several other secondary infections may cause ocular problems in patients with HIV. P. jirovecii can cause a lesion of the choroid that may be detected as an incidental finding on ophthalmologic examination. These lesions are typically bilateral, are from half to twice the disc diameter in size, and appear as slightly elevated yellow-white plaques. They are usually asymptomatic and may be confused with cotton-wool spots. Chorioretinitis due to toxoplasmosis can be seen alone or, more commonly, in association with CNS toxoplasmosis. KS may involve the eyelid or conjunctiva, while lymphoma may involve the retina. Syphi lis may lead to a uveitis that is highly associated with the presence of neurosyphilis. Additional Disseminated Infections and Wasting Syndrome

Infections with species of the small, gram-negative, Rickettsia-like organism Bartonella (Chap. 177) are seen with increased frequency in patients with HIV infection. While it is not considered an AIDSdefining illness by the CDC, many experts view infection with Bar tonella as indicative of a severe defect in cell-mediated immunity. It is usually seen in patients with CD4+ T cell counts <100/µL and is a significant cause of unexplained fever in patients with advanced HIV infection. Among the clinical manifestations of Bartonella infection are bacillary angiomatosis, cat-scratch disease, and trench fever. Bacillary angiomatosis is usually due to infection with B. henselae and is linked to exposure to flea-infested cats. It is characterized by a vascular pro liferation that leads to a variety of skin lesions that have been confused with the skin lesions of KS. In contrast to the lesions of KS, the lesions of bacillary angiomatosis generally blanch, are painful, and typically occur in the setting of systemic symptoms. Infection can extend to the lymph nodes, liver (peliosis hepatis), spleen, bone, heart, CNS, respira tory tract, and GI tract. Cat-scratch disease is also due to infection with B. henselae and generally begins with a papule at the site of inoculation. This is

followed several weeks later by the development of regional adenopathy and malaise. Infection with B. quintana is transmitted by lice and has been associated with case reports of trench fever, endocar ditis, adenopathy, and bacillary angiomatosis. The organism is quite difficult to culture, and diagnosis often relies on identifying the organ ism in biopsy specimens using the Warthin-Starry or similar stains, PCR, and/or seroconversion. Treatment is with either doxycycline or erythromycin for at least 3 months. Histoplasmosis is an opportunistic infection that is seen most fre quently in patients in the Mississippi and Ohio River valleys, Puerto Rico, the Dominican Republic, and South America. These are all areas in which infection with H. capsulatum is endemic (Chap. 218).

Because of this limited geographic distribution, histoplasmosis is only seen in approximately 0.5% of AIDS cases in the United States. Histo plasmosis is generally a late manifestation of HIV infection; however, it may be the initial AIDS-defining condition. In one study, the median CD4+ T cell count for patients with histoplasmosis and AIDS was 33/μL. While disease due to H. capsulatum may present as a primary infection of the lung, disseminated disease, presumably due to reactiva tion, is the most common presentation in patients with HIV. Patients usually present with a 4- to 8-week history of fever and weight loss. Hepatosplenomegaly and lymphadenopathy are each seen in about 25% of patients. CNS disease, either meningitis or a mass lesion, is seen in 15% of patients. Bone marrow involvement is common, with throm bocytopenia, neutropenia, and anemia occurring in 33% of patients. Approximately 7% of patients have mucocutaneous lesions consisting of a maculopapular rash and skin or oral ulcers. Respiratory symptoms are usually mild, with chest x-ray showing a diffuse infiltrate or dif fuse small nodules in ~50% of cases. The gastrointestinal tract may be involved. Diagnosis is made by silver staining of tissue, by culturing the organisms from blood, bone marrow, or tissue, or by detecting antigen in blood or urine. Treatment is typically with liposomal amphotericin B followed by maintenance therapy with oral itraconazole until the serum Histoplasma antigen is <2 units, the patient has been on antiret rovirals for at least 6 months, and the CD4 count is >150 cells/μL. In the setting of mild infection, it may be appropriate to initiate therapy with itraconazole alone. Following the spread of HIV infection to southeast Asia, dissemi nated infection with the fungus Talaromyces (formerly Penicillium) marneffei was recognized as a complication of HIV infection and is considered an AIDS-defining condition in those parts of the world where it occurs. T. marneffei is the third most common AIDS-defining illness in Thailand, following TB and cryptococcosis. It is more fre quently diagnosed in the rainy than the dry season. Clinical features include fever, generalized lymphadenopathy, hepatosplenomegaly, anemia, thrombocytopenia, and papular skin lesions with central umbilication resembling the lesions of Molluscum contagiosum. Treat ment is with amphotericin B followed by itraconazole until the CD4+ T cell count is >100 cells/μL for at least 6 months. Visceral leishmaniasis (Chap. 233) is recognized with increasing frequency in patients with HIV infection who live in or travel to areas endemic for this protozoal infection transmitted by sandflies. The clin ical presentation is one of hepatosplenomegaly, fever, and hematologic abnormalities. Lymphadenopathy and other constitutional symptoms may be present. A chronic, relapsing course is seen in two-thirds of coinfected patients. Organisms can be detected by PCR and, with special techniques, isolated from cultures of bone marrow aspirates. Histologic stains are often diagnostic but may be negative. Antibody titers are of little help. Patients with HIV infection usually respond well initially to standard therapy with amphotericin B or pentavalent antimony com pounds. Eradication of the organism is difficult, however, and relapses are common. Patients with HIV infection are at a slightly increased risk of infec tion with malaria and of clinical malaria. This is particularly true for patients from

nonendemic areas who are at risk for primary infec tion and in patients with lower CD4+ T cell counts. HIV-positive A B C FIGURE 208-42 Kaposi’s sarcoma in three patients with AIDS demonstrating (A) periorbital edema and bruising; (B) classic truncal distribution of lesions; and (C) upper extremity lesions.

individuals with CD4+ T cell counts <300 cells/μL have a poorer response to malaria treatment than others. Co-infection with malaria is associated with a modest increase in HIV viral load. The risk of malaria may be decreased with TMP-SMX prophylaxis.

Generalized wasting is an AIDS-defining condition; it is defined as involuntary weight loss of >10% associated with intermittent or constant fever and chronic diarrhea or fatigue lasting >30 days in the absence of a defined cause other than HIV infection. Prior to the widespread use of ART it was the initial AIDS-defining condition in ~10% of patients with AIDS in the United States. Generalized wast ing is rarely seen today with the earlier initiation of antiretrovirals. A constant feature of this syndrome is severe muscle wasting with scattered myofiber degeneration and occasional evidence of myositis. Glucocorticoids may be of some benefit; however, this approach must be carefully weighed against the risk of compounding the immunode ficiency of HIV infection. Androgenic steroids, growth hormone, and total parenteral nutrition have been used as therapeutic interventions with variable success. Neoplastic Diseases The neoplastic diseases considered to be AIDS-defining conditions are Kaposi’s sarcoma, non-Hodgkin’s lym phoma, and invasive cervical carcinoma. In addition, there is also an increase in the incidence of a variety of non-AIDS-defining malig nancies including Hodgkin’s disease; multiple myeloma; leukemia; melanoma; and cervical, brain, testicular, oral, lung, gastric, liver, renal, and anal cancers. Since the introduction of potent ART, there has been a marked reduction in the incidence of KS (Fig. 208-34). The non-AIDS-defining malignancies now account for more morbidity and mortality in patients with HIV infection than the AIDS-defining malignancies and are responsible for approximately 10% of the deaths in patients with HIV infection. Rates of non-Hodgkin’s lymphoma have declined; however, this decline has not been as dramatic as the decline in rates of KS. In contrast, ART has had little effect on human papillomavirus (HPV)-associated malignancies. As patients with HIV infection live longer, a wider array of cancers is seen in this population. While some may only reflect known risk factors (e.g., smoking, alcohol consumption, co-infection with other viruses such as hepatitis B) that are increased in patients with HIV infection, some may be a direct consequence of HIV and are clearly increased in patients with lower CD4+ T cell counts. CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders
Kaposi’s sarcoma is a multicentric neoplasm presenting as multiple vascular nodules in the skin, mucous membranes, and viscera. The clinical course of KS ranges from indolent, with only minor skin or lymph node involvement, to fulminant, with extensive cutaneous and visceral involvement. In the initial period of the AIDS epidemic, KS was a prominent clinical feature of the first cases of AIDS, occurring in 79% of the patients diagnosed in 1981. By 1989 it was seen in only 25% of cases, by 1992 the number had decreased to 9%, and by 1997 the number was <1%. HHV-8 (KSHV) has been strongly implicated as a viral cofactor in the pathogenesis of KS. Clinically, KS has varied presentations and may be seen at any stage of HIV infection, even in the presence of a normal CD4+ T cell count. The initial lesion may be a small, raised, reddish-purple nodule on the skin (Fig. 208-42), a discoloration on the oral mucosa (Fig. 208-35D),

or a swollen lymph node. Lesions often appear in sun-exposed areas, particularly the tip of the nose, and have a propensity to occur in areas of trauma (Koebner phenomenon). Because of the vascular nature of the tumors and the presence of extravasated red blood cells in the lesions, their colors range from reddish to purple to brown and often take the appearance of a bruise, with yellowish discoloration and tat tooing. Lesions range in size from a few millimeters to several centi meters in diameter and may be either discrete or confluent. KS lesions most commonly appear as raised macules; however, they can also be papular, particularly in patients with higher CD4+ T cell counts. Con fluent lesions may give rise to surrounding lymphedema and may be disfiguring when they involve the face and disabling when they involve the lower extremities or the surfaces of joints. Apart from skin, the lymph nodes, GI tract, and lung are the organ systems most commonly affected by KS. Lesions have been reported in virtually every organ, including the heart and the CNS. In contrast to most malignancies, in which lymph node involvement implies metastatic spread and a poor prognosis, lymph node involvement may be seen very early in KS and is of no special clinical significance. In fact, some patients may present with disease limited to the lymph nodes. These are generally patients with relatively intact immune function and thus the patients with the best prognosis. Pulmonary involvement with KS generally presents with shortness of breath. Some 80% of patients with pulmonary KS also have cutaneous lesions. The chest x-ray characteristically shows bilat eral lower lobe infiltrates that obscure the margins of the mediastinum and diaphragm (Fig. 208-43). Pleural effusions are seen in 70% of cases of pulmonary KS, a fact that is often helpful in the differential diagno sis. GI involvement is seen in 50% of patients with KS and usually takes one of two forms: (1) mucosal involvement, which may lead to bleeding that can be severe; these patients sometimes also develop symptoms of GI obstruction if lesions become large; and (2) biliary tract involve ment. KS lesions may infiltrate the gallbladder and biliary tree, leading to a clinical picture of obstructive jaundice similar to that seen with sclerosing cholangitis. Several staging systems have been proposed for KS. One in common use was developed by the National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group; it distin guishes patients on the basis of tumor extent, immunologic function, and presence or absence of systemic symptoms (Table 208-17).

PART 5 Infectious Diseases A diagnosis of KS is based on biopsy of a suspicious lesion. Histo logically one sees a proliferation of spindle cells and endothelial cells, extravasation of red blood cells, hemosiderin-laden macrophages, and, in early cases, an inflammatory cell infiltrate. Included in the differ ential diagnosis are lymphoma (particularly for oral lesions), bacillary angiomatosis, and cutaneous mycobacterial infections. FIGURE 208-43 Chest x-ray of a patient with AIDS and pulmonary Kaposi’s sarcoma. The characteristic findings include dense bilateral lower lobe infiltrates obscuring the heart borders and pleural effusions.

TABLE 208-17 National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group TIS Staging System for Kaposi’s Sarcoma GOOD RISK (STAGE 0): ALL OF THE FOLLOWING POOR RISK (STAGE 1): ANY OF THE FOLLOWING PARAMETER Tumor (T) Confined to skin and/ or lymph nodes and/or minimal oral disease Tumor-associated edema or ulceration Extensive oral lesions GI lesions Nonnodal visceral lesions Immune system (I) CD4+ T cell count ≥200/µL CD4+ T cell count <200/µL Systemic illness (S) No B symptomsa B symptomsa present Karnofsky performance status ≥70 Karnofsky performance

status <70 No history of opportunistic infection, neurologic disease, lymphoma, or thrush History of opportunistic infection, neurologic disease, lymphoma, or thrush aDefined as unexplained fever, night sweats, >10% involuntary weight loss, or diarrhea persisting for more than 2 weeks. Management of KS (Table 208-18) should be conducted in con sultation with an expert since definitive treatment guidelines do not exist. In the majority of cases, effective ART will go a long way in achieving control. ART has been associated with the spontaneous regression of KS lesions. Paradoxically, it has also been associated with the initial appearance of KS as a form of IRIS. For patients in whom tumor persists or is compromising vital functions or in whom control of HIV replication is not possible, a variety of options exist. In some cases, lesions remain quite indolent, and many of these patients can be managed with no specific treatment. Fewer than 10% of AIDS patients with KS die as a consequence of their malignancy, and death from secondary infections is considerably more common. Thus, whenever possible one should avoid treatment regimens that may further sup press the immune system and increase susceptibility to opportunistic infections. Treatment is indicated under two main circumstances. The first is when a single lesion or a limited number of easily accessible lesions are causing significant discomfort or cosmetic problems, such as with prominent facial lesions, lesions overlying a joint, or lesions in the oropharynx that interfere with swallowing or breathing. Under these circumstances, treatment with localized radiation, intralesional vinblastine, topical 9-cis-retinoic acid, or cryotherapy may be helpful. It should be noted that patients with HIV infection are particularly sensitive to the side effects of radiation therapy. This is especially true with respect to the development of radiation-induced mucositis; doses of radiation directed at mucosal surfaces, particularly in the head and TABLE 208-18 Management of AIDS-Associated Kaposi’s Sarcoma Observation and optimization of antiretroviral therapy Single or limited number of lesions Radiation Intralesional vinblastine Cryotherapy Extensive disease; inadequate response to ART Initial therapy Interferon α (if CD4+ T cells >150/μL) Liposomal daunorubicin Subsequent therapy Liposomal doxorubicin Paclitaxel Pomalidomide Combination chemotherapy with low-dose doxorubicin, bleomycin, and vinblastine (ABV) Targeted radiation

neck region, should be adjusted accordingly. The second indication for KS-directed treatment is for patients with a large number of lesions or in patients with visceral involvement. In these patients, systemic ther apy, either IFN-α or chemotherapy, should be considered. The single most important determinant of response appears to be the CD4+ T cell count. This relationship between response rate and baseline CD4+

T cell count is particularly true for IFN-α. The response rate to IFN-α for patients with CD4+ T cell counts >600/μL is ~80%, while the response rate for patients with counts <150/μL is <10%. In contrast to the other systemic therapies, IFN-α provides an added advantage of having antiretroviral activity; thus, it may be the appropriate first choice for single-agent systemic therapy for early patients with dissemi nated disease. A variety of chemotherapeutic agents also have been shown to have activity against KS. Five of them—liposomal daunorubi cin, liposomal doxorubicin, vinblastine, paclitaxel, and the thalidomide analogue pomalidomide—have been approved by the FDA for this indication. Liposomal daunorubicin and pomalidomide are approved as first-line therapy for patients with advanced KS despite ART. They have fewer side effects than conventional chemotherapy. In contrast, liposomal doxorubicin and paclitaxel are approved only for KS patients who have failed standard chemotherapy. Response rates vary from 23% to 88%, appear to be comparable to what had been achieved earlier with combination chemotherapy regimens, and are

greatly influenced by CD4+ T cell count. Vinblastine is most commonly used as an intra lesional injection or as part of a combination regimen. Lymphomas (Chaps. 113 and 114) occur with an increased fre quency in patients with congenital or acquired T cell immunodeficien cies. AIDS is no exception; at least 6% of all patients with AIDS develop lymphoma at some time during the course of their illness. This is a 10- to 20-fold increase in incidence compared with the general popu lation. In contrast to the situation with KS, primary CNS lymphoma, and most opportunistic infections, the incidence of AIDS-associated systemic lymphomas has not experienced a dramatic decrease as a con sequence of the widespread use of effective ART. Lymphoma occurs in all risk groups, with the highest incidence in patients with hemophilia and the lowest incidence in patients from the Caribbean or Africa with heterosexually acquired infection. Lymphoma is a late manifestation of HIV infection, generally occurring in patients with CD4+ T cell counts <200/μL. As HIV disease progresses, the risk of lymphoma increases. The attack rate for lymphoma increases exponentially with increas ing duration of HIV infection and decreasing level of immunologic function. At 3 years following a diagnosis of HIV infection, the risk of lymphoma is 0.8% per year; by 8 years after infection, it is 2.6% per year. As individuals with HIV infection live longer as a consequence of improved ART and better treatment and prophylaxis of opportu nistic infections, it is anticipated that the incidence of lymphomas may increase. Three main categories of lymphoma are seen in patients with HIV infection: grade III or IV immunoblastic lymphoma, Burkitt's lym phoma, and primary CNS lymphoma. Approximately 90% of these lymphomas are B cell in phenotype; more than half contain EBV DNA. Some are associated with KSHV. These tumors may be either mono clonal or oligoclonal in nature and are probably in some way related to the pronounced polyclonal B cell activation seen in patients with HIV infection. Immunoblastic lymphomas account for ~60% of the cases of lym phoma in patients with AIDS. The majority of these are diffuse large B cell lymphomas (DLBCL). They are generally high grade and would have been classified as diffuse histiocytic lymphomas in earlier clas sification schemes. This tumor is more common in older patients, increasing in incidence from 0% in people with HIV <1 year old to >3% in those >50 years of age. Two variants of immunoblastic lymphoma that are seen primarily in patients with HIV are primary effusion lym phoma (PEL) and its solid variant, plasmacytic lymphoma of the oral cavity. PEL, also referred to as body cavity lymphoma, presents with lymphomatous pleural, pericardial, and/or peritoneal effusions in the absence of discrete nodal or extranodal masses. The tumor cells do not express surface markers for B cells or T cells and are felt to represent a preplasmacytic stage of differentiation. While both KSHV and EBV

DNA sequences have been found in the genomes of the malignant cells from patients with body cavity lymphoma, KSHV is felt to be the driv ing force behind the oncogenesis (see above).

Small noncleaved cell lymphoma (Burkitt's lymphoma) accounts for ~20% of the cases of lymphoma in patients with AIDS. It is most frequent in patients 10–19 years old and usually demonstrates char acteristic c-myc translocations from chromosome 8 to chromosome 14 or 22. Burkitt's lymphoma is not commonly seen in the setting of immunodeficiency other than HIV-associated immunodeficiency, and the incidence of this particular tumor is more than 1000-fold higher in the setting of HIV infection than in the general population. In con trast to African Burkitt's lymphoma, where 97% of the cases contain EBV genome, only 50% of HIV-associated Burkitt's lymphomas are EBV-positive. Primary CNS lymphoma accounts for ~20% of the cases of lym phoma in patients with HIV infection. In contrast to HIV-associated Burkitt's lymphoma, primary CNS lymphomas are usually positive for EBV. In one study, the incidence of Epstein-Barr positivity

was 100%. This malignancy does not have a predilection for any particular age group. The median CD4+ T cell count at the time of diagnosis is ~50/μL. Thus, CNS lymphoma generally presents at a later stage of HIV infec tion than does systemic lymphoma. This may explain, at least in part, the poorer prognosis for this subset of patients. The clinical presentation of lymphoma in patients with HIV infec tion is quite varied, ranging from focal seizures to rapidly growing mass lesions in the oral mucosa (Fig. 208-44) to persistent unexplained fever. At least 80% of patients present with extranodal disease, and a similar percentage have B-type symptoms of fever, night sweats, and/or weight loss. Virtually any site in the body may be involved. The most com mon extranodal site is the CNS, involved in approximately one-third of all patients with lymphoma. Approximately 60% of these cases are primary CNS lymphoma. Primary CNS lymphoma generally presents with focal neurologic deficits, including cranial nerve findings, head aches, and/or seizures. MRI or CT generally reveals a limited number (one to three) of 3- to 5-cm lesions (Fig. 208-45). The lesions often show ring enhancement on contrast administration and may occur in any location. Contrast enhancement is usually less pronounced than that seen with toxoplasmosis. Lesions of CNS lymphoma are most commonly seen deep in the white matter. The main diseases in the differential diagnosis are cerebral toxoplasmosis and cerebral Chagas' disease. In addition to the 20% of lymphomas in people with HIV that are primary CNS lymphomas, CNS disease is also seen in patients with HIV and systemic lymphoma. Approximately 20% of patients with systemic lymphoma have CNS disease in the form of leptomeningeal involvement. This fact underscores the importance of lumbar puncture in the staging evaluation of patients with systemic lymphoma. CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders
Systemic lymphoma is seen at earlier stages of HIV infection than primary CNS lymphoma. In one series the mean CD4+ T cell count was 226/μL. In addition to lymph node involvement, systemic
FIGURE 208-44 Immunoblastic lymphoma involving the hard palate of a patient with AIDS.

FIGURE 208-45 Central nervous system lymphoma. Postcontrast T1-weighted MRI scan in a patient with AIDS, altered mental status, and hemiparesis. Multiple enhancing lesions, some ring-enhancing, are present. The left sylvian lesion shows gyral and subcortical enhancement, and the lesions in the caudate and splenium (arrowheads) show enhancement of adjacent ependymal surfaces. lymphoma may commonly involve the GI tract, bone marrow, liver, and lung. GI tract involvement is seen in ~25% of patients. Any site in the GI tract may be involved, and patients may complain of difficulty swallowing or abdominal pain. The diagnosis is usually suspected on the basis of CT or MRI of the abdomen. Bone marrow involvement is seen in ~20% of patients and may lead to pancytopenia. Liver and lung involvement are each seen in ~10% of patients. Pulmonary disease may present as a mass lesion, multiple nodules, or an interstitial infiltrate. PART 5 Infectious Diseases Both conventional and unconventional approaches have been employed in an attempt to treat HIV-related lymphomas. Systemic lymphoma is generally treated by the oncologist with combination chemotherapy. Earlier disappointing figures are being replaced with more optimistic results for the treatment of systemic lymphoma follow ing the availability of more effective ART and the use of rituximab in CD20+ tumors. While there is some controversy regarding the use of antiretrovirals during chemotherapy, there is no question that their use overall in patients with HIV lymphoma has improved survival. Con cerns regarding synergistic bone marrow toxicities with chemotherapy and ART are mitigated with the use of ART regimens that avoid myelosuppressive antiretrovirals. As in most situations in patients with HIV disease, those with higher CD4+ T cell counts tend to fare better although not as well as patients with lymphoma without HIV. Response rates as high as 72% with a median survival of 33 months and disease-free

intervals up to 9 years have been reported. Treatment of primary CNS lymphoma remains a significant challenge. Treatment is complicated by the fact that this illness usually occurs in patients with advanced HIV disease. Palliative measures such as radiation therapy provide some relief. The prognosis remains poor in this group, with a 2-year survival of 20–30%. Multicentric Castleman's disease (MCD) is a KSHV-associated lym phoproliferative disorder that is seen with an increased frequency in patients with HIV infection. While the incidence of Kaposi's sarcoma has decreased, the incidence of MCD has increased in the setting of ART. While not a true malignancy, MCD shares many features with lymphoma including generalized lymphadenopathy, hepatospleno megaly, and systemic symptoms of fever, fatigue, and weight loss. Pul monary symptoms may be seen in ~50% of patients. KS is present in 75–82% of cases. Lymph node biopsies reveal a predominance of inter follicular plasma cells and/or germinal centers with vascularization and an "onion skin" (hyaline vascular) appearance. Prior to the availability of ART, patients with HIV and multicentric Castleman's disease had a 15-fold increased risk of developing non-Hodgkin's lymphoma com pared with patients with HIV in general. Treatment typically involves chemotherapy. Rituximab may be of benefit, but it has been associated

with worsening of coexisting KS. Similarly, the use of corticosteroids may increase the risk of developing KS. The median survival of patients with treated multicentric Castleman's disease pre-ART was initially reported as 14 months. This has increased to a 2-year survival of more than 90% in the era of ART. Evidence of infection with human papillomavirus (HPV), associated with intraepithelial dysplasia of the cervix or anus, is approximately twice as common in people with HIV as in the general population and can lead to intraepithelial neoplasia and eventually invasive cancer. In a series of studies, men with HIV were examined for evidence of anal dysplasia, and Papanicolaou (Pap) smears were found to be abnormal in 20–80%. These changes tend to persist and are generally not affected by ART, raising the possibility of a subsequent transition to a more malignant condition. While the incidence of an abnormal Pap smear of the cervix is ~5% in otherwise healthy women, the incidence of abnormal cervical smears in women with HIV infection is 30–60%, and invasive cervical cancer is included as an AIDS-defining condition. While only small increases in the absolute numbers of cervical or anal cancers have been seen as a consequence of HIV infection, the relative risk of these conditions when one compares men and women with HIV to men and women without HIV infection is on the order of 10- to 100-fold and decreased with ART. Given the high rates of dysplasia and relative risks for cervical and anal cancer, a comprehensive gyne cologic and rectal examination, including Pap smear, is indicated at the initial evaluation and 6 months later for all patients with HIV infec tion. If these examinations are negative at both time points, the patient should be followed with yearly evaluations. If an initial or repeat Pap smear shows evidence of severe inflammation with reactive squamous changes, the next Pap smear should be performed at 3 months. If, at any time, a Pap smear shows evidence of squamous intraepithelial lesions, colposcopic examination with biopsies as indicated should be performed. The 2-year survival rate for women with HIV and invasive cervical cancer is 64% compared with 79% for women without HIV. In addition to rectal and cervical lesions, HPV can also lead to head and neck cancers. In one study of men who have sex with men, 25% were found to have oral HPV; high-risk HPV genotypes were three times more common in men with HIV. The most common HPV genotypes in the general population and the genotypes upon which current HPV vaccines are based are 6, 11, 16, and 18. In the population of people with HIV, other genotypes such as 58 and 53 also are prominent. This raises a concern about the level of effectiveness of the current HPV vaccines for patients with HIV. Despite this, it is recommended that patients with HIV infection be

vaccinated against HPV. IDIOPATHIC CD4+ T LYMPHOCYTOPENIA A syndrome was recognized in 1992 characterized by an absolute CD4+ T cell count of <300/μL or <20% of total T cells on a minimum of two occasions at least 6 weeks apart; no evidence of HIV-1, HIV-2, HTLV-1, or HTLV-2 on testing; and the absence of any defined immu nodeficiency or therapy associated with decreased levels of CD4+

T cells. By mid-1993, ~100 patients had been described. After extensive multicenter investigations, a series of reports were published in early 1993, which together allowed a number of conclusions. Idiopathic CD4+ lymphocytopenia (ICL) is a very rare syndrome, as determined by studies of blood donors and cohorts of HIV-seronegative men who have sex with men. Cases were clearly identified as early as 1983. The definition of ICL based on CD4+ T cell counts coincided with the ready availability of testing for CD4+ T cells in patients suspected of being immunodeficient. However, as a result of immune deficiency, certain patients with ICL develop some of the opportunistic diseases (par ticularly cryptococcosis, nontuberculous mycobacterial infections, and HPV disease) seen in patients with HIV. In one study, HPV-associated disease was seen in 29% of patients, cryptococcosis in 24%, molluscum contagiosum in 95%, and nontuberculous mycobacterial disease in 5%. Approximately 10–30% of patients may exhibit an autoimmune disease; this is more common in those with higher CD4 counts. The syndrome is demographically, clinically, and immunologically unlike HIV infection and AIDS. Fewer than half of the reported ICL patients had risk factors for HIV infection, and there were wide geographic

and age distributions. The fact that a significant proportion of initially diagnosed patients did have risk factors probably reflects a selection bias, in that physicians who take care of patients with HIV were more likely to monitor CD4+ T cells. Approximately half of the patients are women, compared with approximately one-fifth among people with HIV in the United States. Many patients with ICL remained clinically stable, and their condition may not deteriorate progressively as is common with seriously immunodeficient patients with HIV. Approxi mately 15% of patients with ICL experience spontaneous reversal of the CD4+ T lymphocytopenia. Immunologic abnormalities in ICL are somewhat different from those of HIV infection. ICL patients often have increases in CD4+ T cell activation with decreases in CD8+ T cells and B cells. Furthermore, immunoglobulin levels are either normal or, more commonly, decreased in patients with ICL, compared with the usual hypergammaglobulinemia of people with HIV. Virologic studies of these patients have revealed no evidence of HIV-1, HIV-2, HTLV-1, or HTLV-2 or of any other mononuclear cell–tropic virus. Further more, there has been no epidemiologic evidence to suggest that a transmissible microbe was involved. The cases of ICL have been widely dispersed, with no clustering. Close contacts and sexual partners who were studied were clinically well and were serologically, immunologi cally, and virologically negative for HIV. ICL is a heterogeneous syn drome, and it is highly likely that there is no common cause; however, there may be common causes among subgroups of patients that are currently unrecognized. Patients who present with laboratory data consistent with ICL should be worked up for underlying diseases that could be responsible for the immune deficiency. If no underlying cause is detected, no spe cific therapy should be initiated. However, if opportunistic diseases occur, they should be treated appropriately (see above). Depending on the level of the CD4+ T cell count, patients should receive prophylaxis for the commonly encountered opportunistic infections. TREATMENT AIDS and Related Disorders GENERAL PRINCIPLES OF PATIENT MANAGEMENT The CDC guidelines call for the testing for HIV infection to be a part of routine medical care. It is recommended that the patient be informed of the intention to test, as is the case

with other routine laboratory determinations, and be given the opportunity to “opt out.” Such an approach is critical to the goal of identifying as many infected individuals as possible since 13% of the 1.2 million indi viduals in the United States with HIV are not aware of their status. In the setting of routine testing, although it is difficult, pretest counseling is an important part of the process. No matter how well prepared a patient is for adversity, the discovery of a diagnosis of HIV infection is a devastating event. Thus, physicians should be sensitive to this fact and, where possible, utilize pretest counseling to at least partially prepare the patient should the results demon strate the presence of HIV infection. Following a diagnosis of HIV infection, the health care provider should be prepared to immedi ately activate support systems for the newly diagnosed patient and initiate ART. These supports should include individuals who can spend time talking to the newly diagnosed person and ensuring that he or she is emotionally stable and ready to begin therapy. Most communities have HIV support centers that can be of great help in these difficult situations. The treatment of patients with HIV infection requires not only a comprehensive knowledge of the possible disease processes that may occur and up-to-date knowledge of and experience with ART, but also the ability to deal with the problems of a chronic, potentially life-threatening illness. A comprehensive knowledge of internal medicine is required to deal with the changing spectrum of illnesses associated with HIV infection, many of which are similar to a state of accelerated aging. The appropriate use of potent ART and other treatment and prophylactic interventions is of critical importance in providing each patient with the best opportunity to

live a long and healthy life with HIV infection. In contrast to the earlier days of this epidemic, a diagnosis of HIV infection needs no longer be equated with having an inevitably fatal disease. In addition to medical interventions, the health care provider has a responsibility to provide each patient with appropriate counseling and education concerning their disease as part of a comprehensive care plan. Patients must be educated about the potential transmis sibility of their infection and about the fact that while health care providers may refer to levels of the virus as “undetectable,” this is only a reflection of the sensitivity of the assay being used to measure the virus, rather than a comment on the presence or absence of the virus. It is important for patients to be aware that the virus is still present in virtually all patients who have ever been diagnosed with HIV infection and capable of being transmitted in the absence of effective ART. Thus, there must be frank discussions concerning sexual practices and the sharing of syringes and other parapher nalia used in illicit drug use. The treating physician not only must be aware of the latest medications available for patients with HIV infection but also must educate patients concerning the natural history of their illness, listen to their concerns, and be sensitive to their fears. As with other diseases, therapeutic decisions should be made in consultation with the patient, when possible, and with the patient’s proxy if the patient is incapable of making decisions. In this regard, it is recommended that all patients with HIV infection, and in particular those with CD4+ T cell counts <200/μL, designate a trusted individual with durable power of attorney to make medical decisions on their behalf, if necessary.

Following a diagnosis of HIV infection, several examinations and laboratory studies should be performed to help determine the extent of disease and provide baseline standards for future refer ence (Table 208-19). In addition to routine chemistry, fasting lipid profile, aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin, fasting glucose and hematology screening pan els, Pap smear, urinalysis, and chest x-ray, one should also obtain a CD4+ T cell count, a plasma HIV RNA level, an HIV resistance test, a rapid plasma reagin (RPR) or

Venereal Disease Research Laboratory (VDRL) test, an anti-Toxoplasma antibody titer, and serologies for hepatitis A, B, and C. A PPD test or IFN-γ release assay should be done and an MMSE performed and recorded. A pregnancy test should be done for any women for whom the drug efavirenz is being considered, and HLA-B5701 testing should be done in all patients in whom the drug abacavir is being considered. CHAPTER 208 Human Immunodeficiency Virus Disease: AIDS and Related Disorders

TABLE 208-19 Initial Evaluation of the Patient with HIV Infection History and physical examination Routine chemistry and hematology AST, ALT, alkaline phosphatase, direct and indirect bilirubin Lipid profile and fasting glucose CD4+ T lymphocyte count Plasma HIV RNA level HIV resistance testing HLA-B5701 screening RPR or VDRL test Anti-Toxoplasma antibody titer Urinalysis PPD skin test or IFN-γ release assay Mini-Mental Status Examination Serologies for hepatitis A, hepatitis B, and hepatitis C Immunization with pneumococcal polysaccharide; influenza; HPV as indicated Immunization with hepatitis A and hepatitis B if seronegative Counseling regarding natural history and transmission Help contacting others who might be infected Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPD, purified protein derivative; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

TABLE 208-20 HIV Resources Available on the World Wide Web CLINICALINFO.HIV.GOV US-approved HIV treatment guidelines CLINICALTRIALS.GOV Information on clinical trials HIV.GOV Epidemiological data and prevention information Patients should be immunized with pneumococcal polysaccharide, with annual influenza and COVID-19 shots, and, if seronegative for these viruses, with HPV, hepatitis A, and hepatitis B vaccines. The status of hepatitis C infection should be determined. In addi tion, patients should be counseled with regard to sexual practices and needle sharing, and counseling should be offered to people whom the patient knows, or suspects, also may be infected. Once these baseline activities are performed, short- and long-term medi cal management strategies should be developed based on the most recent information available and modified as new information becomes available. The field of HIV medicine is changing rapidly, and it is difficult to remain fully up to date. Fortunately, there are a series of excellent sites on the Internet that are frequently updated, and they provide the most recent information on a variety of topics, including consensus panel reports on treatment (Table 208-20). ANTIRETROVIRAL THERAPY Combination antiretroviral therapy (ART), also referred to as highly active antiretroviral therapy (HAART), is the cornerstone of man agement of patients with HIV infection and should be initiated as soon as possible following a diagnosis of HIV infection. One excep tion to immediate initiation of ART is in the setting of cryptococ cal meningitis or TB where several weeks of specific antimicrobial therapy prior to initiation of ART may decrease the risk of severe IRIS. Following the initiation of widespread use of ART in the United States in 1995–1996, marked declines were noted in the inci dence of most AIDS-defining conditions (Fig. 208-34). Suppression of HIV replication is an important component in prolonging and improving the quality of life for the patient as well as minimizing the risk of transmission of HIV to others. Adequate suppression of HIV replication requires strict adherence to prescribed regimens of antiretroviral drugs. This has been facilitated by the coformula tions of antiretrovirals and the development of once-daily, monthly regimens, and every-six-month regimens with the expectation that even longer-lasting drugs are on the horizon. Among the decisions that need to be made in the context of prescribing ART are selec tion of the best initial regimen, determining when a given regimen should be changed, and deciding what regimen should be selected when a change is made. The care provider and patient must come to a mutually agreeable plan based on the best available data. In an effort to facilitate this process, the U.S.

Department of Health and Human Services makes available on the Internet (clinicalinfo.hiv.gov/en/guidelines) a series of periodically updated guidelines, including “Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents” and “Guidelines for the Prevention and Treatment of Opportunistic Infections in Persons Infected with Human Immu nodeficiency Virus.” At present, an extensive clinical trials network, involving both clinical investigators and patient advocates, is in place attempting to develop improved approaches to therapy. Consor tia comprising representatives of academia, industry, independent foundations, and the federal government engage in drug develop ment, including a wide-ranging series of clinical trials. As a result, new therapies and new therapeutic strategies are continually emerg ing. New drugs are often available through expanded-access pro grams prior to official licensure. Given the complexity of this field, decisions regarding ART are best made in consultation with experts. PART 5 Infectious Diseases Currently available drugs for the treatment of HIV infection as part of a combination regimen fall into five categories: those that inhibit the viral reverse transcriptase enzyme (nucleoside and nucleo tide reverse transcriptase inhibitors; nonnucleoside reverse tran scriptase inhibitors), those that inhibit the viral protease enzyme (protease inhibitors), those that inhibit the viral integrase enzyme (integrase strand transfer inhibitors), those that interfere with viral

entry (fusion inhibitors; CCR5 antagonists; CD4 antagonists) and those that interfere with the viral capsid (Table 208-21; Fig. 208-46). A typical regimen will include two nucleoside/nucleotide reverse tran scriptase inhibitors (usually a tenofovir-based drug or abacavir +

3TC or FTC) plus a nonnucleoside reverse transcriptase inhibitor, an integrase inhibitor, or a protease inhibitor boosted with a phar macokinetic enhancer (ritonavir or cobicistat). More recent studies have also supported the two-drug regimen of dolutegravir plus 3TC for initial therapy in hepatitis B–negative patients with baseline HIV RNA levels <500,000 copies/mL. Numerous fixed-drug formula tions combining two or more of these antiretroviral drugs have been licensed (Table 208-22). Prior to initiation of therapy and at any time a change in therapy due to treatment failure is being consid ered, drug resistance testing should be performed to help guide the selection of drugs to be used in combination. A summary of known resistance mutations for antiretroviral drugs is shown in Fig. 208-47. While most patients with HIV infection will be infected with HIV-1, some patients, especially those with an epidemiologic link to West Africa, may be infected with HIV-2. While the principles of treatment are the same as those for persons infected with HIV-1, it is important to note that the nonnucleoside reverse transcriptase inhibitors, enfuvirtide, and fostemsavir are not active against HIV-2 and should not be used as part of ART regimens in HIV-2–infected individuals. The FDA-approved reverse transcriptase inhibitors include the nucleoside analogues zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, and emtricitabine; the nucleotide analogues tenofovir disoproxil and tenofovir alafenamide; and the nonnucleo side reverse transcriptase inhibitors nevirapine, delavirdine, efavi renz, etravirine, rilpivirine, long-acting rilpivirine, and doravirine (Table 208-21). These represent the first class of drugs licensed for the treatment of HIV infection. They are indicated for this use as part of combination regimens. It should be stressed that none of these drugs should be used as monotherapy for HIV infection due to the relative ease with which drug resistance may develop under such circumstances. Thus, when lamivudine, emtricitabine, or tenofovir is used to treat hepatitis B infection in the setting of HIV infection, one should ensure that the patient is also on additional antiretroviral medication. Similarly, when any of these three medications are discontinued, one needs to be vigilant for a flare of hepatitis B in coinfected patients. The reverse transcriptase inhibitors block the HIV

replication cycle at the point of RNAdependent DNA synthesis, the reverse transcription step. While the nonnucleoside reverse transcriptase inhibitors are quite selective for the HIV-1 reverse transcriptase, the nucleoside and nucleotide ana logues inhibit a variety of DNA polymerases in addition to those of the HIV-1 reverse transcriptase. For this reason, serious side effects are more varied with the nucleoside analogues and include mitochondrial damage that can lead to hepatic steatosis and lactic acidosis as well as peripheral neuropathy and pancreatitis. The use of either of the thymidine analogues zidovudine and stavudine has been associated with a syndrome of hyperlipidemia, glucose intol erance/insulin resistance, and fat redistribution often referred to as lipodystrophy syndrome (discussed in “Diseases of the Endocrine System and Metabolic Disorders,” above). For these reasons, the older drugs in this class, zidovudine, didanosine, zalcitabine, and stavudine, are no longer recommend for use in the United States due to their side-effect profiles. The nucleoside and nucleotide transcriptase inhibitors preferred for use in combination regimens according to the DHHS Panel on the use of antiretroviral drugs are lamivudine, emtricitabine, abacavir, tenofovir disoproxil, and tenofovir alafenamide. Given its renal toxicity, tenofovir disoproxil should be limited to use in patients with creatinine clearance (CrCl)

> 70 while tenofovir alafenamide should generally be limited to use in patients with CrCl >30. The preferred nonnucleoside reverse transcriptase inhibitors are efavirenz, rilpivirine, and doravirine. Of note, rilpivirine is approved for treatment only in ART-naïve patients with HIV RNA levels <100,000 copies/mL and is contrain dicated in patients taking proton pump inhibitors.

TABLE 208-21 Antiretroviral Drugs Licensed in the United States for the Treatment of HIV Infection DOSE IN COMBINATION SUPPORTING DATA TOXICITY DRUGa INDICATION Nucleoside or Nucleotide Reverse Transcriptase Inhibitors Lamivudine (Epivir, 2′3′-dideoxy-3′- thiacytidine, 3TC) In combination with other antiretroviral agents for the treatment of HIV infection 150 mg bid 300 mg qd Emtricitabine

(FTC, Emtriva) In combination with other antiretroviral agents for the treatment of HIV infection 200 mg qd Comparable to lamivudine in combination with stavudine and nevirapine/efavirenz Abacavir (Ziagen) For treatment of HIV infection in combination with other antiretroviral agents 300 mg bid Abacavir + zidovudine + 3TC equivalent to indinavir + zidovudine + 3TC with regard to viral load suppression (~60% in each group with <400 HIV RNA copies/mL plasma) and CD4+ T cell increase (~100/μL in each group) at 24 weeks Tenofovir disoproxil fumarate (Viread) For use in combination with other antiretroviral agents when treatment is indicated 300 mg qd Reduction of ~0.6 log in HIV-1 RNA levels when added to background regimen in treatmentexperienced patients Tenofovir alafenamide (Vemlidy) In combination with emtricitabine and other antiretroviral agents for treatment of HIV-1 infection 25 mg qd 92% of patients treated in combination with emtricitabine, elvitegravir, and cobicistat had HIV-1 RNA levels <50 copies/mL Nonnucleoside Reverse Transcriptase Inhibitors Nevirapine (Viramune) In combination with other antiretroviral agents for treatment of progressive HIV infection 200 mg/d × 14 days then 200 mg bid or 400 mg extended release qd Efavirenz (Sustiva) For treatment of HIV infection in combination with other antiretroviral agents 600 mg qhs Efavirenz + zidovudine + 3TC comparable to indinavir + zidovudine + 3TC with regard to viral load suppression (a higher percentage of the efavirenz group

achieved viral load <50 copies/ mL, but the discontinuation rate in the indinavir group was unexpectedly high, accounting for most treatment “failures”); CD4 cell increase (~140/μL in each group) at 24 weeks Etravirine (Intelence) In combination with other antiretroviral agents in treatment-experienced patients whose HIV is resistant to nonnucleoside reverse transcriptase inhibitors and other antiretroviral medications 200 mg bid Higher rates of HIV RNA suppression to <50 copies/mL (56% vs 39%); greater increases in CD4+ T cell count (89 vs 64 cells) compared to placebo when given in combination with an optimized background regimen Rilpivirine (Edurant) In combination with other drugs in previously untreated patients when treatment is indicated 25 mg qd Noninferior to efavirenz with respect to suppression at week 48 in 1368 treatmentnaïve individuals, except in patients with pretherapy HIV RNA levels >100,000 where it was inferior Protease Inhibitors Ritonavir (Norvir) In combination with other antiretroviral agents for treatment of HIV infection when treatment is warranted 600 mg bid (also used in lower doses as pharmacokinetic booster) Atazanavir (Reyataz) For treatment of HIV infection in combination with other antiretroviral agents 400 mg qd or 300 mg qd + ritonavir 100 mg qd when given with efavirenz

In combination with zidovudine superior to zidovudine alone with respect to changes in CD4+ T cell counts in 495 patients who were zidovudine-naïve and 477 patients who were zidovudine-experienced; overall CD4+ T cell counts for the zidovudine group were at baseline by 24 weeks, while in the group treated with zidovudine plus lamivudine they were 10–50 cells/μL above baseline; 54% decrease in progression to AIDS/death compared with zidovudine alone Flare of hepatitis in HBV-coinfected patients who discontinue drug Hepatotoxicity in HBV-co-infected patients who discontinue drug, skin discoloration Hypersensitivity reaction In HLAB5701+ individuals (can be fatal); fever, rash, nausea, vomiting, malaise or fatigue, and loss of appetite Renal, osteomalacia, flare of hepatitis in HBV-co-infected patients who discontinue drug Nausea, less renal toxicity than tenofovir disoproxil fumarate CHAPTER 208 Increase in CD4+ T cell count, decrease in HIV RNA when used in combination with nucleosides Skin rash, hepatotoxicity Human Immunodeficiency Virus Disease: AIDS and Related Disorders
Rash, dysphoria, elevated liver function tests, drowsiness, abnormal dreams, depression, lipid abnormalities, potentially teratogenic Rash, nausea, hypersensitivity reactions Nausea, dizziness, somnolence, vertigo, less CNS toxicity and rash than efavirenz Reduction in the cumulative incidence of clinical progression or death from 34% to 17% in patients with CD4+ T cell count

<100/μL treated for a median of 6 months Nausea, abdominal pain, hyperglycemia, fat redistribution, lipid abnormalities, may alter levels of many other drugs, paresthesias, hepatitis Comparable to efavirenz when given in combination with zidovudine + 3TC in a study of 810 treatment-naïve patients; comparable to nelfinavir when given in combination with stavudine + 3TC in a study of 467 treatmentnaïve patients Hyperbilirubinemia, PR prolongation, nausea, vomiting, hyperglycemia, fat maldistribution, rash transaminase elevations, renal stones (Continued)

TABLE 208-21 Antiretroviral Drugs Licensed in the United States for the Treatment of HIV Infection DOSE IN COMBINATION SUPPORTING DATA TOXICITY DRUGa INDICATION Darunavir (Prezista) In combination with 100 mg ritonavir for combination therapy in treatmentexperienced adults 600 mg + 100 mg ritonavir bid with food Entry Inhibitors Enfuvirtide (Fuzeon) In combination with other agents in treatmentexperienced patients with evidence of HIV-1 replication despite ongoing

antiretroviral therapy 90 mg SC bid In treatment of experienced patients, superior to placebo when added to new optimized background (37% vs 16% with <400 HIV RNA copies/mL at 24 weeks; + 71 vs + 35 CD4+ T cells at 24 weeks) Maraviroc (Selzentry) In combination with other antiretroviral agents in adults infected with only CCR5tropic HIV-1 150–600 mg bid depending on concomitant medications (see text) Ibalizumab (Trogarzo) In combination with other antiretroviral agents in patients with multidrugresistant HIV-1 Single loading dose of 2000 mg followed by a maintenance dose of 800 mg every 2 weeks Fostemsavir (Rukobia) In combination with other antiretroviral agents in patients with multi-drug resistant HIV-1 600 mg bid At 96 weeks, 64% of patients with multi-drug resistant HIV-1 treated with an optimized background and fostemsavir achieved an HIV-1 RNA level <200 copies/mL PART 5 Infectious Diseases Integrase Inhibitors Raltegravir (Isentress) In combination with other antiretroviral agents 400 mg bid At 24 weeks, among 436 patients with 3-class drug resistance, 76% of patients randomized to receive raltegravir achieved HIV RNA levels <400 copies/mL compared with 41% of patients randomized to receive placebo Elvitegravir (Available only in combination with cobicistat, tenofovir, and emtricitabine [Stribild]) Fixed-dose combination 1 tablet daily Noninferior to raltegravir or atazanavir/ ritonavir in treatment-experienced patients Dolutegravir (Tivicay) In combination with other antiretroviral agents 50 mg daily for treatment-naïve patients 50 mg twice daily for treatment-experienced patients or those also receiving efavirenz or rifampin Bictegravir (Available only in combination with tenofovir alafenamide and emtricitabine [Biktarvy]) For treatment of HIV infection in adults 50 mg bictegravir/

25 mg tenofovir alafenamide/200 mg emtricitabine qd Cabotegravir (Vocabria) In combination with rilpivirine for treatment of HIV infection in adults Oral lead-in of 30 mg + 25 mg rilpivirine for 1 month; followed by an initial injection of 600 mg (3 mL) IM + 900 mg (3 mL) rilpivirine IM; followed by monthly injections of 400 mg

(2 mL) IM + 600 mg

(2 mL) rilpivirine IM

(Continued) At 24 weeks, patients with prior extensive exposure to antiretrovirals treated with a new combination including darunavir showed a –1.89-log change in HIV RNA levels and a 92-cell increase in CD4+ T cells compared with –0.48 log and 17 cells in the control arm Diarrhea, nausea, headache, skin rash, hepatotoxicity, hyperlipidemia, hyperglycemia Local injection reactions, hypersensitivity reactions, increased rate of bacterial pneumonia At 24 weeks, among 635 patients with CCR5tropic virus and HIV-1 RNA >5000 copies/mL despite at least 6 months of prior therapy with at least 1 agent from 3 of the 4 antiretroviral drug classes, 61% of patients randomized to maraviroc achieved HIV RNA levels <400 copies/mL compared with 28% of patients randomized to placebo Hepatotoxicity, nasopharyngitis, fever, cough, rash, abdominal pain, dizziness, musculoskeletal symptoms At 25 weeks, 50% of patients with multidrugresistant HIV-1 with HIV-1 RNA >1000 copies/ mL treated with an optimized background of 1 active drug and ibalizumab achieved HIV RNA levels <200 copies/mL Rash, diarrhea, nausea QTc prolongation at higher doses, elevation in liver enzymes in those with hepatitis B or C Nausea, headache, diarrhea, CPK elevation, muscle weakness, rhabdomyolysis Diarrhea, nausea, upper respiratory infections, headache Noninferior to raltegravir, superior to efavirenz or darunavir/ritonavir Insomnia, headache, hypersensitivity reactions, hepatotoxicity Noninferior to dolutegravir/tenofovir/

emtricitabine and noninferior to dolutegravir/ abacavir/lamivudine Nausea, diarrhea, headache Noninferior to abacavir/dolutegravir/ lamivudine or dolutegravir + 2 nucleoside/tide reverse transcriptase inhibitors Noninferior to nonnucleoside reverse transcriptase inhibitor + 2 nucleoside/ tide reverse transcriptase inhibitors or a protease inhibitor + 2 nucleoside/tide reverse transcriptase inhibitors or an integrase inhibitor and 2 nucleoside/tide reverse transcriptase inhibitors Injection-site reactions (Continued)

TABLE 208-21 Antiretroviral Drugs Licensed in the United States for the Treatment of HIV Infection DOSE IN COMBINATION SUPPORTING DATA TOXICITY DRUGa INDICATION Lenacapavir (Sunlenca) In combination with other agents for treatment of multidrug-resistant HIV infection in adults Induction with either (927 mg SC + 600 mg orally day 1; 600 mg orally day 2) or (600 mg orally days 1 and 2; 300 mg orally day 8; 927 mg SC day 15) followed by 927 mg SC every 6 months aInitial trade names are provided. Generic forms may be available. Abbreviations: ARC, AIDS-related complex; bid, twice daily; CPK, creatine phosphokinase; HBV, hepatitis B virus; IM, intramuscular; qd, once daily; qhs, once daily at bedtime; SC, subcutaneous. Nucleoside or Nucleotide Reverse Transcriptase Inhibitors O CH3 HN NH2 O O N O O P HN N NH O HOCH2 HO– N N N HO O O H N3 H Zidovudine Zalcitabine Didanosine NH2 O H CH3 N N N H2N O O N O O OH N N O HO F S H H Lamivudine Tenofovir disoproxil fumarate Emtricitabine Stavudine Nonnucleoside Reverse Transcriptase Inhibitors CH3 CH–CH3 CH3 SO2 H CH3 NH N N N N N H N O N H C O N OH CH3 SO2 N C Delavirdine C N NH HN N Rilpivirine Protease Inhibitors O O O O N H N H N N H O N N S S HO O CH3 H3C OH OH CH3 Nelfinavir mesylate Ritonavir NH2 OH OH H N N N H N O N H NH NH N O O NHC(CH3)3 O OH O O NHC(CH3)3 ×CH3SO3H Saquinavir mesylate Indinavir sulfate O H OH H N O O H H N S H SO2 N H OH O O O N H CF3 Tipranavir Darunavir FIGURE 208-46 Molecular structures of antiretroviral agents.

(Continued) At 52 weeks, 83% of patients with multi-drug resistant HIV-1 treated with an optimized background and lenacapavir achieved an HIV-1 level <50 copies/mL Injection site reactions, nausea NH2 HN HO N N N O N N H2N H2SO4 N O OPh N N N OH NH CH3 H3C 1/2 O O CH2OH 2 O Tenofovir alafenamide Abacavir NH2 N N O O H C C N CO2H N O P CHAPTER 208 O O O H CH3 HO2C O O O O OH S O N Human Immunodeficiency Virus Disease: AIDS and Related Disorders
O N H F3C H3C CH3 O H N N O Cl N N N N Br NH2 Nevirapine Efavirenz Etravirine CH3 CH3 H3C S NHtBu O H N N H N O O H N HN N H O OH H3C H Lopinavir NH2 N O HN O O S O OH O O H3CO OCH3 • H2S H N N H H N N H • H2SO4 N O N OH O O Amprenavir Atazanavir O O • C2H5OH H3C NH2 CH3

Entry Inhibitors NH2 NH2 O OH O O O O O O H N N H H2N H N N H H N N H O O O NH H2N HO O O O O OH HN OH O O NH O H2N HN O O H2N NH HO HO O O O O HN N H N H O O H N H N H N N H H2N O O O O HO F N N Me F H N N N O Me Me Maraviroc PART 5 Infectious Diseases O O N N N N N Integrase Inhibitors FO O H N N H N N N H N H N O N F O O OH Me Raltegravir Elvitegravir Me ONa O O F F O

N H N N 11a O H O Cabotegravir Capsid Inhibitor F F F F H N N N O N N F3C Me S O O Lenacapavir FIGURE 208-46 (Continued)

HO HO HO O O O O H N N N H H N N N H H N N N H O O H N N N H N H O O O HO N NH Ibalizumab NH2 H N O O N H NH O H N N H N O N H N H O O OH O OH O HN O NH O NH2 HN O N H N H Enfuvirtide O NH2

O N N OH OH O H2N O OH P O OH HO Fostemsavir O F Cl N F O O HO O N O F H N N H OH N O Dolutegravir F F O OH Bictegravir Cl N– Na+ S Me N O O CF3

TABLE 208-22 Combination Formulations of Antiretroviral Drugs NAME COMBINATION ABC/3TC (generic) Abacavir 600 mg/lamivudine 300 mg EFV/TDF/FTC (generic)a Efavirenz 600 mg/tenofovir disoproxil fumarate 300 mg/ emtricitabine 200 mg Biktarvya Bictegravir 50 mg/tenofovir alafenamide 25 mg/emtricitabine 200 mg Cabenuvaa Cabotegravir + rilpivirine (long-acting injection) Cimduo Tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg Compleraa Rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg/ emtricitabine 200 mg Delstrigoa Doravirine 100 mg/tenofovir disoproxil fumarate 300 mg/ lamivudine 300 mg Descovy Tenofovir alafenamide 25 mg/emtricitabine 200 mg Dovatoa Dolutegravir 50 mg/lamivudine 300 mg Genvoyaa Elvitegravir 150 mg/cobicistat 150 mg/tenofovir alafenamide

10 mg/emtricitabine 200 mg Julucaa Dolutegravir 50 mg/rilpivirine 25 mg Odefseya Rilpivirine 25 mg/tenofovir alafenamide 25 mg/emtricitabine 200 mg Stribilda Elvitegravir 150 mg/cobicistat 150 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg Symfia Efavirenz 600 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg Symfi Loa Efavirenz 400 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg Symtuzaa Darunavir 800 mg/cobicistat 150 mg/tenofovir alafenamide 10 mg/ emtricitabine 200 mg Triumeqa Dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg Truvada Tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg aComplete, once-daily, single-tablet regimens. Source: Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, USPHS. The HIV-1 protease inhibitors (saquinavir, indinavir, ritona vir, nelfinavir, amprenavir, fosamprenavir, lopinavir/ritonavir, ata zanavir, atazanavir/cobicistat, tipranavir, darunavir, and darunavir/

cobicistat) are an important part of the therapeutic armamentarium of antiretrovirals. While possessing antiviral properties of its own, ritonavir is typically used as a pharmacokinetic enhancer due to its high affinity for several isoforms of cytochrome P450 (3A4, 2D6) leading to large increases in the plasma concentrations of coadministered drugs metabolized by these pathways. As in the case of reverse transcriptase inhibitors, resistance to protease inhibitors can develop rapidly in the setting of monotherapy, and thus these agents should be used only as part of combination therapeutic regi mens. Based on superior efficacy and side-effect profile, ritonavirboosted darunavir in combination with emtricitabine and tenofovir (disoproxil or alafenamide) is the preferred protease inhibitor strat egy according to the DHHS Panel on the use of antiretroviral drugs. Integrase strand transfer inhibitors act by blocking the action of the HIV integrase enzyme and thus preventing integration of the HIV provirus into the host cell genome. They are among the most potent and safest of the antiretroviral drugs and frequently part of initial combination regimens. The five licensed integrase inhibitors are raltegravir, cabotegravir, elvitegravir, dolutegravir, and bictegravir. Cabotegravir is an integrase inhibitor that is given in combination with rilpivirine as a monthly injection. Prior to initiation of the monthly injections, patients should initially be treated with oral preparations of the two drugs to be sure they are well tolerated. Elvitegravir is always given in combination with cobicistat, which acts to boost the concentrations of elvitegravir. Cobicistat also inhibits tubular secretion of creatinine, resulting in increases in serum creatinine, and is not recommended for patients with estimated creatinine clearances <70 mL/min. Bictegravir is available only in combination with tenofovir alafenamide and emtricitabine. When used as part of initial ART, integrase inhibitor– containing regimens have been

associated with greater weight gain

than nonnucleoside reverse transcriptase inhibitor– or protease inhibi tor–containing regimens.

Entry inhibitors act by interfering with the binding of HIV to its receptor or co-receptor or by interfering with the process of fusion (see above). The first drug in this class to be licensed was the fusion inhibitor enfuvirtide, or T-20, followed by the CCR5 antagonist maraviroc. The anti-CD4 monoclonal antibody ibalizumab was licensed in 2018, and the small molecule fostemsavir in 2020. Given that maraviroc is effective only against CCR5-tropic viruses, a coreceptor tropism assay should be performed when use of this agent is being considered. The capsid inhibitor lenacapavir acts by interfering with viral rep lication by binding to the interface between p24 capsid subunits in hexamers. This then interferes with multiple steps in the viral life cyle including nuclear uptake of proviral DNA, virus assembly and release, and capsid core formation. It is licensed for treatment of individuals who are heavily treatment-experienced with multidrugresistant virus that is not suppressed on the current regimen. It is given by subcutaneous injection every 6 months after an oral or oral plus subcutaneous loading regimen. PRINCIPLES OF THERAPY The principles of therapy for HIV infection have been articulated by a panel sponsored by the U.S. Department of Health and Human Services as a working group of the NIH Office of AIDS Research Advisory Council. These principles are summarized in Table 208-23. As noted in these guidelines, ART of HIV infection does not lead to eradication or cure of HIV. The possible exceptions are a limited num ber of individuals with HIV infection and cancer who received alloge neic stem cell transplants from donors who were homozygous for the CCR5Δ32 mutation (see above) and thus resistant to HIV infection. CHAPTER 208 Treatment decisions must consider the fact that one is dealing with a chronic infection that requires life-long therapy. Patients initiating antiretroviral therapy must be willing to commit to ongoing treatment and understand the importance of adherence to their prescribed regi men. The importance of adherence is illustrated by the observation that treatment interruption is associated with rapid increases in HIV RNA levels, rapid declines in CD4+ T cell counts, and an increased risk of clinical progression. While it seems reasonable to assume that the complications associated with ART could be minimized by intermittent treatment regimens designed to minimize exposure to the drugs in question, all efforts to do so have paradoxically been associated with an increase in serious adverse events in the patients randomized to intermittent therapy, demonstrating that some “nonAIDS-defining” serious adverse events such as heart attack and stroke are linked to HIV replication. Thus, unless contraindicated for reasons of toxicity, patients started on ART should remain on ART. Human Immunodeficiency Virus Disease: AIDS and Related Disorders
At present, the U.S. Department of Health and Human Services Guidelines panel recommends that everyone with HIV infection be treated with ART and that therapy be initiated a soon as pos sible after diagnosis with some exceptions noted below. ART has been associated with a decrease in disease progression in patients at all stages of HIV infection and leads to a decrease in the risk of transmission of infection. In addition, one may wish to administer a 6-week course of therapy to uninfected individuals immediately fol lowing a high-risk exposure to HIV. The combination of tenofovir and emtricitabine is also licensed for pre-exposure prophylaxis in individuals at high risk of HIV infection, as is an injectable, longacting formulation of cabotegravir that may be even more effective. For patients diagnosed with an opportunistic infection and HIV infection at the same time and a CD4+ count ≥50 cells/μL, one may consider a 2- to 4-week delay in the initiation of antiretroviral therapy during which time treatment is focused on the opportunis tic infection. This delay may decrease the severity of any subsequent immune reconstitution inflammatory syndrome

by lowering the antigenic burden of the opportunistic infection. This is particularly true for patients with TB or cryptococcal meningitis. For patients with advanced HIV infection (CD4+ <50 cells/μL), however, ART should be initiated as soon as possible.

PART 5 Infectious Diseases FIGURE 208-47 Amino acid substitutions conferring resistance to antiretroviral drugs. For each amino acid residue, the letter above the bar indicates the amino acid associated with wild-type virus and the letter(s) below indicate the substitution(s) that confer viral resistance. The number shows the position of the mutation in the protein. Mutations selected by protease inhibitors in Gag cleavage sites are not listed. HR1, first heptad repeat; NAMs, nRTI-associated mutations; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor. Amino acid abbreviations: A, alanine; C, cysteine; D, aspartate; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine. (Reproduced with permission from AM Wensing et al: 2022 Update of the drug resistance mutations in HIV-1. 13, 2022. Reproduced with permission from IAS–USA.)

Human Immunodeficiency Virus Disease: AIDS and Related Disorders

CHAPTER 208 FIGURE 208-47 (Continued)

TABLE 208-23 Principles of Therapy of HIV Infection

1. Ongoing HIV replication leads to immune system damage, progression to AIDS, and systemic immune activation.
2. Plasma HIV RNA levels indicate the magnitude of HIV replication and the rate of CD4+ T cell destruction. CD4+ T cell counts indicate the current level of competence of the immune system.
3. Maximal suppression of viral replication is a goal of therapy; the greater the suppression the less likely the appearance of drug-resistant quasispecies.
4. The most effective therapeutic strategies involve the simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been previously treated and that are not cross-resistant with antiretroviral agents that the patient has already received.
5. The antiretroviral drugs used in combination regimens should be used according to optimum schedules and dosages.
6. The number of available drugs is limited. Any decisions on antiretroviral therapy have a long-term impact on future options for the patient.
7. Women should receive optimal antiretroviral therapy regardless of pregnancy status.
8. The same principles apply to children and adults, but the treatment of HIVinfected children involves unique pharmacologic, virologic, and immunologic considerations.
9. Compliance is an important part of ensuring maximal effect from a given regimen. The simpler the regimen, the easier it is for the patient to be compliant. Source: Modified from Principles of Therapy of HIV Infection, USPHS, and the Henry J. Kaiser Family Foundation. Once the decision has been made to initiate therapy, the health care provider must decide which drugs to use as the first regi men. The decision regarding choice of drugs not only

will affect the immediate response to therapy but also will have implications regarding options for future therapeutic regimens. The initial regi men is usually the most effective insofar as the virus has yet to be under any selective pressure to develop significant drug resistance. HIV is capable of rapidly developing resistance to any single agent, and therapy must be given as a multidrug combination. Given that patients can be infected with viruses that harbor drug resistance mutations, it is recommended that a viral genotype be done at the time of initiation of therapy to ensure that appropriate antiretroviral agents have been selected. The combination regimens currently rec ommended for initial therapy in most treatment-naïve patients are listed in Table 208-24. It is currently debated whether treatmentnaïve individuals with <50 copies/mL of HIV RNA benefit from ART. While these individuals are at low risk of disease progression in the short term, they do have evidence of persistent immune acti vation that may have long-term consequences. PART 5 Infectious Diseases Following the initiation of therapy, one should expect a rapid, at least 1-log (10-fold) reduction in plasma HIV RNA levels within 1–2 months and then a slower decline in plasma HIV RNA levels to <50 copies/mL within 6 months. During this same time there should be a rise in the CD4+ T cell count of 100–150/cells μL that is also TABLE 208-24 Initial Combination Regimens Recommended for Most Treatment-Naïve Patients Regardless of HIV RNA Level or CD4 Count For people who do not have a history of using Carbotegravir-LA as PrEP: Bictegravir + tenofovir alafenamide + emtricitabine (Biktarvy) Dolutegravir + tenofovira + emtricitabineb Dolutegravir + lamivudine (Dovato) only for those with HIV

RNA ≤ 500,000 copies/ml For people who have a history of Carbotegravir-LA as PrEP, INSTI genotype resistance testing should be performed; if starting prior to resistance testing results: Darunavir/cobicistat or darunavir/ritonavir + tenofovira + emtricitabineb aTenofovir alafenamide and tenofovir disoproxil fumarate are two forms of tenofovir approved by FDA. Tenofovir alafenamide has fewer bone and renal toxicities, while tenofovir disoproxil fumarate is associated with lower lipid levels. bLamivudine may substitute for emtricitabine and vice versa. Source: Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, USPHS.

TABLE 208-25 Indications for Changing Antiretroviral Therapy in Patients with HIV Infectiona Less than a 1-log drop in plasma HIV RNA by 4 weeks following the initiation of therapy A reproducible significant increase (defined as threefold or greater) from the nadir of plasma HIV RNA level not attributable to intercurrent infection, vaccination, or test methodology Persistently declining CD4+ T cell numbers Clinical deterioration Side effects aGenerally speaking, a change should involve the initiation of at least two drugs felt to be effective in the given patient. The exception to this is when a change is being made to manage toxicity, in which case a single substitution is reasonable. Source: Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, USPHS. particularly brisk during the first month of therapy. Subsequently, one should anticipate a CD4+ T cell count increase of 50–100 cells/ year until numbers approach normal. Many clinicians feel that failure to achieve these endpoints is an indication for a change in therapy. Other reasons for a change in therapy include a persistently declining CD4+ T cell count, a consistent increase in HIV RNA levels to >200 copies/mL, clinical deterioration, or drug toxicity (Table 208-25). As in the case of initiating therapy, changing therapy may have a lasting impact on future therapeutic options. When changing therapy because of treatment failure (clinical progression or worsening laboratory parameters), it is important to attempt to provide a regimen with at least two new

active drugs. This deci sion can be guided by resistance testing (see below). In the patient in whom a change is made for reasons of drug toxicity, a simple replacement of one drug is reasonable. It should be stressed that in attempting to sort out a drug toxicity it may be advisable to hold all therapy for a period of time to distinguish between drug toxicity and disease progression. Drug toxicity will usually begin to show signs of reversal within 1–2 weeks. Prior to changing a treatment regimen because of drug failure, it is important to ensure that the patient has been adherent to the prescribed regimen. As in the case of initial therapy, the simpler the new therapeutic regimen, the easier it is for the patient to be compliant. Plasma HIV RNA levels should be mon itored within 2–4 weeks after initiation of ART or following a change in regimen, every 4–8 weeks until HIV RNA levels are suppressed to <200 copies/mL, and then every 3–6 months during therapy. In order to determine an optimal therapeutic regimen for ini tial therapy or for a patient on a failing regimen, one may attempt to measure antiretroviral drug susceptibility through genotyping or phenotyping of HIV quasispecies and to determine adequacy of dosing through measurement of drug levels. Genotyping may be done through cDNA sequencing. Phenotypic assays typically measure the enzymatic activity of viral enzymes in the presence or absence of different concentrations of different drugs and have also been used to determine co-receptor tropism. These assays will generally detect quasispecies present at a frequency of ≥10%. Nextgeneration sequencing may allow detection of quasispecies at fre quencies down to 1%. It is generally recommended that resistance testing be used in confirming initial therapy choices in settings where the risk of transmission of resistant virus is high (such as the United States and Europe) and in determining new regimens for patients experiencing virologic failure while on therapy. Resistance testing may be of particular value in distinguishing drug-resistant virus from poor patient compliance. Due to the rapid rate at which drug-resistant viruses revert to wild-type, it is recommended that resistance testing performed in the setting of drug failure be con ducted while the patient is still on the failing regimen. Measure ment of plasma drug levels can also be used to tailor individual treatment. The inhibitory quotient, defined as the trough blood level/IC50 of the patient’s virus, is used by some to determine the adequacy of dosing of a given treatment regimen. Despite the best of efforts there will still be patients with ongoing high levels of HIV

replication while receiving the best available therapy. These patients will receive benefit from remaining on antiretroviral therapy even though it is not fully suppressive. In addition to the licensed medications discussed above, a large number of experimental agents are being evaluated as possible therapies for HIV infection. Therapeutic strategies are being devel oped to interfere with virtually every step of the replication cycle of the virus (Fig. 208-3) and in an attempt to eliminate the reservoir of infected cells to “cure” HIV infection. In addition to directly acting antiviral drugs, other strategies, generically referred to as “immune-based therapies,” are being developed as a complement to antiviral therapy. Among the antiviral agents in early clinical trials are additional nucleoside and nucleotide analogues, protease inhibitors, fusion inhibitors, receptor and co-receptor antagonists, and integrase inhibitors—as well as new antiviral strategies includ ing long-acting injectables, antisense nucleic acids, and maturation inhibitors. Among the immune-based therapies being evaluated are monoclonal antibodies, bone marrow transplantation, adoptive transfer of lymphocytes genetically modified to resist infection or enhance HIV-specific immunity, active immunotherapy with inac tivated HIV or its components, IL-7, and IL-15. HIV AND THE HEALTH CARE WORKER Health care workers, especially those who deal with large numbers of patients with HIV, have a small but definite risk of becoming infected with HIV as a result of professional activities (see “Occupational Trans mission of HIV: Health Care Workers, Laboratory

Workers, and the Health Care Setting," above). In the United States, 58 health care workers for whom case investiga tions have been completed have had documented seroconversions to HIV following occupational exposures. Only one of these has occurred since 1999. Approximately 85% of the exposures resulting in infection have been due to percutaneous (puncture/cut injury) exposures to HIV-infected blood. In addition, at least 150 possible cases of occu pationally acquired HIV infection have been reported among health care personnel in the United States. The number of these workers who actually acquired their infection through occupational exposures is not known. Taken together, data from several large studies suggest that the risk of HIV infection following a percutaneous exposure to HIV-

contaminated blood in an individual who does not receive postexposure prophylaxis (PEP) is ~0.23%, and after a mucous membrane exposure, ~0.09%. Although episodes of HIV transmission after nonintact skin exposure have been documented, the average risk for transmission by this route has not been precisely quantified but is estimated to be less than the risk for mucous membrane exposures. The risk for transmis sion after exposure to body fluids or tissues other than HIV-infected blood also has not been quantified but is probably considerably lower than for blood exposures. A seroprevalence survey of 3420 orthopedic surgeons, 75% of whom practiced in an area with a relatively high prevalence of HIV infection and 39% of whom reported percutaneous exposure to patient blood, usually through an accident involving a suture needle, failed to reveal any cases of possible occupational infec tion, suggesting that the risk of infection with a suture needle may be considerably less than that with a blood-drawing (hollow-bore) needle. Most cases of health care worker seroconversion have occurred as a result of needle-stick injuries. When one considers the circum stances that result in needle-stick injuries, it is immediately obvious that adhering to the standard guidelines for dealing with sharp objects would result in a significant decrease in this type of accident. In one study, 27% of needle-stick injuries resulted from improper disposal of the needle (more than half of these were due to recapping the needle), 23% occurred during attempts to start an IV line, 22% occurred during blood drawing, 16% were associated with an IM or SC injection, and 12% were associated with giving an IV infusion. Occupational exposures to HIV should be considered as a medical emergency to ensure timely postexposure management and admin istration of PEP. A delay of even sending 72 h in the initiation of PEP may be the difference preventing and not preventing infection.

Recommendations regarding PEP must take into account that a variety of circumstances determine the risk of transmission of HIV following occu pational exposure. In this regard, several factors have been associated with an increased risk for occupational transmission of HIV infection, including deep injury, the presence of visible blood on the instrument causing the exposure, injury with a device that had been placed in the vein or artery of the source patient, and advanced HIV disease in the source patient. Other important considerations when considering PEP in the health care worker include known or suspected pregnancy or breast-feeding, the possibility of exposure to drug-resistant virus, and the toxicities of different PEP regimens. Regardless of the decision to use PEP, the wound should be cleansed immediately and antiseptic applied. If a decision is made to offer PEP, U.S. Public Health Service guidelines recommend that PEP regimens contain three (or more) antiretroviral drugs administered for a 4-week duration for all occupational exposures to HIV. Detailed guidelines are available from the Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis (CDC, 2018). The report emphasizes the importance of adherence to PEP when it is

indicated, and close follow-up of exposed workers should be provided including counseling, baseline and follow-up HIV testing, and monitor ing for drug toxicity. Follow-up appointments should begin within 72 h of an HIV exposure and may be concluded 4 months after exposure. For consultation on the treatment of occupational exposures to HIV and other bloodborne pathogens, the clinician managing the exposed patient can call the National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline) at 888-448-4911. This service is available 24 hours a day at no charge. (Additional information is available at www.nccc.ucsf.edu.) PEPline support may be especially useful in challenging situations, such as when drug-resistant HIV strains are suspected or if the health care worker is pregnant.

CHAPTER 208 Health care workers can minimize their risk of occupational HIV infection by following the CDC guidelines of June 2015, which include adherence to universal precautions and assuming that blood and other body fluids from all patients are potentially infectious. Therefore, the following infection control precautions should be adhered to at all times: (1) routinely use barriers (such as gloves and/or goggles) when anticipating contact with blood or body fluids; (2) immediately wash hands and other skin surfaces after contact with blood or body fluids; and (3) carefully handle and dispose of sharp instruments during and after use. For further information contact the CDC at 800-CDC-INFO (232-4636) or see www.cdc.gov/cdc-info/. The risk of HBV infection fol lowing a needle-stick injury from a hepatitis antigen–positive patient is much higher than the risk of HIV infection (see "Transmission," above). There are multiple examples of needle-stick injuries where the patient was positive for both HBV and HIV and the health care worker became infected only with HBV. For these reasons, it is advisable, given the high prevalence of HBV infection in people with HIV, that all health care workers dealing with patients with HIV be immunized with the HBV vaccine. Human Immunodeficiency Virus Disease: AIDS and Related Disorders
TB is another infection common to patients with HIV that can be transmitted to the health care worker. For this reason, all health care workers should know their PPD status, have it checked yearly, and, where appropriate, receive 6 months of isoniazid treatment if their skin test converts to positive. In addition, all patients in whom a diagnosis of active pulmonary TB is being entertained should be placed immedi ately in respiratory isolation, pending results of the diagnostic evalua tion. The emergence of drug-resistant organisms, including extensively drug-resistant TB strains, has made TB an increasingly important problem for health care workers. This is particularly true for the health care worker with pre-existing HIV infection. HIV PREVENTION Many proven interventions, usually applied in combination, have a role in preventing the transmission of HIV (Fig. 208-48). Education, counseling, and behavior modification are the cornerstones of any HIV prevention strategy. A major problem in the United States and elsewhere is that many infections are passed on by those who do not know that they are infected. Of the ~1.2 million persons in the United States

HIV Testing PrEP PEP Treatment as Prevention Microbicides Clean Syringes and SSPs STI Testing and Treatment Medical Male Circumcision Treatment/ Prevention of Drug/ Alcohol Addiction Blood Supply Screening PMTCT Condoms Education/ Behavior Modification FIGURE 208-48 The HIV prevention "toolkit." See text for detailed description. PMTCT, prevention of mother-to-child transmission of HIV; PEP, postexposure prophylaxis with antiretroviral drugs; PrEP, pre-exposure prophylaxis with antiretroviral drugs; SSPs, syringe services programs. (From: The White House. 2021. National HIV/AIDS Strategy for the United States 2022–2025. Washington, DC.) with HIV, it is estimated that ~13% do not know their HIV status and that a substantial proportion of all new

infections are transmitted by those people. In this regard, the CDC has recommended HIV testing as part of routine medical care and that all individuals between the ages of 13 and 64 years be tested at least once. These individuals should be informed of the testing and be tested without the need for written informed consent. Each individual can “opt out” of testing; however, testing should otherwise be routinely administered. Individuals who are practicing high-risk behavior should be tested more often and should use pre-exposure prophylaxis (PrEP) (see below). Partners engaged in monogamous sexual relationships who wish to be assured of safety should both be tested for HIV antibody. If both are negative, it must be understood that any divergence from monogamy puts both partners at risk; open discussion of the importance of honesty in such relationships should be encouraged. PART 5 Infectious Diseases When the HIV status of either partner is not known, or when one partner is positive, there are a number of options. Use of condoms can markedly decrease the chance of HIV transmission. It should be remembered that condoms are not 100% effective in preventing trans mission of HIV infection, and there is a ~10% failure rate of condoms used for contraceptive purposes. Most condom failures result from breakage or improper usage, such as not wearing the condom for the entire period of intercourse. Latex condoms are preferable since viruses have been shown to leak through natural skin condoms. Petroleumbased gels should never be used for lubrication of the condom, since they increase the likelihood of condom rupture. Microbicides composed of gels or rings containing antiretroviral drugs have been shown to be variably efficacious in preventing acquisi tion of HIV infection in women engaging in vaginal intercourse. The considerable degree of variability in efficacy relates to the generally poor adherence of participants to the use of the intervention. One product, a vaginal ring that releases the antiretroviral drug dapivirine from the ring into the vagina slowly over 28 days, has been recom mended by WHO as an additional prevention choice for women at substantial risk of HIV infection as part of combination prevention approaches. Large, prospective clinical trials have clearly demonstrated that ART for people with HIV has an important role in HIV prevention. The initial results of the HPTN 052 clinical trial published in 2011 demonstrated a 96% reduction in HIV transmission risk among het erosexual HIV-discordant couples where the partner with HIV started ART immediately versus delayed ART initiation. The final results of HPTN 052, published in 2016, reported no HIV transmissions within these couples when the partner with HIV had a suppressed viral load (defined as having a viral load of <400 copies of HIV RNA per mil liliter). Three subsequent studies reported similar results, with no

genetically linked infections while the partner with HIV was virally suppressed even though couples were engaging in sex without a condom and not using PrEP. These three studies included >500 HIVdiscordant heterosexual couples and >1100 HIV-discordant couples of men who have sex with men. Combined, these couples engaged in >125,000 sex acts without a condom or PrEP over more than 2600 couple-years of observation. Collectively, the studies demonstrated that if the viral load of the infected partner is decreased to below detectable levels by antiretroviral therapy, sexual transmission to the uninfected partner does not occur. This is true for heterosexuals and men who have sex with men, leading, as noted above, to the commonly used phrase “undetectable equals untransmittable” or U = U. Pre-exposure prophylaxis (PrEP) with antiretroviral medication also is highly effective in preventing HIV acquisition by at-risk uninfected men who have sex with men and heterosexual men and women. Accumulated data indicate that high adherence to a PrEP regimen of emtricitabine + tenofovir disoproxil fumarate, taken as 1 pill per day or on demand (immediately before and following a sexual encoun ter), is 99% effective in preventing HIV acquisition if subjects adhere strictly to the regimen. Subsequent studies indicated similar, if not better, efficacy with cabotegravir injections given every 2 months as a maintenance regimen. A recent phase 3 clinical

trial conducted in South Africa and Uganda indicated that the twice-yearly injectable HIV capsid inhibitor lenacapavir demonstrated even greater efficacy in preventing HIV infection in cisgender women. Additional phase 3 studies of lenacapavir for PrEP are being conducted in cisgender men, transgender women, transgender men, and gender-nonbinary individ uals. More limited data demonstrate the utility of PrEP for people who inject drugs. CDC estimates that approximately 1.2 million people in the United States are at “substantial” risk for HIV infection and should be counseled about PrEP. Adult male circumcision, which has been shown to result in a 50–65% reduction in HIV acquisition in the circumcised subject, is currently being pursued, particularly in developing nations, as a component of HIV prevention (see above). The most effective way to prevent trans mission of HIV infection among IDUs is to stop the use of injectable drugs. Unfortunately, that is extremely difficult to accomplish unless the individual enters a treatment program. For those who will not or cannot participate in a drug treatment program and who will continue to inject drugs, the avoidance of sharing of needles and other parapher nalia (“works”) is the next best way to avoid transmission of infection. However, the cultural and social factors that contribute to the sharing of paraphernalia are complex and difficult to overcome. Under these circumstances, paraphernalia should be cleaned after each usage with a virucidal solution, such as sodium hypochlorite (undiluted house hold bleach). Needle exchange programs have been highly successful in decreasing HIV transmission among injection drug users without increasing the use of injection drugs. As noted, above, oral PrEP also is effective in preventing acquisition of HIV infections among IDUs. It is important for IDUs to be tested for HIV infection and counseled to avoid transmission to their sexual partners. Prevention of transmission through blood or blood products and prevention of mother-to-child transmission are discussed in “Transmission,” above. ■ ■HIV VACCINES There is currently no safe and effective vaccine approved for the pre vention of HIV infection. Successful vaccines for other diseases are predicated on the assumptions that the body can mount an adequate immune response to the microbe or virus in question during natural infection and that the vaccine will mimic the natural response to infection. Even with serious diseases, such as smallpox, poliomyelitis, measles, and influenza among others, the body usually clears the infec tious agent and provides protection, which is usually lifelong against future exposure to the same pathogen. Unfortunately, this is not the case with HIV infection since the natural immune response to HIV infection is unable to clear the virus from the body and cases of super infection are not rare. Some of the factors that contribute to the problematic nature of developing a preventive HIV vaccine are (1) the high mutability of the

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