PATHOLOGY
OF
AIDS

Version 16

by

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CHAPTER 1 - HUMAN IMMUNODEFICIENCY VIRUS

INTRODUCTION

The human immunodeficiency virus (HIV) was unknown until the early 1980's but since that time has infected millions of persons in a worldwide pandemic. The result of HIV infection is relentless destruction of the immune system leading to onset of the acquired immunodeficiency syndrome (AIDS). The AIDS epidemic has already resulted in the deaths of over half its victims. All HIV-infected persons are at risk for illness and death from opportunistic infectious and neoplastic complications as a consequence of the inevitable manifestations of AIDS.[1]

The AIDS pandemic has evolved over time, with four main phases of evolution. In the initial phase, HIV emerged from endemic rural areas to spread among urban populations at an accelerating rate. In the second phase dissemination occurred and involved definable risk groups. Behaviors in these risk groups, including sexual promiscuity and injection drug use, led to the third phase of escalation which occurred through the 1980's. A fourth phase of stabilization has occurred in some regions such as western Europe, North America, and Australia, where control measures appear to be having a positive effect. However, some regions such as central Africa and Asia continued to experience escalation of the pandemic through the 1990's.[2,3]

Although the HIV infection rate in the United States increased rapidly in the 1980's, peaked in the early 1990's, and has declined since, the reservoir of HIV-infected persons developing AIDS and requiring therapy continued to increase through the 1990's and into the 21st century.[4,5] At the end of the 20th century, over 21 million persons worldwide had died from AIDS, over 34 million were living with HIV infection, and over 95% of HIV infected persons resided in developing nations.[6,7] The scope of the AIDS pandemic has already led to serious consequences, not only for health care systems of countries unable to cope with many AIDS victims, but also for the national economies of those countries because of the loss of young to middle aged who are economically most productive. Worldwide, about half the victims of AIDS are women, and a consequence of this is perinatal infection resulting in a significant number of children born with HIV infection.[2]

Costs for detection, diagnosis, and treatment are considerable when effective therapies for persons with complications of HIV infection are instituted to prolong survival. In the 1990's in the U.S., the average cost for medical care of an HIV-infected patient was double the average income for half of all such patients.[8] Though the pharmacologic therapies exist for prolonging the lives of persons infected with HIV, such therapies are expensive and out-of-reach for most persons worldwide. The years of useful life lost by the predominantly younger population infected by HIV has a serious economic impact.[9]

According to the United Nations Development Program, when the prevalence of AIDS reaches 1% of the adult population, the epidemic will become difficult to constrain or reverse unless drastic and effective measures are taken.[10] In Eastern Europe, Asia, and Africa governmental responses to the spread of HIV have often been delayed and haphazard. The notable exception has been Thailand, which mounted a country-wide campaign to educate and screen its population. When less than 5% of adult men visit commercial sex workers, or barrier precaution use is high, and rates of injection drug use remain low, then the spread of HIV remains low. Treatment programs for those with AIDS are expensive and difficult to administer. Some pharmaceutical manufacturers have agreed to subsidize the costs, or allowed generic production of antiretroviral agents, lessening therapy to about 1$ U.S. per day, but the numbers of infected persons make treatment an expensive option for many countries. Lack of resources for health care have limited budgets to deal with HIV when other health problems loomed large.[11]

Considerable effort has been placed into education of persons potentially at risk for acquiring HIV.[12] A proper understanding of AIDS issues, including the nature of HIV and its means of spread, should precede decisions regarding allocation of health care resources and control measures.[13] Prevention strategies for HIV will require ongoing education, despite a general

public perception, particularly among young persons, that AIDS is a peripheral threat that does not call for changes in lifestyle. The battle against AIDS will require political alliances that allow prevention strategies to be implemented across national borders. The reservoir of infected persons is so large, global human interaction so broad, and costs of AIDS so high that everyone on earth is affected in some way by the AIDS pandemic.[14,15] Prevention strategies can include the following:[16]

- Make HIV testing a routine part of medical care.
- Implement new models for diagnosing HIV infections outside medical settings.
- Prevent new infections by working with persons diagnosed with HIV and their partners.
- Further decrease perinatal HIV transmission.

BIOLOGY OF HUMAN IMMUNODEFICIENCY VIRUS

Human immunodeficiency virus (HIV) and its subtypes are retroviruses, and they are the etiologic agents of AIDS. Human retroviruses were unknown until the 1980's, though animal retroviruses such as feline leukemia virus had been detected previously. HIV belongs to a large family of ribonucleic acid (RNA) lentiviruses that are characterized by association with diseases of immunosuppression or central nervous system involvement and with long incubation periods following infection before manifestations of illness become apparent.[17,18]

Lentiviruses similar to HIV have been found in a variety of primate species, and some of these are associated with a disease process called simian AIDS. Unlike other retroviruses, the primate lentiviruses are not transmitted through the germ line, and no endogenous copies of the virus exist in the genome of susceptible species.[19] Molecular epidemiologic data suggest that HIV type 1, the most common subtype of HIV that infects humans, has been derived from the simian immunodeficiency virus, called SIVcpz, of the *Pan troglodytes troglodytes* subspecies of chimpanzee. The lentivirus strain SIVcpz is highly homologous with HIV-1, and another form of simian immunodeficiency virus found in sooty mangabeys (SIVsm) has similarities as well. There is molecular epidemiologic evidence for at least seven cross-species transmissions of SIV to humans occurring in the first half of the 20th century, probably through exposures to primate blood.[20,21]

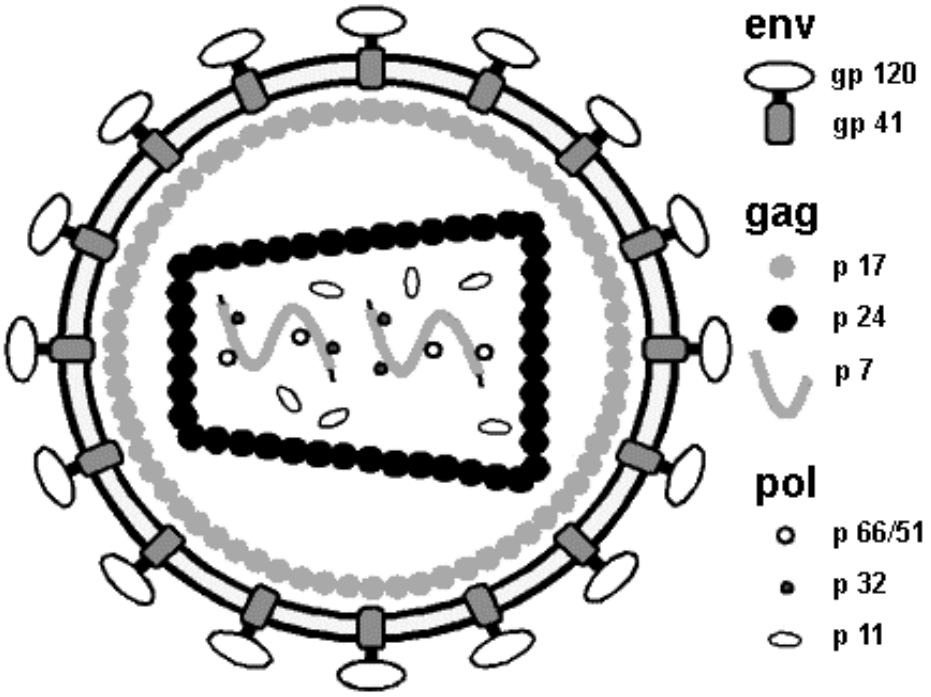
Zoonotic infection of humans may have occurred long in the past, but only in the late 20th century did demographic and social conditions change significantly to permit more rapid spread of the virus. Zoonotic infection of man with retroviruses is possible, as documented by infection of primate handlers with simian foamy retroviruses.[22] Retrospective studies performed on frozen sera have shown evidence for HIV in patients in Africa prior to 1960.[23] Reports in the early 1980's referred to the agent causing AIDS as either human T-lymphocytotropic virus, type III (HTLV-III) or as lymphadenopathy associated virus (LAV). This originally discovered virus is known as HIV-1, with one additional major subtype discovered, called HIV-2, which has more similarity to simian immunodeficiency virus (SIV) than to HIV-1.[24]

The mature virus consists of a bar-shaped electron dense core containing the viral genome--two short strands of ribonucleic acid (RNA) about 9200 nucleotide bases long--along with the enzymes reverse transcriptase, protease, ribonuclease, and integrase, all encased in an outer lipid envelope derived from a host cell. This envelope has 72 surface projections containing an antigen, gp120, that aids in the binding of the virus to the target cells with CD4 receptors. A second glycoprotein, gp41, binds gp120 to the lipid envelope. By electron microscopy, the plasma membrane of an infected CD4+ lymphocyte exhibits budding virus particles approximately 90 to 100 nanometers in diameter.[18,25,26]

The genome of HIV, similar to retroviruses in general, contains three major genes--*gag*, *pol*, and *env*. These genes code for the major structural and functional components of HIV, including envelope proteins and reverse transcriptase. The major structural components coded by *env* include the envelope glycoproteins, including the outer envelope glycoprotein gp120 and transmembrane glycoprotein gp41 derived from glycoprotein precursor gp160. Major components coded by the *gag* gene include core nucleocapsid proteins p55, p40, p24 (capsid, or “core" antigen), p17 (matrix), and p7 (nucleocapsid); the important proteins coded by *pol* are the enzyme proteins p66 and p51 (reverse transcriptase), p11 (protease), and p32 (integrase). [18,25,26]

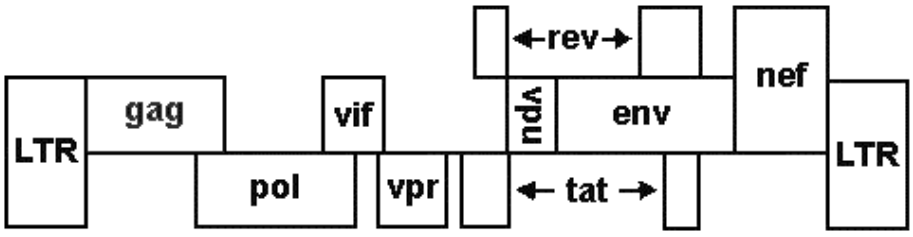
Although most of the major HIV viral proteins, which include p24 (core antigen) and gp41 (envelope antigen), are highly immunogenic, the antibody responses vary according to the virus load and the immune competence of the host. The antigenicity of these various components provides a means for detection of antibody, the basis for most HIV testing.[27]

A diagrammatic representation of HIV is shown below:



Accessory genes carried by HIV include *tat*, *rev*, *nef*, *vif*, *vpr*, and *vpu* (for HIV-1) or *vpx* (for HIV-2). The functions of some of these genes is known. The *tat* gene produces a regulatory protein that speeds up transcription of the HIV provirus. The *rev* gene encodes for a regulatory protein which switches the processing of viral RNA transcripts to a pattern that predominates with established infection, leading to production of viral structural and enzymatic proteins. The *nef* gene produces a regulatory protein that modifies the infected cell to make it more suitable for producing HIV virions. The *vif*, *vpr*, and *vpu* genes encode proteins that appear to play a role in generating infectivity and pathologic effects.[18,25,26]

The viral genome for HIV-1 is shown below:

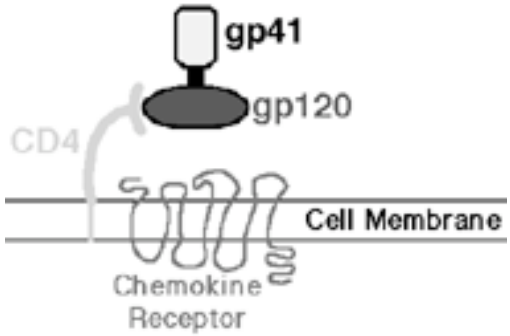


Retroviruses are unable to replicate outside of living host cells and do not contain deoxyribonucleic acid (DNA). The pathogenesis of HIV infection is a function of the virus life cycle, host cellular environment, and quantity of viruses in the infected individual. After entering the body, the viral particle is attracted to a cell with the appropriate CD4 receptor molecules where it attaches by fusion to a susceptible cell membrane or by endocytosis and then enters the cell. The probability of infection is a function of both the number of infective HIV virions in the body fluid which contacts the host as well as the number of cells available at the site of contact that have appropriate CD4 receptors.[26]

HIV infection can occur through oropharyngeal, cervical, vaginal, and gastrointestinal mucosal surfaces, even in the absence of mucosal disruption. Routes of HIV entry into mucosal lamina propria include M cells, dendritic cells, and epithelial cells. Dendritic cells can bind to gp120 through a C type lectin, suggesting that dendritic cells that squeeze between "tight" epithelium may capture HIV-1 and deliver it to underlying T cells, resulting in dissemination to lymphoid organs. HIV can cross a tight epithelial barrier by transcytosis during contact between HIV-infected cells and the apical surface of an epithelial cell.[28]

HIV primarily infects cells that have CD4 cell-surface receptor molecules, using the surface receptors to gain entry. Many cell types share common epitopes with this protein, though CD4 lymphocytes play a crucial role. Cells with CD4 receptors susceptible to HIV infection may include cells of the mononuclear phagocyte system, principally blood monocytes and tissue macrophages, T lymphocytes, natural killer (NK) lymphocytes, dendritic cells (Langerhans cells of epithelia and follicular dendritic cells in lymph nodes), hematopoietic stromal cells, and microglial cells in brain. The galactosylceramide receptors on cells within the brain and bowel may play a role as well.[18,29]

In addition to the CD4 receptor, a coreceptor known as a chemokine is required for HIV to infect cells. Chemokines are cell surface membrane-bound fusion-mediating molecules found on many cells. A diagrammatic representation of the relationship of the chemokine receptor to the CD4 receptor is shown below.



HIV entry into a host cell begins with gp120 binding to CD4 receptor, which induces a conformational change in gp120, exposing coreceptor binding sites. The V3 loop region of gp120 determines whether the host cell CCR5 or CXCR4 chemokine coreceptor will be engaged. After the chemokine coreceptor is engaged, the gp41 on the HIV surface undergoes a conformational cchange. The gp41 transmembrane coreceptor consists of HR1 and HR2 helical regions along with a fusion peptide. Conformational change in gp41 through HR1 and HR2 interaction leads to formation of a stable structure that allows fusion of HIV and host cell membranes, with a fusion pore through which the viral core enters the host cell. These cores can utilize host cell microtubules to move toward the cell nucleus.[30]

The chemokine coreceptors include the CXC family (CXCR1 to CXCR5) and the CC family (CCR1 to CCR9). Their presence on cells can aid binding of the HIV envelope glycoprotein gp120, promoting infection. Initial binding of HIV to the CD4 receptor is mediated by conformational changes in the gp120 subunit, but such conformational changes are not sufficient for fusion. The chemokine receptors produce a conformational change in the gp41 subunit of HIV which allows fusion of HIV.[31]

The differences in chemokine coreceptors that are present on a cell also explains how different strains of HIV may infect cells selectively. There are strains of HIV known as T-tropic strains which selectively interact with the CXCR4 chemokine coreceptor to infect lymphocytes. The M-tropic strains of HIV interact with the CCR5 chemokine coreceptor, and also CCR2 and CCR3, to infect macrophages and dendritic cells. CCR8 has been identified as a cofactor to permit infection by either T-cell tropic or by M-tropic strains of HIV. Dual tropic HIV strains have been identified that can use more than one chemokine coreceptor.[31] Over time, mutations in HIV may

increase the ability of the virus to infect cells via these routes. [32] Infection with cytomegalovirus may serve to enhance HIV infection via this mechanism, because CMV encodes a chemokine receptor similar to human chemokine receptors.[33]

The presence of chemokine coreceptor mutations may explain the phenomenon of resistance to HIV infection in some persons. Four mutational chemokine variants, including CCR5-delta32, CCR2-64I, CCR5-P1, and a primary ligand of CXCR4 known as SDF-1-3'A, have been discovered. These variants may impart resistance to HIV-1 infection and explain differences in infectivity within and among populations.[34]

Cellular localization of chemokine receptors may help explain how HIV infection can occur. Macrophages and monocytes, as well as subpopulations of lymphocytes, can express the CCR5 receptor. Neurons, astrocytes, and microglia in the central nervous system also express this chemokine receptor. In other tissues, CCR5 is expressed on epithelium, endothelium, vascular smooth muscle, and fibroblasts. Areas of inflammation contain increased numbers of mononuclear cells with CCR5, and this may facilitate transmission of HIV at those sites.[35]

Once within the cell, the viral particle uncoats from its spherical envelope to release its RNA. The enzyme product of the *pol* gene, a reverse transcriptase that is bound to the HIV RNA, provides for reverse transcription of HIV RNA to host cellular proviral DNA. It is this HIV proviral DNA which is then inserted into the host cell genomic DNA by the integrase enzyme of the HIV. Proviral DNA is activated and transcribed under direction of HIV *tat* and *rev* genes. The viral components are assembled at the inner part of the host cell membrane and begin to bud off. During the budding process, HIV protease cleaves viral proteins into their functional forms.[27,36]

Cells with CD4 receptors at the site of HIV entry become infected and viral replication begins within them. The infected cells can then release virions by surface budding, or infected cells can undergo lysis with release of new HIV virions which can then infect additional cells. Some of the HIV virions are carried via the lymphatics to regional lymph nodes.[27,36,37]

Though most macrophages become infected via HIV binding to gp120 and chemokine coreceptor with cell membrane fusion, macropinocytosis without cell surface binding can introduce HIV into macrophages. Most of the HIV is taken up into cytoplasmic macropinosomes and destroyed, but some HIV becomes localized to intracellular vesicles, escaping destruction and causing infection.[38]

Within the lymph nodes, HIV virions are trapped in the processes of follicular dendritic cells, where they may infect CD4 lymphocytes that are percolating through the node. Langerhans cells in the epithelia perform similarly. The dendritic cells themselves become infected, but are not destroyed. Dendritic cells have a surface protein called DC-SIGN which can capture HIV by binding to the HIV envelope. DC-SIGN-bound HIV is more infectious and has a longer half-life than free HIV.[38] Dendritic cells can migrate in lymph and blood to carry HIV throughout the body.[39] The presence of gp120 of HIV appears to reduce the capacity of dendritic cells to produce interleukin-12, suppressing cell-mediated immune responses.[40]

Within the cytoplasm of an infected cell, HIV reverse transcription begins in a reverse transcription complex (RTC). The RTC complex migrates to the cell nucleus. Proviral DNA is then transcribed. Proviral DNA is detectable within hours in infected CD4 lymphocytes, but may require 36 to 48 hours to appear within macrophages. Integration of HIV into host cellular DNA can occur without mitosis.[38]

Release of HIV from the host cell occurs in several steps. The p55 protein of HIV directs formation of a capsid (CA) protein that surrounds the RNA of HIV, a nucleocapsid (NC) protein that interacts with the RNA within the capsid, and matrix (MA) protein that surrounds the capsid and lies just beneath the viral envelope. A protease enzyme encoded by the *pol* gene of HIV cleaves the large precursor proteins to produce the MA, CA, and NC proteins. Budding virions utilize host cell membrane to help form the outer virion envelope of the budding virion necessary for production of infectious particles. The process of viral budding relies on cellular endosomal sorting complexes required for transport (ESCRT) that sort proteins and form multvesicular bodies (MVBs) that are intermediates in the formation of secretory lysosomes.[30]

After initial entry of HIV into host cells and the establishment of infection, HIV virions released from infected cells may then enter the systemic circulation and be carried to widespread

sites within the body. Cells of the mononuclear phagocyte system, including those in lymph nodes, spleen, liver, and bone marrow can then become infected with HIV. Besides lymph nodes, the gut associated lymphoid tissue in gastrointestinal submucosa provides a substantial reservoir for HIV. Primary HIV infection is followed by a burst of viremia in which virus is easily detected in peripheral blood in mononuclear cells and plasma. In the period of clinical latency of HIV infection, there is little detectable virus in peripheral blood, but viral replication actively continues in lymphoid tissues.[37]

Infection of the central nervous system by HIV requires that HIV-infected peripheral blood mononuclear cells cross the blood-brain barrier. Then infection of macrophages and microglial cells can occur. The immune activation leads to release of neurotoxic factors that further stimulate microglial activation along with neuronal apoptosis.[38]

Once the HIV proviral DNA is within the infected cell's genome, it cannot be eliminated or destroyed except by destroying the cell itself. The HIV proviral DNA then directs its replication by infected host cells. This replication may at first occur within inflammatory cells at the site of infection or within peripheral blood mononuclear cells (CD4 lymphocytes and monocytes) but then the major site of replication quickly shifts to lymphoid tissues of the body (lymph nodes and gastrointestinal tract). The initial burst of viral replication that follows infection is followed by replication at a lower level, which accounts for the clinically apparent latency of infection. However, viral replication is stimulated by a variety of cytokines such as interleukins and tumor necrosis factor which activate CD4 lymphocytes and make them more susceptible to HIV infection.[27,36]

Activation of viral synthesis leads to release of new infective particles from the host cell surface by budding. Replication may also cause cell lysis with release of additional infective viral particles. Host cell death may be mediated via several diverse mechanisms: direct viral cytopathic effects, fusion to multinucleated giant cells (syncytia formation), cytotoxic immune response by other lymphocytes (CD8+ cytotoxic T-lymphocytes), autoimmune mechanisms, disruptive interaction of HIV envelope proteins with the cell membrane, immune clearance from alteration of antigenicity of the host cell, activation of apoptosis (programmed cell death), or toxic accumulation of viral DNA, RNA, or proteins.[17,18,27,36]

Apoptosis plays a key role in the decline in T cell numbers during HIV infection. Mechanisms that contribute to HIV-associated lymphocyte apoptosis include chronic immunologic activation via gp120/160 of the CD4 receptor, enhanced production of cytotoxic ligands or viral proteins by monocytes, macrophages, B cells, and CD8 cells, and direct infection of target cells by HIV resulting in apoptosis. Apoptosis of lymphocytes is increased with progression of HIV disease and diminished with effective antiretroviral therapy.[41]

Subsets of the CD4+ lymphocyte population are important in determining the host response to infection. The subset known as TH1 (T helper 1) is responsible for directing a cytotoxic CD8+ T-lymphocyte response, but the TH2 (T helper 2) subset of CD4+ and CD8+ T-lymphocytes diminishes the cytotoxic lymphocyte response while increasing antibody production. Persons infected with HIV who have a dominant TH1 response tend to survive longer. CD8+ lymphocytes can inhibit HIV infection though both HLA-restricted cytolysis as well as suppressive activity mediated through release of multiple suppressive factors collectively termed CD8 antiviral factor (CAF).[38]

The switch from a TH1 to a TH2 response has been suggested as a factor in the development of AIDS. Production of interleukin-5 (IL-5) and interferon-gamma (IFN-gamma) by CD4+ and CD8+ T-lymphocytes expressing CD30 is associated with promotion of B-lymphocyte immunoglobulin production.[42,43] The imbalance in the TH response to a predominantly TH2 response is mediated by HIV proteins gp120 and Tat, which trigger the release of cytokines necessary for a TH2 response. These HIV proteins stimulate mast cells and basophils. The Tat protein upregulates chemokine receptor CCR3 on mast cells and basophils, rendering them susceptible to infection by CCR3 tropic HIV. Increased serum IgE levels suggest that a TH2 response has occurred and predict a poorer prognosis.[44]

Macrophages and dendritic (Langerhans) cells in epithelial tissues of the body, such as the genital tract, are also important both as reservoirs and vectors for spread of HIV in the body. Macrophages originate from blood monocytes and give rise to the body's mononuclear phagocyte

system. Langerhans cells (a subset of blood dendritic cells) originate in bone marrow and migrate to peripheral epithelial locations in skin and mucus membranes, acting as antigen presenting cells for lymphocytes. Dendritic cells can cross endothelium and circulate freely into both lymphoid and mucosal tissues. HIV can be replicated within dendritic cells for up to 45 days.[45]

Both macrophages and Langerhans cells can be HIV-infected but are not destroyed. Dendritic cells can capture HIV in their processes, providing a focus for infection of other cells. HIV can be carried elsewhere in the body, particularly to regional lymph nodes, by antigen-presenting cells such as macrophages or dendritic cells which act as a "Trojan horses".[46] Macrophages proliferating in response to other infections, such as mycobacterial infections, may increase this reservoir capacity and promote progression of HIV infection.[47] Langerhans cells can become infected with HIV, even at sites distant from initial infection and during primary infection.[48]

In the host, HIV continues to replicate, mainly within lymphoid tissues. Germinal centers of lymph nodes contain many follicular dendritic cells (FDCs). Such FDCs not only have CD4 receptors on surface membranes, but also a surface protein, CD-SIGN, to which HIV envelope protein can bind. The FDCs can accumulate high numbers of HIV virions, acting as virion "warehouses". Any CD4 lymphocytes percolating through the germinal centers of lymph nodes may become infected through contact with FDCs harboring HIV virions on their surfaces. The virions can become trapped in the interdendritic spaces of FDCs, or they may even undergo receptor-mediated endocytosis to become localized within the FDCs, and may escape to reside freely within the FDC cytoplasm, providing a significant reservoir of HIV infection. The FDCs also proliferate in response to early HIV infection, leading to lymphadenopathy.[36,37,39,49]

The magnitude of HIV-1 production in infected persons is enormous. The numbers of "productively infected cells" (those cells with 20 or more copies of HIV-1 RNA) are quite high. When primary HIV-1 infection occurs, most of the productively infected cells are CD4 lymphocytes, accounting for about 80% of all infected cells at the site(s) of mucosal inoculation and 90% of infected cells in lymphoid tissues. However, follicular dendritic cells (FDCs) within the lymphoid tissues provide the greatest reservoir in well-established HIV-1 infections, particularly throughout the clinically latent period before the onset of AIDS, harboring an estimated 10^{11} copies of HIV-1 RNA. The pool of 10^{7} to 10^{8} productively infected CD4 cells within the body, averaging 50 - 100 copies per cell, gradually diminishes over time, eventually leading to immune failure and the onset of AIDS. The total virion production per day in an infected person averages greater than 10^{9} to 10^{10} copies. Additional reservoirs of HIV-infected cells may be present in the central nervous system, lung, and liver.[50]

Since the HIV provirus becomes part of the infected host's cellular DNA, the host's cells may be infectious even in the absence of a demonstrable HIV serum viremia or detectable HIV antibodies.[36] However, antibodies formed against HIV are not protective, and a viremic state can persist despite the presence of even high antibody titers. HIV has the additional ability to mutate easily, in large part due to the error rate in production of the reverse transcriptase enzyme, which introduces a mutation approximately once per 2000 incorporated nucleotides. This high mutation rate leads to the emergence of HIV variants within the infected person's cells that can then resist immune attack, exhibit greater cytotoxicity, generate syncytia more readily, or can impart drug resistance. Over time, various tissues of the infected host’s body may harbor differing HIV variants.[17,18,25,51]

Moreover, the primary target of HIV is the immune system itself, which is gradually destroyed. Viral replication actively continues following initial HIV infection, and the rate of CD4 lymphocyte destruction is progressive. Clinically, HIV infection may appear "latent" for years during this period of ongoing immune system destruction. During this time, enough of the immune system remains intact to provide immune surveillance and prevent most infections. Eventually, when a significant number of CD4 lymphocytes have been destroyed and when production of new CD4 cells cannot match destruction, then failure of the immune system leads to the appearance of clinical AIDS.[18,25]

HIV infection is sustained through continuous viral replication with reinfection of additional host cells. Both HIV in host plasma and HIV-infected host cells appears to have a short lifespan,

and late in the course of AIDS the half-life of plasma HIV is only about 2 days. Thus, the persistent viremia requires continuous reinfection of new CD4 lymphocytes followed by viral replication and cell turnover. This rapid turnover of HIV and CD4 lymphocytes promotes the origin of new strains of HIV as a consequence of the continuing mutation of HIV. Presence or emergence of different HIV subtypes may also account for the appearance of antiretroviral drug resistance as well as the variability in pathologic lesions as different cell types are targeted or different cytopathic effects are elicited during the course of infection.[18,52,53]

Active replication of HIV occurs at all stages of the infection. However, soon after initial infection an equilibrium is established between HIV replication and control of HIV by the body's immune system. In general, clearance rates of HIV are similar among persons, but the rate of HIV production determines the viral load in the steady state. This marks the clinically latent phase of HIV infection. The presence of viremia, as detected by serum HIV-1 RNA, suggests that the immune system is less able to contain the virus. Increasing levels of serum HIV-1 RNA suggest a loss of the equilibrium and emergence from latency to a more rapid progression to AIDS. The absence of a detectable serum HIV-1 RNA suggests a slower progression to clinical AIDS. Greater HIV-1 RNA levels in patients with symptomatic acute HIV infection suggest that such persons may progress more rapidly to AIDS.[54] As the number of CD4 cells diminishes in the late stages of AIDS, macrophages still serve as key sites for continuing viral replication.[38]

Cytokine activation of CD4 lymphocytes can increase the production of HIV by infected cells. Cytokines that stimulate virion production include tumor necrosis factor alpha (TNF-α), interleukin 2 (IL-2), and interleukin 6 (IL-6). These cytokines help to promote production of a cellular protein kinase called TAK that mediates the stimulation of HIV proviral transcription by the HIV Tat protein.[55]

Genetic variability in HIV also leads to differences in biological phenotypic characteristics of viral pathogenetic effects. HIV can be divided into three groups: (1) non-syncytium-inducing (NSI) variants that have a low replicative capacity; (2) non-syncytium-inducing variants with a high replicative capacity; and (3) syncytium-inducing (SI) variants. From 30 to 60% of HIV-infected persons may eventually develop such variants. The SI variants appear to evolve from NSI variants, with a change in surface gp120, during the course of HIV infection, usually at a time marked by a peripheral blood CD4 lymphocyte count between 400 and 500/μL. The appearance of SI variants is associated with CD4+ cell tropism, rapid CD4+ cell decline, higher HIV-1 RNA plasma levels, symptomatic HIV disease, male sex, and rapid progression of HIV infection. However, only about half of patients with AIDS have the SI variants, and NSI variants can also be seen with disease progression.[54,56]

Phylogenetic studies can identify genetic clusters of HIV-1 *env* genes which are known as subtypes, or clades, that have arisen along with progression of the AIDS epidemic worldwide. The V3 loop amino acid sequences of these genetic variants influence HIV phenotype and immune response.[57] Thus, the biologic properties of HIV can vary with the subtype. This is possible even within an individual HIV-infected person, where variants of HIV may arise over time that are "neurotropic" or "lymphocytotropic" for example.[18,51] Variability in transmission may occur, as with clade E, which is associated with greater heterosexual transmission, aided by its propensity to infect dendritic cells that can be found in mucosal epithelium.[58] However, the role of HIV-1 subtypes in transmission and pathogenesis of HIV remains, for the most part, unclear.[59]

Different subtypes of HIV-1 that have arisen and will continue to arise in the course of the AIDS epidemic have been identified with certain geographic distributions, though movement of individuals among populations creates more variability over time.[60] Variability of HIV subtypes may also confound testing strategies, because diagnostic sensitivity and specificity of laboratory tests may not be the same across all subtypes.[61]

At the beginning of the 21st century, over 90% of new HIV infections are emerging in Asia, Africa, and Eastern Europe. The HIV-1 subtypes A, C, and E more prevalent in these regions appear to be transmitted more efficiently than the subtype B which more common to developed nations of Europe and North America. The more virulent subtype C accounts for half of all new infections. The evolutionary changes in HIV accounting for differences in subtype transmission

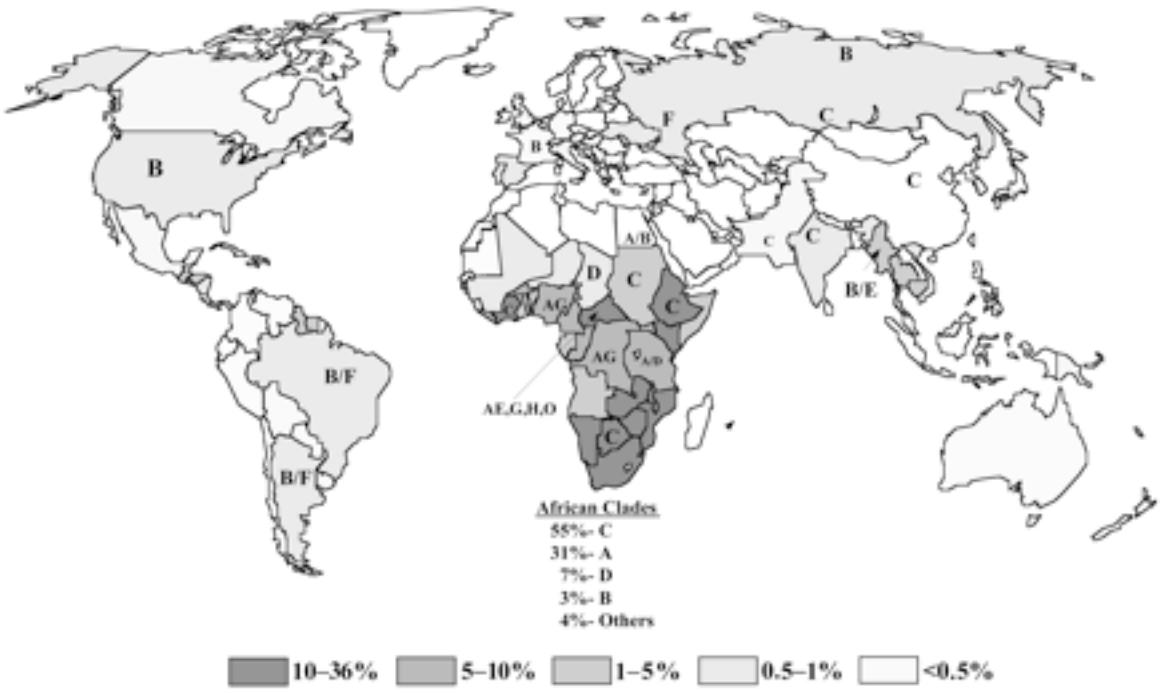
have included *env* gene mediated receptor affinity and LTR and *tat* gene mediated transcriptional activation.[62]

The detection of mosaic HIV-1 sequences suggests that persons can become coinfected with differing HIV-1 subtypes that can then undergo recombination to new strains which may have different biologic characteristics from the original strains. This has happened in Southeast Asia and Africa, where the recombinants A/E and A/G comprise the major circulating forms of HIV-1.[20] The major subtypes of HIV-1 are listed below. Subtypes A through H belong to the major group M, while group O is distinctly different and genetically more closely related to simian immunodeficiency virus (SIV) and HIV-2.[61,63] Group N appears to have arisen from interaction between a group M and a group O virus.[64]

The major subgroups of HIV-1 are given below, with epidemiologic correlates for probable locations in the first decade of the AIDS epidemic. Recombinant forms (e.g., A/E or A/G or B/F are appearing more frequently as the epidemic progresses.[60]

Subgroups of HIV-1

Group M		
•	Subtype A	West and Central Africa
•	Subtype B	South America (including Brazil and Argentina), United States, Europe, Thailand, Russia
•	Subtype C	India, Sudan, Southern and Eastern Africa
•	Subtype D	East and Central Africa
•	Subtype E	Thailand, Philippines, China, Central Africa
•	Subtype F	Brazil, Argentina, Eastern Europe, Central Africa
•	Subtype G	Western and Eastern Africa, Central Europe
•	Subtype H	Central Africa
•	Subtype J	Central America
•	Subtype K	Democratic Republic of Congo, Cameroon
Group N		Cameroon
Group O		West Africa



HIV-1 prevalence rate

OTHER HUMAN RETROVIRUSES

HIV-2:-- The numerous strains of HIV-1 isolated from various geographic regions of the world are all immunologically similar and differ only slightly in their DNA sequences. A second retrovirus designated HIV-2 has been isolated from a number of patients with AIDS, first in West African countries and subsequently in Western Europe, the United States, and elsewhere. Most cases have appeared in West Africa and have appeared only sporadically in other parts of the world.[65] HIV-2 is believed to have been present in Africa as early as the 1940's. HIV-2, which has greater homology to simian immunodeficiency virus (SIV) than to HIV-1, appears to have become established in human populations as a zoonotic infection from the primate reservoir of sooty mangabeys (*Cercocebus atys*).[20,29]

HIV-2 is spread in a manner similar to HIV-1, though the high-risk groups are commercial sex workers and persons with other sexually transmitted diseases.[66] The peak age of persons infected with HIV-2 appears to be higher than that of HIV-1, but there appears to be no sex difference in rates of infection. HIV-2 appears to utilize the same cellular mechanisms for infection as HIV-1, including the use of CD4 receptors and chemokine coreceptors. Persons infected with HIV-2 live longer and have a course of disease much more variable than persons with HIV-1 infection.[31,67]

Just as HIV-1 has distinct subtypes, so does HIV-2. The subtypes of HIV-2 have been designated from A through F. There is up to a 25% difference in genetic homology among these subtypes. All five subtypes can be detected by enzyme immunoassay (EIA) and Western blot assays for HIV-2 similar to those for HIV-1. The reverse transcriptase enzyme is similar in structure and function in both HIV-1 and HIV-2. Infection with HIV-2 eventually leads to AIDS. Persons can be coinfected with HIV-1 and HIV-2.[65,6668]

The genetic sequences of HIV-1 and HIV-2 are only partially homologous. HIV-2, or other as yet uncharacterized members of the HIV-group of viruses, will not necessarily be detected by using the various laboratory tests for HIV-1 antibody, including enzyme immunoassay (EIA) and Western blot (WB) tests, in general use for HIV-1. Instead, separate EIA and WB assays are employed for diagnosis of HIV-2. HIV-2 is genetically more closely related to simian immunodeficiency virus (SIV) than HIV-1.[69]

This potential problem of genetic variation with HIV was illustrated in 1994 with the detection of a strain of HIV-1 (designated MVP-5180, or subtype O), a new HIV variant originating in the region of West-Central Africa, which showed only slightly more homology with other HIV-1 strains than with HIV-2. This variant was still detectable with many testing methods for HIV-1, but false negative results may occur. This subtype O of HIV-1 demonstrates higher heterogeneity in *env* sequences than the more prevalent HIV-1 subtypes such as B.[63,70]

The appearance of additional HIV subtypes requires more complex testing schemes in locations where HIV-2, or other possible HIV virus subtypes, are prevalent. The transmission of HIV-2 is similar to that for HIV-1, though perinatal transmission is much less frequent. The natural history of HIV-2 infection is characterized by a longer latent period before the appearance of AIDS, a less aggressive course of AIDS, and a lower viral load with higher CD4 lymphocyte counts than HIV-1 infection until late in the course of the disease, when clinical AIDS is apparent. Thus, the pathogenicity of HIV-2 appears to be lower than that of HIV-1. This may explain the more limited spread of HIV-2, compared to HIV-1, both in West African countries and elsewhere, due to less efficient transmission, particularly via heterosexual and perinatal modes.[65] The mortality rate from HIV-2 infection is only two-thirds that for HIV-1.[71]

HTLV:-- Another group of human retroviruses different from HIV are the human T-lymphotrophic viruses, types 1 and 2 (HTLV-1 and HTLV-2). Along with simian T-cell lymphoma virus type 1, they constitute a group of retroviruses known as the primate T-cell leukemia/lymphoma viruses. HTLV's can be transmitted in the same manner as HIV, though even less efficiently. Persons can be coinfected with HIV and HTLV. The CD4 lymphocytes are the

cells primarily infected by HTLV. Laboratory testing methodology for HTLV's is similar to that for HIV. The enzyme immunoassay test for HTLV-1 will also detect HTLV-2. Confirmatory Western blot testing, in combination with testing for the presence of envelope peptide p21env-r helps to distinguish HTLV-1 from HTLV-2.[72,73]

HTLV-1 infection is widespread in tropical and subtropical regions, with the main endemic foci in the Caribbean, southern Japan, central Africa, South Africa, and South America, particularly Brazil. Other endemic foci are found in southern India, northern Iran, aboriginal populations of northern Australia, and islands in the tropics. In Europe and North America, HTLV-1 infection is primarily associated with injection drug users and with immigrants from endemic areas. In endemic areas, the seroprevalence varies widely, even in communities located close together, and ranges from 0.1 to 30%. The seroprevalence is higher in costal communities.[74]

HTLV-1 is associated with adult T-cell leukemia/lymphoma (ATLL), with a form of chronic progressive neurologic disease known as HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP).[75] HTLV-1 is also associated with inflammatory conditions including polymyositis, arthropathy, infective dermatitis, and uveitis. The time from exposure to onset of HTLV-1 related disease is long--from 2 to 3 decades on average. However, the lifetime risk for ATLL in infected persons is only about 5% for persons infected before the age of 20. There is an additional 5% risk for the less serious complications of infectious dermatitis, uveitis, polymyositis, and arthropathy. The lifetime risk for HAM/TSP is about 1-2%. ATLL is uniformly fatal, while HAM/TSP is not. Men are more likely to develop ATLL, while HAM/TSP is more common in women.[74] Persons infected with HTLV-1 infection tend to have higher creatine kinase and lactate dehydrogenase levels in serum than seronegative persons.[76]

HTLV-2 has been identified as an endemic infection in two distinct populations: native peoples of the New World and pygmy tribes of Africa. In other populations, the spread of HTLV-2 occurs primarily as a result of injection drug use, particularly in metropolitan areas.[77] There is no clear association between HTLV-2 and HTLL, but chronic neurologic disease, particularly spinocerebellar syndrome, may be linked to HTLV-2 infection.[78]

EPIDEMIOLOGY OF AIDS

Considerable epidemiologic and clinical work has been performed to understand the transmission of HIV from one person to another. As in past epidemics, the spread of AIDS is facilitated by human travel. Syphilis in the 16th century, bubonic plague in the 17th century, and influenza early in the 20th century also arose from endemic foci to become widespread. Modern means of travel by jet aircraft readily available to many people provide an easy route for the spread of AIDS from one location or population to another.[79]

However, unlike most infections in past epidemics, AIDS is distinguished by a very long latent period before the development of any visible signs of infection in affected persons. The average HIV-infected person may have an initial acute self-limited illness, may take up to several weeks to become seropositive, and then may live up to 8 or 10 years, on average, before development of the clinical signs and symptoms of AIDS. In virtually all past infectious disease epidemics, infected persons were soon easily recognized so that measures could be taken to prevent the spread of disease. But persons infected with HIV cannot be recognized by appearance alone, are not prompted to seek medical attention, and are often unaware that they may be spreading the infection.[25,36,80]

The transmission of HIV is a function both of where the virus appears in the body and how it is shed. HIV can be present in a variety of body fluids and secretions, as shown in Table 1. The presence of HIV in genital secretions and in blood, and to a lesser extent breast milk, is significant for spread of HIV. However, the appearance of HIV in saliva, urine, tears, and sweat is of no major clinical or social importance, as transmission of HIV through these fluids does not routinely occur, primarily because of the low concentration of HIV in these fluids.[81] Though infectious particles of HIV are frequent in cerebrospinal fluid, contact with this fluid in daily life is extremely rare.[18,82]

The most important feature of HIV is the means of spread (Table 2). Unlike most epidemics of infectious diseases wherein much of a population is at risk, HIV infects definable population subgroups ("risk groups"). This happens because HIV is primarily a sexually transmissible disease. Homosexual, bisexual, and heterosexual transmission all can occur. Although sexual intercourse between males has remained the greatest risk for transmission in developed nations of Western Europe and the United States, heterosexual transmission is increasing in those regions but still remains less common than in Africa, Asia, or parts of the Caribbean.[80,83,84]

Transmission of HIV can occur from male to male, male to female, and female to male. Female to female transmission remains extremely rare, though women with same-sex contact are also often bisexual and have additional risk factors for HIV infection.[85,86] Even a partial modification of sexual behavior practices may help retard the rate and extent of HIV transmission. Amongst males having sex with males in the U.S. in the 1990's, the prevalence of HIV infection remained high at 7.2%, and the prevalence of unprotected anal intercourse over a prior 6 month period was 41%.[87]

Educational efforts in AIDS prevention must be ongoing and must specifically target not only persons belonging to identifiable risk groups for HIV infection but also teenagers beginning sexual intercourse (and who often lack a sense of their own mortality), as well as young adults. The Centers for Disease Control in the U.S. has a strategic plan to reduce HIV infection through a three-part plan that includes: (1) intensifying efforts to help all infected persons learn their HIV status; (2) establishing new prevention programs to help HIV-infected persons establish and maintain safer behaviors, combined with improved linkages to treatment and care; and (3) expanding highly targeted prevention programs to reach all HIV-negative persons at greatest risk.[88]

Worldwide, heterosexual transmission accounts for the majority of cases of HIV infection. The important factors that promote heterosexual transmission include:[89]

- More sexual partners
- Frequent change of sexual partners
- Unprotected sexual intercourse (lack of barrier precautions)
- Presence of additional sexually transmitted diseases
- Lack of male circumcision
- Social vulnerability of women and young persons
- Economic and political instability of the community

The lack of economic and political stability makes it difficult to institute programs to change behavior, to promote condom use, to treat sexually transmitted diseases, to test for HIV infection, and to treat HIV infection with antiretroviral therapies that reduce viral load and the risk of transmission.[89]

Practicing "safe" sex will diminish the prevalence of HIV infection in populations where HIV has become well established. Though transmission of HIV can be reduced, it cannot be completely eliminated once it is established in a population.[12,13,90] Risk reduction interventions, including education on abstinence and safer sex, are beneficial. Abstinence intervention has a short term effect over months, while safer sex interventions have a longer lasting effect, particularly amongst adolescents who have previously had sexual intercourse. These interventions appear to reduce the frequency of sexual intercourse.[91] Promotion of the use of condoms as a barrier precaution has also been shown to reduce the rate of HIV infection, and is a mainstay of prevention efforts.[92] The availability of condoms has a significant effect upon condom use and does not appear to increase rates of sexual activity.[93]

There are three major variables that explain the sexual transmission of HIV: (1) transmission efficiency, (2) number of sexual partners, and (3) seroprevalence (numbers of infected individuals in a population). HIV transmission through sexual exchange of semen or vaginal fluids is much less efficient than transmission of either gonorrhea or hepatitis B virus. Usually, multiple sexual exposures are necessary to increase the likelihood for transmission of HIV from infected persons. It is estimated that gonorrhea may be transmitted in 22 to 25% of sexual encounters involving an infected individual, hepatitis B virus in 20 to 30% of encounters, and hepatitis C in 2% of sexual encounters, while HIV transmission occurs much less often--approximately 0.3% per sexual contact with an HIV-infected person. However, some persons have become HIV-infected after a single sexual contact, while other persons have remained uninfected after hundreds of contacts.[94,95]

The rate of sexual transmission of HIV may depend upon the number of viral particles in genital secretions. The number of CD4 cells per μL of seminal fluid ranges from 10^2 to 10^3, while the number of virions can range from undetectable to over 10^6. The numbers of virions in the female genital tract is generally lower. Transmission can occur both cell-to-cell as well as from cell-free fluid.[96,97] Thus, the transmission rate is two to three times higher from infected males to females than from infected females to males, without other cofactors.[98]

The location of HIV in cells of the genital tract of infected persons varies between men and women. In men, both the cells within seminal fluid, as well as the seminal fluid, harbor virions of HIV, but spermatozoa are not a major source for HIV. In women, the greatest number of virions are present at the squamocolumnar junction of the cervix, with far less HIV in vaginal epithelium. Langerhans cells and macrophages in the lamina propria capable of harboring HIV can be found in a variety of epithelia.[99] Since most of the cell-free HIV in the semen of men arises distal to the vas deferens, a vasectomy may have minimal impact on the infectivity of seropositive males to sexual partners.[100]

For persons who have regular intercourse with a single HIV infected (index) partner, risk of transmission of HIV-1 depends upon the stage of HIV-1 infection. The risk is highest, 0.0082/coital act, within 2.5 months of seroconversion of the index partner. The risk drops to 0.0015/coital act within 6 to 15 months after index partner seroconversion and remains low throughout the stage of clinical latency of HIV-1 infection. The risk rises again in the late stage of clinical AIDS, 0.0028/coital act, within 6 to 25 months of death of the index partner.[101]

The rate of HIV sexual transmission may also be due to the low infectivity of an individual strain of virus, propensity for only selected individuals to transmit infective virus in secretions, or presence of individual susceptibility factors.[68] Some HIV-1 subtypes may be more easily transmitted heterosexually, particularly subtype E which is more prevalent in Asia and sub-Saharan Africa. There is a greater tropism of the E subtype for Langerhans cells than subtype B which is more prevalent in the U.S. and Europe.[60,99]

Sexual contact with persons whose HIV viral load is greater increases the transmission risk. The risk for HIV transmission from an HIV-infected person increases as that person's immune status diminishes, as measured by a decrease in CD4 lymphocytes or an increase in HIV-1 RNA in plasma, so that infectivity is greater in the later stages of AIDS; likewise, a greater risk for transmission exists with the pronounced HIV viremia during primary HIV infection. Transmission rarely occurs when the HIV-1 RNA level in serum is less than 1500 copies/mL.[102] Persons with HIV infection undergoing antiretroviral therapy that measurably lowers the viral burden in blood will have a reduction in viral particles in genital fluids of men and women that will render them less infective to others.[103,104] However, even with aggressive antiretroviral therapy, HIV may be detectable at low levels in blood and genital fluid.[105]

The presence of specific chemokine receptors plays a role in HIV transmission. Chemokine receptors provide a pathway, separate from CD4 receptors, for entry of HIV into cells. Mutations in the chemokine receptor genes appear to afford increased resistance to HIV infection or progression of disease for hosts homozygous for this genetic trait. Approximately 11% of Caucasians and 2% of Blacks are homozygous for the CCR5-delta32 mutation.[99]

The presence of cervical ectopia, oral contraceptive use, or pregnancy or menstruation in women, intact foreskin in men, and genital ulcer disease in either sex increases the risk for HIV infection. Thus, male circumcision affords some degree of protection, perhaps due to the large numbers of Langerhans cells in foreskin, so that the incidence of infection is reduced 8-fold over uncircumcised men. Cervical ectopy, with replacement of squamous by columnar epithelium, may increase the risk of HIV infection for women 5-fold.[94,99,106] The greatest determinant of HIV in cervical and vaginal secretions is the plasma level of HIV-1 RNA.[107] Increased detection of HIV can occur in women with vitamin A deficiency and in women receiving high dose oral contraceptives or depot contraceptives.[108]

There are a variety of mechanisms by which the coexistence of other sexually transmissible diseases (STDs) may increase the infectivity of HIV. Both *Chlamydia trachomatis* and *Treponema pallidum* infection appear to increase HIV-1 replication, while *Haemophilus ducreyi* infection increases CCR5 chemokine coreceptor expression by macrophages. In men, urethritis with infection by *Neisseria gonorrhoeae* and *Trichomonas* has been shown to increase the amount of HIV-1 in semen. Likewise, in women cervicovaginal fluids contain more HIV-1, as well as CD4 cells when additional STDs are present. *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas*, or diseases producing genital ulcers such as herpes simplex virus, chancroid (*Haemophilus ducreyi*) or syphilis (*Treponema pallidum*), all enhance infectivity by HIV. For example, HIV-1 virions can consistently be detected in genital ulcers caused by herpes simplex virus-2. Treatment of these STDs can help to reduce the number of new HIV-1 cases.[99,109,110] The cofactor effect of genital ulcer disease is approximately five times higher for female-to-male than for male-to-female transmission. A higher prevalence of STD's in the population will equalize HIV transmission between the sexes.[98]

The use of crack cocaine can increase the transmission rate for HIV with oral sex. This increase in infectivity can be due either to the greater numbers of oral sores with inflammatory cells containing HIV in the infected person or to the increased numbers of inflammatory cells with CD4 receptors in the contact person waiting to become infected, from the loss of an intact epithelial barrier.[111]

Genital ulcers with inflammation also provide a more direct route to lymphatics draining to lymph nodes containing many CD4 lymphocytes, macrophages, and follicular dendritic cells.[112] Tissue trauma during intercourse does not appear to play a role in HIV transmission.[94] HIV-1 can be demonstrated in semen even in the first few weeks following infection.[113] The

transmission of HIV can occur with the act of sexual intercourse in any style or position, though a greater relative risk exists with anal receptive intercourse.[94]

Once HIV is introduced into a promiscuous population, seroprevalence increases with time. Increasing the number of sexual partners increases the likelihood of contacting a seropositive individual.[114,115] If the number of infected individuals in a population is high, then even one sexual encounter carries a significant probability of contacting an infected individual. This was demonstrated in one high risk group over a three year period (1978-1981) early in the AIDS epidemic in which the HIV infection rate was 44%.[116] Overall, the most important factor for both the spread and the risk of infection from HIV is the degree of sexual activity with multiple sexual partners.[95]

HIV has another important secondary means of spread through blood or blood products (Table 2). Parenteral exposure to blood and blood products is the most highly efficient method of HIV transmission--close to 90%.[117] There are many more peripheral blood mononuclear cells capable of either harboring or becoming infected by HIV in blood than are present in other body fluids or secretions. The number of infectious HIV particles free in peripheral blood can range from undetectable to well over a million per mL.[102]

The primary risk group for HIV transmission via blood is intravenous drug users sharing infected needles. If needles are not shared, then this form of transmission will not occur. Less common practices of blood commingling, or use of instruments such as tattoo needles not properly disinfected, also carries a potential risk (Table 2). Health care workers with percutaneous exposures to HIV-containing blood, however, are infected fewer than 1 in 300 times.[118,119]

Before laboratory tests were developed to detect HIV, persons who received blood or blood products by transfusion were also at risk. Now when rigorous testing of donor blood is routinely done, this form of infection is extremely rare-- with a risk for occurrence of 1 case for 1 900 000 single donor units of screened blood for persons receiving transfusions of blood products in the U.S.[120] However, in developing nations where economic and political problems interfere with screening programs for blood products, 5 to 10% of HIV infections may occur from exposure to infected blood products.[121]

Even though HIV has been found in a variety of body fluids such as saliva, urine, feces, and tears, non-sexual transmission of HIV by these body fluids is improbable.[118,122,123] There is no evidence for HIV transmission by the aerosol route.[119] The lack of transmission is related in part to the paucity of HIV-infected cells in such secretions. Oral transmission of HIV is further impeded by the hypotonic inactivation of HIV-transmitting inflammatory cells by saliva. Oral transmission of HIV by seminal fluid, milk, and colostrum may be due to their isotonicity, which overcomes hypotonic salivary inactivation. Even though the amount of virus is small in body secretions and presents a very small risk with routine household contact, prolonged contact or contact in sexually intimate situations with such fluids should be avoided.[124]

Routine transmission of HIV occurs only through semen, vaginal fluid, blood or blood components, and breast milk.[18,125] In a liquid environment at room temperature, the virus can survive for at least 15 days, but despite HIV presence and survival in such an environment, infection through casual household and institutional contacts is rare, even when hepatitis is transmitted in the same setting.[122,126,127] Significantly, HIV transmission by insect vectors such as mosquitos appears highly improbable.[123]

HIV infection can also be acquired as a congenital infection perinatally or in infancy (Table 2). Mothers with HIV infection can pass the virus to their babies transplacentally, at the time of delivery through the birth canal, or through breast milk. In the absence of breast-feeding, intrauterine transmission accounts for 25 to 40% of infections, while 60 to 75% occur during labor and delivery.[128] The probability of breast-milk transmission of HIV-1 is calculated to be 0.00064 per liter ingested and 0.00028 per day of breast-feeding. Breast-milk infectivity is significantly higher for mothers with more advanced disease with higher prenatal HIV-1 RNA plasma levels and CD4 cell counts. The probability of HIV-1 infection per liter of breast milk ingested by an infant is similar in magnitude to the probability of heterosexual transmission of HIV-1 per unprotected sex act in adults.[129]

Vertical transmission of HIV-1 from mother to child from breastfeeding has been estimated to occur in 14% to 16% of women who breast-feed with established maternal HIV-1 infection and in 29% with acute maternal HIV-1 infection. The risk for HIV-1 transmission from an infected mother to an infant through breast feeding is increased with the duration of breast feeding and with increased maternal viral load.[130] The risk is also increased with mastitis or breast abscess.[131] Most cases of transmission occur early during breastfeeding. HIV-1 can be detected in over half of breast milk samples from infected mothers.[125,128,132]. Replication of HIV-1 within mammary epithelial cells has been demonstrated, and is increased by hormonal stimulation in pregnancy.[133]

Perinatal transmission with congenital AIDS occurs, on average, in about one fourth of babies born to HIV-1 infected mothers, with actual rates of transmission varying from 7 to 71%, depending upon the presence of risk factors for transmission during the course of HIV infection and pregnancy. The most significant maternal risk factor for perinatal transmission is the HIV-1 DNA load, followed by the HIV-1 RNA load.[134] Additional maternal factors cited for congenital HIV-1 transmission are: a low CD4 lymphocyte count, p24 antigenemia, prematurity, and placental chorioamnionitis or funisitis. Parity, race, mode of HIV acquisition, and sex of the baby do not appear to be factors in the vertical transmission of HIV.[135,136] The likelihood of vertical HIV-1 transmission is reduced by half with delivery by elective cesarean section, as compared with other modes of delivery.[137]

Features of HIV-1 that appear to correlate with perinatal transmission include: rapid or high-titered replication in maternal human peripheral blood mononuclear cells, T-cell tropism, and resistance to neutralization or a sensitivity to enhancement of infection by maternal serum.[136] Also, an amniocentesis procedure, premature rupture of membranes, preterm labor, genital warts, and the presence of sexually transmitted diseases during pregnancy also increases the risk for transmission. Transmission most likely occurs in late third trimester and intrapartum.[138,139]

Measurement of maternal HIV-1 RNA can predict perinatal transmission risk. High levels of HIV-1 RNA late in gestation and/or during labor and delivery increase the risk for perinatal transmission.[140] The frequency of perinatal HIV-1 transmission in the first and second trimesters is low.[141] Though HIV-1 transmission from mother to fetus may still occur over a wide range of plasma HIV-1 RNA levels and of CD4 lymphocyte counts, antiretroviral therapy that reduces the HIV-1 RNA level to below 500 copies/mL appears to minimize the risk of perinatal transmission as well as improve the health of the mother. Thus, the maternal HIV-1 RNA level can predict the risk, but not the timing, of HIV transmission to their infants.[142,143]

To date, most reported perinatal HIV-1 cases in the United States have been a consequence of intravenous drug use by mothers, but an increasing proportion of cases is appearing from heterosexually acquired HIV by mothers.[135] Congenital AIDS is most common in populations where heterosexual HIV transmission and the frequency of women infected with HIV is higher. In contrast, perinatal transmission of HIV-2 occurs far less frequently, with a rate of only 1 to 2%.[144]

PATTERNS FOR HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Worldwide, three patterns of HIV infection have been identified. In pattern 1, affecting primarily urban areas of the Americas and western Europe, the majority of HIV infections occur in males having sexual intercourse with other males (homosexual and bisexual males), followed by infections in intravenous drug users. Fewer cases are observed among heterosexuals. Pattern 2 occurs in those areas in which HIV has been present longer and the number of HIV-infected persons in the population is greater. Men and women are affected equally, and heterosexual intercourse is the major means of transmission for HIV. These areas include sub-Saharan Africa and parts of the Caribbean where HIV infection occurs throughout the heterosexual population, and congenital AIDS is a significant problem. Pattern 3 occurs in areas of the world in which HIV has been introduced only recently, defined risk groups have not emerged, and only sporadic cases are reported.[145] Once HIV is well-established in a population, the median age at infection declines over time.[146]

RISK GROUPS FOR HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Risk groups for HIV infection based upon behavior patterns that put persons at risk are detailed in Table 2. In Pattern 1 countries such as the United States, through the first decade of the AIDS pandemic, about half of AIDS cases have been reported in homosexual or bisexual. The second largest risk group is comprised of intravenous drug users, accounting for 20% to 25% of reported AIDS cases in the United States.[80,147] The percentage of HIV infections seen in heterosexual adults is increasing in developed nations. Pediatric AIDS in the United States is largely a function of maternal risk factors, particularly from intravenous drug use. In Pattern 2 countries, particularly in Africa, HIV infection is spread more widely in the population through heterosexually active urban adults.[115]

The demography of the spread of HIV depends upon the population subgroups into which HIV has been introduced and the contact that other segments of the population have with them. Thus, prostitution and intravenous drug use may both be an important means for spread of HIV through the heterosexual population. AIDS among heterosexual adults in the United States is increasing more than any other risk group, and over half of all heterosexually acquired HIV infections occur in women. This represents a significant risk to the promiscuous or intravenous drug using heterosexual person. Screening of blood products for HIV has almost completely eliminated the risk from transfusion or blood product therapy in locations where such screening is routinely performed.[148]

On average, about 5 to 10% of persons who develop AIDS will report no identifiable risk factor for HIV infection. Over time, many of them will be found to have a defined risk factor when historical data becomes available. The number of cases of HIV infection with no identifiable risk factor has not increased significantly over time, confirming the observation that HIV infection is not acquired through casual contact.[80,127]

NATURAL HISTORY OF HIV INFECTION

On average, there is a period of 8 to 10 years from initial infection to clinical AIDS in adults, though AIDS may be manifested in less than two years or be delayed in onset beyond 10 years.[149] About 10% of persons will rapidly progress to AIDS in 2 to 3 years following HIV infection, while about 10% have not progressed to AIDS even after 10 years.[150] It is clear that the longer an individual is infected, the more likely the development of illness and subsequent death will be. Thus, HIV infection does not follow the pattern of more traditional viral diseases in which the risk of serious illness or death decreases with time. There has been no study to date that shows a failure of HIV-infected persons to evolve to clinical AIDS over time, though the speed at which this evolution occurs may vary, and a small number of HIV-infected persons will not progress to AIDS for many years.[80]

Primary HIV infection, also known as acute retroviral syndrome, may produce a mild and self-limited disease in 50 to 90% of persons infected with HIV, regardless of the mode of transmission. The time from mucosal infection to viremia is about 4 to 11 days. The time from exposure to development of symptoms averages 2 to 6 weeks. The symptoms may persist for 1 to 2 weeks, after which symptoms subside over 1 to 2 months. Prospective studies of acute HIV infections show that fever, fatigue, arthralgia or myalgia, lymphadenopathy, pharyngitis, diffuse erythematous macular or mixed maculopapular rash (often involving the trunk), diarrhea, nausea or vomiting, weight loss, night sweats, mucocutaneous ulcerations, and headache are the most common symptoms seen with acute HIV infection. An acute meningoencephalitis may be seen in some recent infections and appear as an "aseptic meningitis." The symptoms of acute HIV infection resemble a flu-like or an infectious mononucleosis-like syndrome. Primary HIV infection is not life-threatening.[151,152] Primary HIV infection in children is usually accompanied by one or more of the following: mononucleosis-like syndrome, dermatitis, or generalized lymphadenopathy.[153]

In acute HIV infection, the peripheral blood may demonstrate lymphopenia and/or thrombocytopenia. However, atypical lymphocytes are absent. Although the CD4 cells are decreasing, the levels may initially remain in the normal range, but depletion continues. Simultaneously, there is an increase in cytotoxic CD8 lymphocytes that continues as symptoms subside and viremia decreases.[152]

During this acute phase of HIV infection, there is active viral replication, particularly in CD4 lymphocytes, and a marked HIV viremia. This peripheral blood viremia is at least as high as 50,000 copies/mL and often in the range of 1,000,000 to 10,000,000 copies/mL of HIV-1 RNA. High titers of cytopathic HIV are detectable in the blood so that the p24 antigen test is usually (but not always) positive, while HIV antibody tests (such as enzyme immunoassay) are often negative in the first three weeks. The viremia is greater in persons whose primary HIV infection is symptomatic.[17,54,151,152]

During this viremic phase, HIV disseminates throughout the body to lymphoid tissues and other organs such as brain. There are alterations in peripheral blood mononuclear cells marked by a decline in CD4+ lymphocytes. Persons acutely infected with HIV are highly infectious as a consequence of the high levels of HIV, both in blood as well as in genital secretions. Over half of all HIV infections may be transmitted during this period.[151]

Generally, within 3 weeks to 3 months following initial infection with HIV, the immune response is accompanied by a simultaneous decline in HIV viremia. Both humoral and cell mediated immune responses play a role. The CD4 lymphocytes rebound in number after primary HIV infection, but not to pre-infection levels. Seroconversion with detectable HIV antibody by laboratory testing such as enzyme immunoassay accompanies this immune response, sometimes in as little as a week, but more often in two to four weeks.[17,18,37] Prolonged HIV-1 infection without evidence for seroconversion, however, is an extremely rare event.[154] Persons infected with HIV who develop an acute retroviral illness and who have a shorter time to seroconversion tend to progress to AIDS faster than persons with longer seroconversion times.[155]

The HIV infection then becomes clinically "latent." During this phase, there is little or no viral replication detectable in peripheral blood mononuclear cells and little or no culturable virus in peripheral blood. The CD4 lymphocyte count remains moderately decreased. However, the immune response to HIV is insufficient to prevent continued viral replication within lymphoid tissues. Though lymph nodes may not become enlarged and their architecture is maintained, active viral replication continues.[29,156] Tests for HIV antibody will remain positive during this time but p24 antigen tests are usually negative. There is no evidence to suggest that seroreversion, or loss of antibody, occurs in HIV-infected persons.[157]

Though the time to development of AIDS is statistically similar in men and women, the viral load of women tends to be lower. Women with half the viral load of men have a similar time to development of AIDS as men. Women with the same viral load as men have a 1.6-fold higher risk of AIDS. The biologic basis for this difference is unclear.[158]

In many viral infections, an immune response consisting of virus-specific CD4 lymphocytes helps to contain the infection. However, such a response is typically lacking in HIV-infected persons. A minority of HIV-infected persons, however, do mount a persistent polyclonal CD4 lymphocyte proliferation directed against HIV which controls viremia. This response results in a cytokine response with elaboration of interferon gamma and beta chemokines. Such a response may also occur with antiretroviral therapy.[159]

As FDC's are diminished over time with HIV infection, the capacity for stimulation of CD4 lymphocytes is also diminished, and CD4 memory cells decline as well. However, remaining FDC's continue to promote ongoing production of antibody to HIV. CD4 memory cells may also be lost by formation of syncytia with infected FDC's. Finally, when the stage of AIDS is reached, development of FDC's from stem cells is diminished.[58]

Though no clinical signs and symptoms are apparent, the immune system, primarily through depletion of CD4 lymphocytes, deteriorates. The virus continues to replicate in lymphoid organs, despite a low level or lack of viremia.[37] HIV can be found trapped extracellularly in the follicular dendritic cell network of germinal centers in lymphoid tissues or intracellularly as either latent or replicating virus in mononuclear cells. The period of clinical latency with HIV infection, when infected persons appear in good health, can be variable--from as short as 18 months to over 15 years. This latent period lasts, on average, from 8 to 10 years.[17,37] This interval tends to be longer with earlier age at time of initial infection with HIV.[146]

The hallmarks of emergence of HIV infection from clinical latency are a marked decline in the CD4 lymphocyte count and an increase in viremia. Replication of HIV increases as the infection progresses. There is loss of normal lymph node architecture as the immune system fails. Before serologic and immunologic markers for HIV infection became available, clinical criteria established emergence from latency by development of generalized lymphadenopathy. This condition, described by the term persistent generalized lymphadenopathy (PGL), is not life-threatening.[18]

Another phase of HIV infection described clinically but no longer commonly diagnosed in practice, is the condition known as AIDS-related complex (ARC), which is not necessarily preceded by PGL. ARC lacks only the opportunistic infections and neoplasms which define AIDS. ARC patients usually show symptoms of fatigue, weight loss, and night sweats, along with superficial fungal infections of the mouth (oral thrush) and fingernails and toenails (onychomycosis). It is uncommon for HIV-infected persons to die at the stage of ARC. The staging of HIV disease progression through the use of CD4 lymphocyte counts and plasma HIV-1 RNA levels has made use of the terms PGL and ARC obsolete.[18]

The stage of clinical AIDS that is reached years after initial infection is marked by the appearance of one or more of the typical opportunistic infections or neoplasms diagnostic of AIDS by definitional criteria. The progression to clinical AIDS is also marked by the appearance of syncytia-forming (SI) variants of HIV in about half of HIV-infected patients. These SI viral variants, derived from non-syncytia-forming (NSI) variants, have greater CD4+ cell tropism and are associated with more rapid CD4+ cell decline. The SI variants typically arise in association with a peripheral blood CD4 lymphocyte count between 400 and 500/μL, prior to the onset of clinical

AIDS. However, appearance of the SI phenotype of HIV is a marker for progression to AIDS that is independent of CD4+ cell counts.[55]

PROGRESSION OF HIV INFECTION

The development of signs and symptoms of AIDS typically parallels laboratory testing for CD4 lymphocytes. A decrease in the total CD4 lymphocyte count below 500/μL presages the development of clinical AIDS, and a drop below 200/μL not only defines AIDS, but also indicates a high probability for the development of AIDS-related opportunistic infections and/or neoplasms. The risk for death from HIV infection above the 200/μL CD4 level is low.[160,161,162]

Other laboratory findings which indicate progression to AIDS include HIV p24 antigen positivity, increased serum beta$_2$-microglobulin (B2-M), elevated serum IgA, or increased neopterin levels in serum, cerebrospinal fluid, or urine. The p24 antigen is a highly specific predictor of progression, but only about 60% of HIV-infected persons develop p24 antigenemia prior to onset of clinical AIDS. B2-M is a polypeptide that forms the light chain of the class I major histocompatibility complex found on the surface membrane of most cells, including lymphocytes. It is increased with lymphocyte activation or destruction associated with HIV disease progression, but B2-M can also be elevated with viral infections such as cytomegalovirus and with malignant lymphomas. Neopterin, a product of macrophages, is also a measure of immune system activation and can predict HIV disease progression. The information provided by these tests is similar, so no advantage accrues from performing all of them simultaneously.[163]

The best laboratory measure for determination of the progression of AIDS is the level of HIV-1 RNA in peripheral blood. The predictive value of HIV-1 RNA levels is independent of the CD4 lymphocyte count and of age in adults. During the acute phase of HIV infection prior to any immune response, plasma levels of HIV-1 RNA typically exceed 10,000 copies/μL. There is a sex difference. The initial viral load following HIV infection is 50,766 copies/mL in males and 15,103 copies/mL in females.[158]

These levels of HIV-1 RNA generally drop, but fluctuate for a period of 6 to 9 months. After this time, a "set point" is reached for the level of HIV-1 RNA that remains relatively constant during the latent phase of HIV infection. Factors influencing this set point include the strain of HIV-1, host anti-HIV response, and the number of cells, including CD4 lymphocytes and macrophages, available for infection. The initial viremia may be higher, and the set point may not be reached until after infancy in cases of congenital HIV infection.[164]

The set point levels of HIV-1 RNA correlate with the time to development of AIDS. The set point can range from <50 to 1,000,000 copies/mL. Persons with a higher set point tend to lose CD4 cells more rapidly and progress to AIDS more quickly. Levels of HIV-1 RNA can remain at a steady state for months to years, but usually fall with time. Levels in any individual person may vary with time and even change rapidly, though a variation of <0.7 $\log_{10}$ copies/mL is typical, but an upward progression is an ominous sign of probable progression to AIDS. Less than half of persons with low levels (<4500 copies/mL) of HIV-1 RNA have progressed to AIDS at 10 years following seroconversion, and those with levels <200 copies/mL do not appear to progress at all. Conversely, persons with >100,000 copies/mL are 10 times more likely to progress to AIDS in 5 years. For persons in the top quartile (>36,270 copies/mL) the median time to development of AIDS is 3.5 years.[54,164] The presence of opportunistic infections and neoplasms increases the risk for progression to death from HIV infection.[165] In spite of the initial viral load difference between men and women, the rates of progression to AIDS are similar.[158]

Persons with HIV infection can be categorized as typical progressors, rapid progressors, and nonprogressors toward AIDS. The typical progressors average 8 to 10 years of "latent" HIV infection before the appearance of clinical AIDS. These persons typically have a fall in HIV viremia following acute infection. They maintain nonsyncytium-inducing HIV variants that replicate slowly over time, until more rapidly replicating variants develop during progression to AIDS. About 10% of HIV-infected persons rapidly progress to AIDS in only 2 to 3 years following initial infection. These persons have a high viral load during acute HIV infection that does not fall to the levels seen with typical progressors. They may be infected with more virulent

strains of HIV.[150] More rapid progression to AIDS is also seen in Caucasians who have the major histocompatibility complex (MHC) class I type HLA-B*35 allele.[166]

Though most HIV infections follow a standard progression, the course can be variable, and previously asymptomatic persons may suddenly die from an overwhelming opportunistic infection, while persons with clinically defined AIDS may survive for years. Progression to AIDS in persons with HIV infection does not appear to be modified by gender, by race, or by pregnancy, and the course of HIV infection is not modified by risk factor for infection. Progression to AIDS does appear to be accelerated in persons who are older or who smoke.[167,168,169,170] Older age at seroconversion is associated with faster progression to AIDS.[171] Persons who manifest symptomatic acute HIV infection have a faster progression to clinical AIDS.[151]

Co-infection with the flavivirus GB virus C (GBV-C), also known as hepatitis G virus, is associated with a slower rate of progression of HIV infection with a reduced mortality rate. Hepatitis G virus itself is not known to be associated with any specific disease process. However, the presence of GBV-C may inhibit HIV replication, as shown in vitro with inhibition of HIV with coinfection of peripheral blood mononuclear cells by GBV-C. The prevalence of GBV-C is 1.8% in blood donors, though its presence does not preclude blood donation. The prevalence of GBV-C in HIV infected persons is about 40%.[172]

Dietary supplementation with the trace element selenium has been demonstrated to partially suppress induction of HIV-1 replication in chronically infected mononuclear cells exposed to tumor necrosis factor (TNF). Selenium supplementation also appears to increase cellular antioxidant activity. These findings may account for the observation that selenium deficiency is associated with increased mortality from HIV-1 infection.[173,174]

About 10% of persons infected with HIV-1 are nonprogressors, or "long survivors," who do not demonstrate a significant and progressive decline in immune function over more than 10 years. They do not appear to progress to AIDS in a manner similar to the majority of HIV-infected persons. Findings in these "long survivors" include: a stable CD4 lymphocyte count, negative plasma cultures for HIV-1, fewer HIV-infected cells, and a strong virus-inhibitory CD8+ T-lymphocyte response. Differences in viral load do not appear to be associated with viral subtype, viral growth kinetics, or with the presence of neutralizing antibodies.[175]

In addition, by microscopic examination the lymph node architecture of "long survivors" with HIV infection is maintained without either the hyperplasia or the lymphocyte depletion that is common to progression to AIDS. Though peripheral blood mononuclear cells contain detectable HIV-1 and viral replication continues in long survivors, their viral burden remains low.[176] A strong host virus-specific CD4 lymphocyte response in these persons may also aid in controlling HIV viremia.[159]

There is evidence that genetic polymorphisms in the chemokine receptors present on cells susceptible to HIV infection may play a role in progression of AIDS. At least in some persons infected with HIV, the presence of chemokine receptor variants, including the CCR5 delta32 deletion or the CCR2B-64I mutation, have a favorable effect in slowing the progression of disease. The CCR5 gene encodes the coreceptor for macrophage-tropic HIV-1, so reduced expression of CCR5 leads to reduced HIV-1 replication in macrophages.[177] A lower density of CCR5 molecules on peripheral blood mononuclear cells has been shown to correlate with lower plasma HIV-1 RNA levels and reduced loss of CD4 cells over time.[178] Patients homozygous for the chemokine receptor CX3CR1 progress to AIDS more rapidly than those with other genotypes.[179]

Genetic variations in major histocompatibility (HLA) genes may determine HIV disease progression. An HIV-1 envelope glycoprotein fragment mimics both HLA class 1C molecules and an immune regulatory epitope in the HLA DR beta chain which furnishes peptides predicted to bind optimally to HLA class 1B alleles. The HLA class I genes A29 and B22 are significantly associated with rapid progression, while the alleles B14 and C8 are significantly associated with non progression of AIDS.[180,181]

For perinatally acquired HIV infection, the time period from birth or neonatal life to the development of clinical AIDS is variable and may be shorter than in adults. Clinical signs associated with HIV infection appear in over 80% of seropositive infants by the age of 5 months.

Infants in whom such signs appear at 3 months or less tend to have decreased overall survival. On average, about half of children with perinatally acquired HIV infection are alive at 9 years, though use of antiretroviral therapy decreased the death rate significantly.[182,183]

The level of HIV-1 RNA rises rapidly in the first one to two months of life but remains high, and declines only slowly during the first two years of life. This suggests that the neonatal and infant immune system is not able to effectively contain HIV replication. Those babies whose HIV-1 RNA levels are very high, not only in the first few months of life, but also in the first two years, tend to progress to AIDS more rapidly than those with lower levels.[184]

Progression of disease appears to be faster in children whose strains of HIV-1 show tropism for monocyte-derived macrophages and whose viral strains are rapidly replicating.[185] Skin test anergy as demonstrated by the loss of delayed-type hypersensitivity to standard antigens such as *Candida* and *Trichophyton* also correlates with HIV disease progression.[186]

Adolescents with HIV infection may have variable courses. Those who acquired HIV infection during adolescence, generally via sexual intercourse or via injection drug use, tend to have progression of their infection similar to adults. Those with congenital AIDS or who acquired their infection from blood products as young children will have a course different from long-term surviving adults.[164]

In summary, there are a variety of factors that can influence the time course over which persons infected with HIV will progress to AIDS. In general the prognosis for infected persons is worse from probable accelerated progression when:

- Less favorable chemokine receptor variants are present
- Syncytia-forming (SI) variants of HIV are present
- Acute HIV infection is symptomatic
- HIV infection occurs with a drug-resistant strain
- A higher "set point" of HIV-1 RNA follows initial viremia after infection
- There is an older age at seroconversion
- The infected person is a smoker
- An opportunistic infection or neoplasm is present
- In congenital cases there are signs of infection at <3 months of age

In addition, progression to AIDS from the period of clinical latency in persons with HIV infection is suggested by:

- CD4 lymphocyte counts <500/μL
- Failure to maintain normal lymph node function
- p24 antigenemia appears in peripheral blood
- Increasing HIV-1 RNA levels

IDIOPATHIC CD4+ T-LYMPHOCYTOPENIA

Increased laboratory testing in patients with immunodeficiency states has led to the recognition that CD4 lymphocyte counts in some cases can be markedly decreased in the absence of laboratory evidence for HIV infection. These uncommon, sporadically reported cases are unlikely to represent infection by new HIV subtypes that are not detectable by current laboratory testing methods. Criteria for diagnosis of ICL include:

- The absolute CD4 lymphocyte count is <300/μL or more in adults and children >2 years (<1000/μL in children <2 years) on more than one determination, or in children a T-lymphocyte count that is <20% of total lymphocytes; and
- There is no serologic evidence for HIV infection (even if in a child and the mother is HIV seropositive); and
- There is no defined immunodeficiency or therapy associated with T-cell depletion

Though some patients with ICL may have a risk factor for HIV infection or even an opportunistic infection, the CD4 lymphocyte count does not progressively decrease over time as with AIDS. Almost all patients with ICL have normal serum immunoglobulin levels. The stable CD4 lymphocyte counts may be accompanied by reductions in the levels of other lymphocyte subsets, including CD8+ T-lymphocytes, natural killer cells, and B-lymphocytes. This disorder appears to be rare and is generally associated with transient illness. The presence of ICL does not constitute evidence for a new transmissible infectious agent.[187,188] A Behçet-like syndrome has been reported in conjunction with ICL.[189] Criteria for diagnosis of ICL include:

PREVENTION OF HIV TRANSMISSION

The transmission of HIV in definable risk groups allows for control measures to be taken that prevent the spread of AIDS. Since HIV is primarily spread as a sexually transmissible disease, then educational efforts must be aimed at sexually active persons and must be explicit regarding the behaviors that lead to the spread of HIV. A significant number of both boys and girls become sexually active as teenagers and must be included in prevention strategies. Given that the level of promiscuity will often be difficult to modify within a population, then educational campaigns are best focused upon the use of barrier precautions, particularly condom use. Sexual activity does not appear to increase with condom use.[93] All sexually active persons with more than one sexual partner, or whose partner is a member of a risk group for AIDS, should use condoms. Persons who know that they are infected with HIV should inform their sexual partners.[190,191,192]

The spread of HIV by injection drug use creates a major reservoir for HIV infection that can then be transmitted to other segments of the population, particularly heterosexual adults, including the sexual partners of injection drug users. Drug users must be educated about the risks of needle sharing. Cleaning of needles with undiluted bleach appears effective in preventing HIV transmission.[193] They can be provided with clean needles to prevent the spread of HIV, and can be advised to use condoms.[194] Congenital AIDS can be prevented by efforts to educate women of childbearing age about the hazards to the fetus if they are HIV-infected. Potential mothers can be provided with means of contraception. Antiretroviral therapy for mothers can reduce perinatal HIV transmission. Confidential HIV testing should be made available along with counseling services to persons in all risk groups to encourage voluntary testing and prevent unknowing transmission of HIV.[195]

Transmission of HIV through blood product therapy has become vanishingly rare when screening and testing of donors is applied. Such screening is costly. Since HIV infection is not spread by casual contact in public places, households, or in the workplace, no modifications of routine activities of daily living or work practices is necessary. HIV is not spread by insect vectors, and insect control programs will have no effect upon HIV transmission in a population.

A summary of AIDS prevention strategies are given below:

Methods to Reduce Rates of HIV Transmission

- Treat HIV infection as an illness, not as a social stigma
- Reduce levels of poverty in society that lead to increased risks through drug abuse and promiscuity
- Provide HIV testing and counseling to identify infected persons who can reduce their risk to others
- Provide educational programs for children and adults which describe how to avoid sexually transmitted diseases
- Promote sexual barrier precautions among high risk commercial sex workers and clients
- Provide clean needles for injection drug users
- Create health care programs providing antiretroviral therapy to extend life and reduce HIV transmission rates
- Give HIV-infected pregnant women antiretroviral therapy to reduce perinatal HIV transmission

AIDS prevention programs have successfully produced long-term behavior change with reduction in incidence of HIV infection.[196] In order for such programs to be effective, several principles must be applied: sustained interventions are more likely to lead to sustained behavior change; more intense interventions are more likely to result in greater risk reduction; accessibility to devices (such as clean needles and condoms) that are necessary to safer practices reduces the risk for HIV infection; modification of community norms appears to enhance behavior change; and explicit HIV prevention programs must be provided prior to the time that adolescents become sexually active.[12]

TREATMENT FOR AIDS

A variety of therapies have been developed since 1984 for persons infected with HIV. Bone marrow transplantation, lymphocyte transfusions, thymic transplantation, and therapeutic apheresis to remove virus-bearing cells were tried without significant success against HIV infection and are no longer employed.[197] Antiretroviral therapies are aimed at diminishing HIV replication and destruction of the immune system with progression to AIDS. A variety of pharmacologic agents have been developed to treat HIV infection. None of them will completely eliminate HIV from infected persons. Moreover, experimental *in vitro* anti-viral effects do not always occur *in vivo*.[198] Table 3 lists drugs available to treat HIV infection.

The first pharmacologic agent that was developed that had significant effectiveness for treatment of HIV infection was the antiretroviral drug zidovudine (ZDV), a nucleoside analog. Some earlier literature refers to ZDV as azidothymidine (3'-azido-3'-deoxythymidine), or AZT. Zidovudine is a thymidine analogue which is phosphorylated by cellular enzymes to an active triphosphate form that, as an analog, interferes with viral reverse transcriptase. Zidovudine proved useful in prolonging the lives of treated patients by decreasing the frequency and severity of opportunistic infections, by partially suppressing HIV replication, and by transiently increasing CD4 lymphocyte counts.[199]

In the 1990's, additional nucleoside analog drugs with clinically useful antiretroviral effect against HIV were developed, including didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), and abacavir. These drugs, known as nucleoside reverse transcriptase inhibitors (NTRIs), have potential effectiveness in persons who cannot tolerate zidovudine or in whom such therapy is unsuccessful, as evidenced by laboratory markers such as decreasing CD4 lymphocyte counts and increasing HIV plasma viremia. All of the NRTI's require phosphorylation to an active triphosphate metabolite. Didanosine is converted to dideoxyadenosine and then phosphorylated to an active triphosphate within cells. Zalcitabine is metabolized within cells to dideoxycytidine (ddC) in an active triphosphate form. Stavudine is also phosphorylated intracellularly to the active form of the drug stavudine-5'-triphosphate. Lamivudine undergoes intracellular phosphorylation to lamivudine triphosphate. Abacavir, unlike the other NRTI's, is a guanine analogue that, when converted to the active form carbovir triphosphate, competes with the natural substrate dGTP.[200, 201]

The acyclic nucleoside phosphonates include adefovir, tenofovir, and cidofovir and have antiretroviral activity but do not require phosphorylation. This feature helps to avoid the potential rate-limiting phosphorylation step that may limit activity in some infected cells. These drugs also have limited cross-resistance to the nucleoside NRTI drugs. Toxicity is similar to the NRTI's, but may also include nephrotoxicity from toxic acute tubular necrosis.[201,202] Another nucleotide reverse transcriptase inhibitor (NtRTI) is tenofovir (tenofovir disoproxil fumarate) that is an acyclic phosphonate analogue and which may be useful for treatment in cases where HIV mutations have rendered nucleoside analogue drugs ineffective.[203]

Drug intolerance and drug toxicity are significant problems for all drugs used to treat HIV infection. Many of these adverse effects appear to be mediated via mitochondrial toxicity, such as liver toxicity with steatosis and lactic acidosis seen with NRTI therapy, manifested by abdominal pain, nausea, or vomiting, and with a mortality rate near 50%.[204] Patients must be monitored carefully for signs and symptoms of these complications. Zidovudine can cause gastrointestinal symptoms of nausea and vomiting, like other NRTI's, as well as headache, but more importantly it can occasionally lead to severe bone marrow suppression with anemia, usually in the first few months of administration. Myopathy may also occur with long term zidovudine therapy.[199] Major toxicities associated with didanosine therapy that limit its use include pancreatitis, peripheral neuropathy, and gastrointestinal problems such as diarrhea.[205] Zalcitabine therapy is most often complicated by peripheral neuropathy (which often limits its use), pancreatitis, maculovesicular cutaneous eruptions, and aphthous oral ulcers (stomatitis).[206] Stavudine's major side effect is peripheral neuropathy, though anemia and pancreatitis may also occur.[207] There are infrequent

major adverse reactions with lamivudine therapy, the most common being gastrointestinal upset.[208] Abacavir therapy can be complicated by a hypersensitivity reaction with flu-like symptoms, abdominal cramping, diarrhea, and skin rash in up to 5% of cases.[201] Stevens-Johnson syndrome and/or toxic epidermal necrolysis has been reported to complicate NRTI, NNRTI, and PI therapy.[209]

In addition to the NRTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been developed to treat HIV infection. These drugs act via non-competitive binding to a hydrophobic pocket close to the active site of the reverse transcriptase enzyme of HIV. These drugs include nevirapine, delavirdine, and efavirenz. They are most useful when either is used in combination with other antiretroviral agents. The major complication with use of these NNRTIs is skin rash, though this rash is milder with efavirenz.[201,210,211] Hepatotoxicity with hepatic enzyme elevation has been reported with NNRTIs.[212] Mutations render HIV-1 group O and HIV-2 strains either resistant or less effective at non-toxic dosages to all drugs within the entire NNRTI class, due to a single amino acid, Leu-188.[66]

Protease inhibitors have been developed as anti-HIV drugs. The processing of large HIV precursor proteins, such as p55 and p40 encoded by the *gag* and *gag-pol* genes of HIV, into structural proteins p17, p24, and p7 of the viral core is performed via proteolytic cleavage by an HIV-encoded aspartic protease and is necessary for maturation of immature viral particles into infectious virions. These drugs are synthetic analogues of the HIV protein and block the action of HIV-protease to interfere with viral replication. Protease inhibitors may also function by decreasing CD4 lymphocyte apoptosis through decreased CD4 interleukin-1ß-converting enzyme (ICE, or caspase 1) expression.[213,214] Tipranavir is a non-peptidic protease inhibitor.[215]

Problems in the development of this class of drugs have included finding an effective, specific inhibitor of HIV protease that does not also interfere with normal cellular proteases, as well as HIV viral resistance. Such drugs include saquinavir (saquinavir mesylate), ritonavir, indinavir (indinavir sulfate), nelfinavir, and amprenavir, all of which are tolerated well and show efficacy by reduction in plasma HIV-1 RNA along with increases in CD4 lymphocyte counts. In addition, protease inhibitors show efficacy in combination with reverse transcriptase inhibitors.[213,216] Nevertheless, HIV resistance to protease inhibitors does occur and limits their effectiveness.[217]

Protease inhibitors are often most effective at high dosages, but adverse reactions to these toxic agents may limit their use as well. All of them may be associated with gastrointestinal symptoms including nausea, vomiting, and diarrhea. Their use may be accompanied by a peculiar adipose tissue redistribution known as protease inhibitor-associated lipodystrophy (PIAL), though this phenomenon may occur in persons with AIDS not taking protease inhibitors. This syndrome is associated with loss of facial fat, dorsocervical tissue accumulation, increased internal abdominal fat accumulation, hyperlipidemia (often exceeding 1000 mg/dL), peripheral insulin resistance and impaired glucose tolerance, but there is a wide variation in the severity and clinical presentation of these metabolic side effects. The dyslipidemia is most pronounced with ritonavir.[218] The agent atazanavir appears to affect glucose metabolism less than other protease inhibitors.[219]

All protease inhibitors, and ritonavir in particular, appear to be associated with hepatic transaminase elevations.[220] Nephrolithiasis may complicate indinavir therapy when patients do no receive adequate hydration. In addition, hyperbilirubinemia may occur with indinavir therapy. Paresthesias may complicate ritonavir therapy. Amprenavir is associated with skin rashes. Dosing regimens for these and other medications can be complex and difficult to follow for patients, but must be followed carefully in order to have maximum effectiveness and prevent development of HIV resistance.[201,213,216] Since protease inhibitors are metabolized by the cytochrome CYP P450 enzymes in the liver and small intestine, there is a potential for drug interactions via this metabolic pathway.[221]

Another form of antiretroviral therapy is based upon blocking fusion of HIV with the target cell surface. A synthetic peptide that corresponds to 36 amino acids within the C-terminal heptad repeat region (HR2) of HIV-1 gp41 subunit of the viral envelope (Env) protein. This prevents conformational changes to form a stable complex required for membrane fusion to target cells. This drug, enfuvirtide, must be delivered by subcutaneous injection.[222]

The significant mutation rate that occurs during reverse transcription of HIV to proviral DNA within host cells (approximately once per 2000 incorporated nucleotides) enhances the development of antiretroviral drug resistance. Resistance to antiretroviral agents increases with the length of therapy, as multiple amino acid changes accumulate over time to yield virus variants. The monitoring of patients with HIV-1 RNA and CD4 lymphocyte counts is the primary means for determination of potential resistance, with possible use of HIV-1 genotypic and phenotypic resistance assays, for subsequent changes in antiretroviral therapy.[223] Non-compliance by patients with dosing regimens may compound this problem.[224] Such patients are then at risk for transmission of resistant viral strains to other persons.[225] Loss of clones of CD4 lymphocytes through HIV-mediated destruction may be slowed by antiretroviral therapy, but such clones will not be replaced, leaving patients at continued risk for opportunistic infections.[216]

The use of highly active antiretroviral therapy (HAART) with combinations of antiretroviral agents forms the basis for therapy of HIV infection. This form of therapy for HIV infection bears similarities to cancer chemotherapy. The use of HAART can reduce the total health care cost for persons with AIDS.[226] Therapy for persons with HIV infection is based upon CD4 cell count and HIV-1 RNA plasma levels as follows:[200,227]

HIV-1 Therapy Based on Viral Load Testing

	Plasma HIV-1 RNA Level (copies/mL)		
CD4 cells (per μL)	<5000	5000 – 30,000	>30,000
<350	Recommend Therapy	Recommend Therapy	Recommend Therapy
350 - 500	Consider Therapy	Recommend Therapy	Recommend Therapy
>500	Defer Therapy	Consider Therapy	Recommend Therapy

The HAART regimens may include combinations of one or more of a nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), and protease inhibitor (PI). Various combinations are possible, based upon clinical trials that determine efficacy, adverse effects, interactions, and ease of use. The standard recommended regimens are as follows[227,228]:

Standard HAART Regimens

- NRTI + NRTI + PI
- NRTI + NRTI + NNRTI
- NRTI + NRTI + PI + PI

With HAART, the CD4 count typically increases.[229] Despite HAART, the reconstitution of the immune system may be partial or incomplete, with considerable variability in the magnitude of the response. CD4 counts may remain below normal. Persons with higher baseline HIV-1 RNA levels and more acute pre-therapy CD4 cell decreases have greater CD4 cell increases following institution of HAART. However, some patient continue to have good suppression of HIV replication in spite of no or only a modest increase in the CD4 cell count. Half of persons starting HAART may not suppress the HIV-1 RNA level below 400 copies/mL

In persons with significant immune reconstitution, there may be a paradoxical increase in symptoms of opportunistic infections because of an increased inflammatory response to smoldering, subclinical infections or to ongoing infections. This is known as immune restoration disease (IRD). IRD is characterized by an atypical presentation of an opportunistic infection or tumor in an HIV-infected persons responding to HAART, along with a decrease in plasma HIV-1 RNA.[230,231] IRD is more likely to occur when HAART is initiated after the CD4 cell count has fallen below 100/microliter.[232]

Additional features of IRD include a polyclonal hypergammaglobulinemia and autoimmune phenomena. Features can include high levels of CD8 lymphocytes, high levels of IL-6 and soluble IL-6 receptor, high levels of CD30 and CD26 activity, increased interferon gamma-producing inflammatory cells such as macrophages with delayed type hypersensitivity reactions, increased chemokine expression on inflammatory cells. Infectious diseases which may manifest with immune restoration include *Mycobacterium tuberculosis*, *Mycobacterium avium*-complex, *Cryptococcus neoformans*, viral hepatitis, CMV retinitis, herpes zoster dermatitis, herpes simplex virus, and JC papovavirus (progressive multifocal leukoencephalopathy) infections.[230,231]

Antiretroviral therapy is recommended for all persons who are in the advanced stage of HIV infection. Problems associated with therapy at this stage include drug interactions with agents used to treat opportunistic infections, as well as problems with toxicity less tolerated by persons who are very ill. Such persons may not respond as well to initial therapy or may require more frequent changes in therapy.[164]

Persons diagnosed with acute HIV infection may derive benefit from antiretroviral therapy. Such therapy may suppress the initial burst of viremia, potentially lower the "set point" of viremia that determines the rate of disease progression, and may reduce the rate of viral mutation.[152] Therapy should include a combination of two NRTI's and one protease inhibitor. However, if the patient is infected with a drug resistant HIV strain, or if viremia is not suppressed significantly, then there is the risk for increasing drug resistance that limits the effectiveness of future therapy. After a year of therapy, assessment of HIV-1 RNA levels and CD4 lymphocyte counts will determine whether continued therapy during asymptomatic HIV infection is warranted.[164] A dramatic reduction in the numbers of infected CD4 lymphocytes is demonstrated following potent antiretroviral therapy.[156]

Pediatric patients may also benefit from antiretroviral therapy. In infants and children with HIV infection, combination therapy begun early, particularly in those infants whose HIV-1 viral load is high, has shown effectiveness. Adverse drug reactions are not significant in most cases.[233] Adolescents with HIV infection who acquired their infection during adolescence will typically have a clinical course of infection similar to adults. The use of highly active antiretroviral therapy (HAART) has been shown to markedly reduce mortality in children and adolescents infected with HIV.[234]

Treatment of HIV-infected pregnant women with antiretroviral therapy is a complex issue. For women already on a treatment regimen when pregnancy is diagnosed, treatment may be discontinued because of a potential risk for teratogenicity during the first trimester, but the inevitable rise in HIV-1 RNA levels following discontinuation of therapy may place the fetus at greater risk for transmission of HIV later in pregnancy. HIV-infected women not on therapy who are diagnosed as pregnant may wish to delay instigation of antiretroviral therapy until after the first trimester. The goal in pregnancy should be to bring the viral load to levels that are undetectable. All pregnant women should receive antiretroviral therapy. In the vast majority of circumstances that therapy should be a highly active regimen that includes zidovudine. Stavudine and didanosine in combination should not be used unless other regimens are not available.[235] Even abbreviated regimens of zidovudine therapy have been demonstrated to reduce the rate of perinatal transmission of HIV.[236] A reduction in likelihood of perinatal transmission <2% is achieved with prenatal, intrapartum, and neonatal use of antiretroviral prophylaxis in combination with elective cesarean section and avoidance of breast feeding.[137] The rate is <1% in women with non detectable plasma HIV-1 RNA.[128]

Response to antiretroviral therapy must be monitored by HIV-1 RNA and/or CD4 lymphocyte counts. The HIV-1 RNA level provides a better indicator of clinical benefit than does

the CD4 count. Before initiation of therapy, baseline values must be established by obtaining at least two measurements of these parameters. Following institution of therapy, response may be monitored aggressively with HIV-1 RNA and/or CD4 lymphocyte assays every 1 to 3 months. More conservative monitoring may occur at 6 month intervals. The goal of aggressive therapy is a complete suppression to a measurable level <50 copies/ml of HIV-1 RNA in plasma.[227]

In general, within two weeks of the start of aggressive antiretroviral therapy, plasma HIV-1 RNA will fall to about 1% of their initial value. A minimum 1.5 to 2.0-log decline should occur by 4 weeks, and an early response by 4 to 8 weeks suggests continued HIV suppression. Persons starting therapy with high plasma levels of HIV (>100,000 copies/mL) may take longer to suppress, but failure to suppress viremia <50 copies/mL by 16 to 24 weeks of therapy suggests poor adherence, inadequate drug absorption, or drug resistance.[228]

Suppression of viremia will reduce the level of HIV in genital secretions and reduce transmissibility of HIV from infected persons.[96,237] In general suppression of viremia in serum to a level below 1500 copies/mL is associated with a low rate of transmission of HIV.[102] Despite suppression of viremia, even to undetectable levels, persons with HIV infection must still be considered infectious and should continue to avoid behaviors that could transmit infection to others. Even persons with undetectable levels of HIV-1 RNA in plasma may still have virus detectable in genital secretions.[105]

Failure of treatment may not necessarily relate to the appearance of drug resistance. The problems of patient adherence to the drug regimen and the drug potency contribute to treatment failure. Though dosing regimens for highly active antiretroviral therapy (HAART) are complex, it is essential that patients adhere to the regimen for adequate and continued suppression of viremia.[238] An adherence rate of 95% is required for optimal suppression of viremia.[228]

Despite antiretroviral therapy, proliferating CD4 lymphocytes and follicular dendritic cells within lymphoid tissues, and macrophages throughout the body, particularly in the central nervous system and gastrointestinal tract, remain as reservoirs of infection.[239,240] Though the turnover of peripheral CD4 cells is rapid, the half-life of FDCs averages two weeks to one month, while some long-lived CD4 memory cells have a half-life of 7 months, Thus, clearance of HIV requires months of antiretroviral therapy.[54] Regeneration of the immune system can occur to some degree even in late stages of HIV infection, but will be slow, variable, and partial.[50]

An important goal of aggressive antiretroviral therapy is suppression of HIV replication to reduce the emergence of antiretroviral drug-resistance strains which are the rate-limiting factor to continued drug effectiveness and survival. At the end of the 20th century, HAART therapy was unable to suppress HIV-1 RNA to less than 400 copies/mL in 10 to 40% of patients starting their first treatment regimen, and 20 to 60% of patients on a second or third antiretroviral regimen demonstrated treatment failure.[241,242] Suppression of viremia is best accomplished with simultaneous initiation of combination antiretroviral therapy, using drugs not previously given and drugs not known to be subject to cross-resistance.[164] If suppression of viremia is not adequate, then drug resistant HIV-1 variants arise that are capable of being transmitted to others and may impact the spread of HIV-1 through inability to suppress HIV-1 in infected persons.[243,244] In one study of newly infected persons, 16% had been infected with HIV-1 variants with known resistance to antiretroviral agents.[245]

A change in the treatment regimen for HIV infection may be instituted for a variety of reasons. Such a change may be prompted by increasing drug resistance, as indicated by detectable HIV-1 RNA reappearing in plasma after complete suppression, or increasing HIV-1 RNA levels in plasma. The HIV-1 RNA in plasma gives a good indication of the level of a therapeutic response.[299] The toxic effects of the medications and intolerance may require that an alternative regimen be considered. In addition, failure of patient compliance may force a change. If the patient were on a suboptimal regimen, such as a single antiretroviral agent, then a change would be indicated.[200] A minimum of two CD4 cell counts and two HIV-1 RNA assays are recommended prior to initiating or changing antiretroviral therapy.[228]

Strategies for dealing with drug resistance have been developed. Among these is the use of multidrug rescue therapy (MDRT), also called mega-HAART therapy, which may combine up to 9 antiretroviral drugs. The use of MDRT is complex and complicated by expense, toxicity, and

difficulty in patient compliance. The use of a "drug holiday" or planned interruption of treatment, may transiently lead to re-emergence of a "wild type" HIV that responds better to reinstitution of therapy, but reemergence of resistant HIV is inevitable. Despite failure of marked suppression of HIV, patients may continue to maintain some degree of immune competence and remain clinically stable, with standard HAART regimens that are continued without modification.[246]

Testing for genotypic antiretroviral drug resistance (GART) can be performed in order to assess the potential for drug efficacy. In primary HIV infection, such testing may detect the transmission of a drug-resistant strain of HIV.[247] In established HIV infection, resistance testing may detect drug resistant HIV for selection of therapeutic regimens. In HIV infected pregnant women, resistance testing can help to optimize maternal treatment and prophylaxis for the neonate. GART is recommended for persons with acute or recent HIV infection, for certain persons who have been infected as long as 2 years or more prior to initiating antiretroviral therapy, in cases where initial or multiple antiretroviral treatment regimen failure has occurred, and during pregnancy.[248]

Another potential complication of HAART that included a protease inhibitor is accelerated bone mineral loss. The incidence of osteopenia and osteoporosis is increased in HIV infected males on such therapy. The relative risk is 2.19. This complication appears to occur independently of another complication of protease inhibitor therapy—lipodystrophy.[249]

Prophylaxis for *Pneumocystis carinii (jirovecii)* pneumonia in adults is indicated with CD4 lymphocyte counts below 200/μL and for patients with a history or oropharyngeal candidiasis.[250] Prophylaxis for PCP is indicated in infants at 4 to 6 weeks of life.[251] In patients receiving highly active antiretroviral therapy in whom the CD4 count has increased above 200/μL for more than 3 months, PCP prophylaxis can be safely discontinued.[252] The use of zidovudine and other antiretroviral agents, as well as increased effectiveness of treatments for opportunistic infections--and the use of prophylactic trimethoprim-sulfamethoxazole, dapsone, or aerosolized pentamidine (pentamidine isethionate) against *Pneumocystis carinii* pneumonia in particular--has significantly prolonged survival in persons with AIDS. Access to prompt medical care for ongoing care, prophylactic therapies, and life-threatening complications of AIDS is also important for survival, as is maintenance of good nutrition and also psychosocial support.[162,168,253]

It is clear that use of combination therapies, particularly with inclusion of protease inhibitors, is quite effective in reducing both the morbidity and the mortality from HIV infection. The use of prophylactic therapies for prevention of *Pneumocystis carinii* pneumonia, cytomegalovirus, and *Mycobacterium avium* complex (MAC) infections are most effective in reducing the prevalence of these infections when aggressive antiretroviral therapy is applied. The declines in morbidity and mortality occur for all risk groups, ages, races, and sexes.[254]

There has been considerable pressure to expedite investigational drug testing and approval, given the uniformly fatal outcome of AIDS. One problem for clinical research trials has been the propensity of AIDS patients to obtain drugs not on experimental protocols, thus confounding results of those trials. Many homeopathic, naturistic medicinal compounds, or other substances such as dinitrochlorobenzene or ozone have also been employed by patients who are understandably desperate to try anything that offers potential hope.

As in other chronic diseases, the use of complementary and alternative medicine (CAM) therapies to standard antiretroviral and antimicrobial therapies is widespread in persons with AIDS, with over half using such alternative therapies. However, less than half of these patients report CAM use to their physician. The most commonly reported alternative therapies include exercise, lifestyle changes, dietary supplements, counseling, herbal medications, megavitamins, and prayer. Of the persons who used such therapies, 70% reported a quality of life improvement.[255]

FUTURE THERAPIES FOR AIDS

A large component of AIDS research has been aimed at development of an effective vaccine. Though a universally efficacious vaccine would help stop the spread of AIDS, such a vaccine would be of little help to the millions of currently HIV-infected persons worldwide. Vaccine development has encountered several obstacles: HIV epitope variability, HIV avoidance of immune response through cell to cell transmission, lack of an effective antibody response, and induction of adverse immune reactions through HIV homology to endogenous human proteins. Several vaccine strategies have been proposed, including induction of cell mediated and/or humoral immunity.[256]

The most advanced vaccine research has centered on the use of the HIV gp120 or gp160 envelope proteins to induce a humoral response. Most neutralizing antibodies formed in persons infected with HIV are aimed at gp160. However most research studies have focused on use of gp120 because it was simpler to manufacture and did not have any major disadvantages compared to gp160. The immunogenic response may be enhanced by removal of carbohydrate moieties from the heavily glycosylated gp120.[257]

Alternative approaches include the use of pox viruses such as vaccinia as recombinant vectors for vaccination with HIV envelope proteins, and this has the advantage of inducing mucosal immunity that could block infection through the portal of entry in mucosal surfaces. Development of an attenuated virus vaccine has the potential for induction of the most effective and long-lasting immunity, but the long latency of HIV infection makes assessment of non-pathogenicity of such a vaccine difficult to ascertain. Also, the vaccine must be effective against the various subtypes of HIV that have arisen or will arise. Through the mid-1990's, no effective HIV vaccine was produced.[28,256,258]

Another approach to control of HIV infection is the use of gene therapy. One approach is immunization by direct injection of plasmid DNA encoding genes for specific HIV protein antigens.[256] Another approach is based upon introduction into susceptible cells, such as CD4 lymphocytes, of a gene that interferes with HIV viral replication. Such a foreign gene, if introduced into bone marrow stem cells, would offer lasting protection against infection. The vector for such gene transfer into the host cells would itself be a retrovirus, but replication-defective and incapable of reproduction to cause infection. The foreign genes introduced into human cells could either interfere with HIV replication within those cells or lead to death of infected cells before replication could occur.[259]

Blocking HIV entry into host cells is another strategy that holds promise. HIV entry is a complex process involving several key steps. The initial step of HIV attachment via the CD4 receptor could be blocked by soluble preparations of CD4 to bind viral gp120 and prevent attachment to cellular CD4. This approach could potentially work in the period immediately following HIV exposure. Trials of a multivalent form of CD4 have been shown to block transmission of HIV, but weekly infusions would be required to maintain plasma levels adequate for sustained efficacy.[260]

An inhibitor of the HIV integrase enzyme, which catalyzes the steps involved in the insertion of HIV proviral DNA into the host cell genome, would have potential use in therapy. The 1,3-diketo acids are potent inhibitors of integrase. Use of such compounds could potentially provide an additional means for blocking HIV replication.[260]

The step involving HIV coreceptor binding (to either CCR5 or CXCR4 coreceptors) can be inhibited by drugs that target this interaction. The step of fusion of HIV with the host cell membrane is another step that could be blocked by peptides that inhibit conformational changes of viral gp41 necessary for fusion. These compounds require concomitant use of antiretroviral drugs.[261]

Use of immunologic therapy to boost the body's immune response with an immunogen has been tried and found unsuccessful. The immunogen was a whole inactivated HIV isolate stripped of envelope proteins and conjugated with incomplete Freund adjuvant.[262]

CHAPTER 2 - DIAGNOSIS OF AIDS

DIAGNOSTIC TESTS FOR HUMAN IMMUNODEFICIENCY VIRUS

There are several testing methods available. Most are serologic methods based upon detection of antibody to HIV in blood or body fluids, while the p24 assay detects HIV antigen. The polymerase chain reaction and *in situ* hybridization techniques are used primarily with fresh and fixed tissue samples, but can also be applied to blood samples. HIV viral culture can be performed on both fluids and tissues. Immunologic alterations detected through lymphocyte subset quantification in blood are used clinically to detect and follow the effect of HIV infection on the immune system.

The serologic tests for HIV antibody make use of the human immunologic response to HIV infection in which antibodies, primarily directed against HIV proteins and glycoproteins such as gp120 and gp160, appear in acute HIV infection. Such antibodies typically appear within 3 to 12 weeks of infection and remain throughout the life of the infected person. The HIV core antigen p24 is useful primarily for detection of perinatal infection because of passively acquired maternal HIV antibody.

ENZYME IMMUNOASSAY.-- The initial most commonly used method for detection of HIV infection is the enzyme-linked immunoassay (EIA) to detect both HIV and HIV-2 antibody. It is a fairly simple test to perform for clinical laboratories with trained technicians and, therefore, is the "gold standard" for testing used extensively in blood banking and patient screening in developed nations.[263] The sensitivity and specificity of EIA testing by standard methods using serum exceeds 99%. Use of rapid serum EIA methods, defined as any test that yields results in less than 30 minutes, provides accuracy nearly as good as routine EIAs. Rapid assays are simpler to perform, by persons without technical expertise, require no instrumentation, and can provide point-of-care testing. These rapid EIAs provide results to patients without a waiting period which loses some patients to follow up and counseling. A rapid EIA can allow post-exposure prophylaxis to begin within 2 hours for persons with occupational exposure to HIV. However, errors in performance and interpretation are more likely with rapid than with routine laboratory EIAs.[264,265]

Use of EIA testing can also be applied to body fluid samples other than blood. Oral mucosal transudate (OMT) is a fluid derived from serum that enters the saliva from the gingival crevice and across oral mucosal surfaces. The OMT contains immunoglobulins that can be concentrated via collection devices such as pads held next to gums and oral mucosa. Testing via EIA of OMT yields results comparable to serum EIA's.[266] Saliva can also be utilized for rapid EIA testing, and has the advantage of simplified collection and processing. However, the results with rapid HIV tests using saliva are slightly less sensitive and specific than for serum EIA's.[267] The sensitivity can be increased by use of an assay that employs an IgG antibody-capture ELISA methodology (GACELISA).[268] An enzyme-linked fluorescent assay (ELFA) methodology has been employed on saliva and urine.[269] Urine testing has the added advantage of safer handling for laboratory personnel (HIV is not transmitted via urine), but urine EIA testing may not match serum EIA in specificity.[270] The use of rapid testing of urine and saliva is a cost-effective strategy in locations with high risk populations where resources limit standard serum EIA testing.[271,272]

The EIA tests for HIV utilize either a whole virus lysate, recombinant proteins, or synthetic peptides for the solid phase antigen, and tests based on the latter two antigens are more sensitive and specific.[263] Kits are available that combine testing for both HIV-1 and HIV-2. These assays are very reliable. When antibodies to one or more antigenic components of HIV including reverse transcriptase (RT), p17, p24, p31, gp41, and gp120/160 are present, as in most cases, sensitivity and specificity are over 99%. Highly sensitive immune complex transfer enzyme immunoassay methods can also be employed.[273]

Many EIA assays detect HIV-2. The emergence of subtypes of HIV-1 complicates testing, as evidenced by subtype O, which is not detected by all routine methods for HIV-1 testing.[70] In addition, the EIA method can be used for screening for HTLV. Tests employing synthetic peptide antigens can distinguish HTLV types I and II.[263]

The standard protocol for EIA testing is initial determination of reactivity. Reactive tests are repeated in duplicate. If both repeat tests are reactive, the sample is considered positive and a confirmatory test is performed, If one of the repeat tests is negative, then there is a high probability of error in testing and another blood specimen should be obtained for testing. The level of reactivity gives an indication of predictive value of an EIA test—the more reactive the test, the more likely the test result is a true positive.[274]

Tests for confirmation of a reactive EIA include Western blot (WB), line immunoassay (LIA), indirect immunofluorescence assay (IFA), and additional EIA testing. The typical confirmatory test is WB. When funding for routine laboratory confirmatory tests is available, WB, LIA, or IFA can be done. When rapid and simple testing is required, then algorithms for use of EIAs include: (1) a standard EIA followed by a rapid EIA, (2) two standard EIAs, or (3) two rapid EIAs. EIA tests can be utilized which have reactivity to different HIV antigens from different sources or using different methodologies.[265]

In a population with a low prevalence for HIV-1 (no risk factors), about 6 or 7 positive EIA test results per million tests performed will be false positives. False positive results may also occur in persons with hematologic malignancies, acute DNA viral infections, serum autoantibodies, autoimmune diseases, alcoholic hepatitis, renal failure, cystic fibrosis, multiple pregnancies or transfusions, hemodialysis, anti-HLA-DR4 antibodies, and vaccinations for hepatitis B, rabies, or influenza. Positive specimens should be repeatedly positive, with confirmation by an additional laboratory test, before reporting them as such. Positive EIA tests are confirmed by the more specific, but expensive and difficult to perform, Western blot test.[274,275]

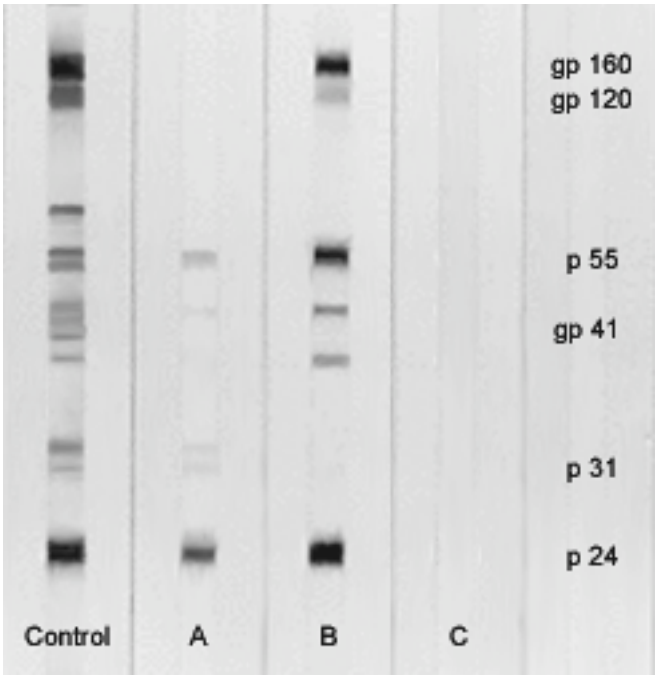
False negative results can occur, and the EIA method will also miss recently infected persons in the "window" of time prior to seroconversion, which can be as little as a week or up to 3 weeks on average. EIA is of no value to detect infected infants of HIV-1 positive mothers since transplacentally acquired maternal antibody may persist up to 15 months postpartum. Though a very rare occurrence, not all HIV-1 infected persons have detectable antibody during all or part of their course because of delayed seroconversion.[154] Explanations for seronegativity include: marked hypogammaglobulinemia, B cell functional defects, chemotherapy, a non-detectable subgroup of HIV, or a laboratory error. In those patients with persistently decreased CD4 counts, the possibility of idiopathic CD4+ T-lymphocytopenia (ICL) may be considered. When there is evidence suggesting HIV infection but a negative EIA, then tests for p24 antigen, HIV-1 RNA, and/or viral culture can be considered.[276] There is no evidence for seroreversion, or loss of detectable antibody to HIV-1 once true seroconversion occurs.[277]

In the U.S., home testing kits utilizing EIA methodology have been marketed. Blood specimens are collected via fingerstick. When properly collected, the accuracy is similar to that of standard serum EIA testing collected by health care workers. However, a sixth of specimens may not be properly collected. When combined with pre- and post-test telephone counseling, the use of home testing for HIV can be an effective alternative to standard testing offered in the health care setting.[278,279]

WESTERN BLOT.-- The Western blot (WB) test is often used to confirm EIA positives because of its high sensitivity and specificity. The method utilizes a substrate made by fractionating purified HIV-1 by molecular weight, using polyacrylamide gel electrophoresis, into discrete bands that are then transferred by electrophoretic blotting to a nitrocellulose membrane that is then cut into strips. A patient serum, urine, or saliva specimen is placed on the strip and any HIV-1 antibodies present will bind to the viral antigens. The bands are visualized by immunohistochemical methods.[280] The Western blot technique can be utilized to distinguish HIV-1, HIV-2, HTLV-I, and HTLV-II infections.[263]

Western blot testing requires high-quality reagents, careful interpretation of the band patterns, and rigorous quality control. Thus, WB testing should be done by or referred to qualified

laboratories according to established criteria. Test strips showing no bands are negative. Positive findings are interpreted by a number of "standard" criteria that require the presence of two or more bands that represent specific denatured HIV-1 proteins including core (p17, p24, and p55), polymerase (p31, p51, p66), and envelope (gp41, gp120, gp160) proteins depending on the particular kit or method.[280]



A Western blot is positive if reactivity is detected with either:

gp41 and gp120/160 bands

or

either the gp41 or gp120/160 bands AND the p24 band

In the example above, the patient sample in lane B is positive while the result for patient C is negative. The presence of any bands that do not meet the criteria for a positive result is considered an indeterminate result, as shown in lane A above. Errors in interpretation occur with sample misidentification, cross-contamination of negative samples by adjacent positive samples, HLA antibodies in the viral lysate used in the preparation, or misinterpretation of band patterns. A WB should not be used as an initial HIV screening test because it has a much higher false positive rate than EIA. Likewise, plasma HIV-1 RNA testing should not be used for screening because of the false positive rate up to 3% (suggested by an assay yielding a low plasma viral load).[274]

The "indeterminate" WB assays may result from repeatedly reactive true positive EIA assays on sera that are negative to WB in individuals at the early stage of HIV infection. Up to 10 to 20% of repeatedly reactive EIA assays can have an indeterminate WB assay.[264] Indeterminate WB assays may also result from cross-reaction from infection with HIV-2, loss of core antibodies late in HIV-1 infection with loss of immunologic competence, and nonspecific antibody reactions with conditions similar to those for EIA. Indeterminate WB assays in persons who are truly HIV negative may occur from contaminating proteins in the viral lysate or from reactivity due to prior exposure to similar proteins or other viruses.[274]

Approximately 3% of persons with indeterminate WB tests will subsequently be shown to be infected with HIV, and most of these persons will have identifiable risk factors for infection.

Indeterminate results can usually be resolved by retesting the patient by EIA assay and WB. About one-third of persons with an indeterminate WB will not be repeatedly reactive by EIA assay after retesting in one month. After 6 or more months most truly HIV-1 infected persons will be positive. However, an indeterminate WB can persist for years in some persons. [281,282] Additional testing to resolve indeterminate results can include detection in plasma of HIV-1 p24 antigen in 75% of early infections or HIV-1 RNA, which can identify virtually all early infections.[283]

Indeterminate WB results may also arise from non-specific reactivity of true negative sera for both EIA and WB assays. Some persons have stable indeterminate patterns and are not HIV-1 infected. Specific risk factors identified among women for presence of an indeterminate WB test include parity and also presence of autoantibodies, while in men the risks include a tetanus booster injection in the past two years or sexual contact with a prostitute.[281] Correlation of test results with clinical status is necessary.[284,285] Western blot testing can also be performed for HIV-2 to confirm EIA positive tests.[65] Long term follow-up of persons donating blood and who have no risk factors for HIV infection reveals no evidence for HIV infection.[286]

LINE IMMUNOASSAY.-- The line immunoassay (LIA) methodology is similar to that of Western blot, but incorporates HIV antigens onto nitrocelluose strips so that each reaction is visualized separately, making interpretation simpler becausee of the absence of additional bands and contaminating proteins. The antigens on the LIA strip are recombinant antigens or synthetic peptides, rather than lymphocyte-derived viral lysates A positive LIA is interpreted by reactive bands to p24 and gp41, and in some cases p31, antigens. The LIA can be used to confirm HIV2 infection by addition of an HIV2 specific antigen such as p36.[265]

INDIRECT IMMUNOFLUORESCENCE ASSAY.-- The indirect immunofluorescence assay (IFA) test may also be used for confirmation of positive screening tests for presence of HIV. The IFA utilizes a cell line, typically lymphocytes, infected with HIV-1 as a substrate. Thus, multiple HIV antigens are present to react with patient antibodies. These substrate cells are fixed to a glass slide, and the test is performed by incubating patient serum on the slides, washing, and then placing a fluorescein-labeled anti-human IgG on the slide for subsequent detection of positives via fluorescence microscopy.[265]

Though IFA is faster and less costly to perform than WB, the reagents are not as readily available, and special technical training and equipment (fluorescence microscope) is needed to perform and interpret the subjective IFA findings properly. Thus, IFA is less commonly used than WB or LIA. The WB performs better for confirmation of HIV positive results from screening of specimens from persons at low risk for AIDS.[287]

HIV-1 P24 ASSAY.-- The HIV-1 p24 assay detects the core antigen p24 which is produced by the HIV-1 *gag* gene. This test is essentially the reverse of the enzyme immunoassay for HIV antibody, because the methodology makes use of an antibody to HIV p24 coated on a solid phase that "captures" the p24 in a patient specimen. An enzyme conjugated second antibody to p24 is then added and a standard enzyme immunoassay method used for detection. The p24 assay can be utilized on non-lipemic or non-hemolyzed serum, on plasma, or on cerebrospinal fluid.[288,289]

The p24 antigen can be detected in some persons only 1 week after initial HIV-1 infection, but in other persons it is transient, disappearing and then reappearing months later. In most cases, p24 antigen can be detected 2 to 3 weeks following infection. The false positive rate is significant because of interfering substances in serum such as immune complexes. In order for a p24 test to be interpreted as positive, it must be repeatedly reactive and have a positive neutralization test. A p24 test is “indeterminate” if it is repeatedly reactive but the neutralization test is negative or invalid. Since HIV antibody is typically detectable within a week of p24 antigen positivity, indeterminate results can be followed up by repeat antigen and EIA testing in a week. If the antigen test remains positive but the antibody test is negative, repeat EIA testing for HIV is recommended in another 8 weeks. Testing for HIV by PCR can be helpful in this setting.[290] False positive p24 assays are rare, but can occur from cross reacting blood proteins.[264]

Though p24 assay is not attractive for routine screening, it does have usefulness in detecting HIV-1 infection in children born to HIV-1 infected mothers. The sensitivity of p24 assay at birth is 100%, but the specificity is only 18%.[291] The p24 antigen assay has a sensitivity and specificity of 100% from 3 to 6 months of age, but specificity begins to fall after 6 months of age.[292] Loss of p24 antigen in HIV-1 seropositive persons may also signal the onset of clinical AIDS, but only about 60% of patients with HIV-1 infection have detectable p24 antigenemia at the time of progression to clinical AIDS.[160,163] Long-term therapy with zidovudine has been shown to decrease p24 antigenemia.[163] Free p24 antigen is often complexed with p24 antibody, limiting detection methods, but immune complex dissociation (ICD) with acid treatment or boiling of specimens improves detection of p24 antigen, which increases the usefulness of the p24 antigen assay as a marker for progression of HIV disease.[289]

HIV-1 IGA ASSAY.-- The HIV-1 IgA antibody assay on serum has been developed for detection of perinatal HIV-1 infection, because maternal IgA antibody does not cross the placenta. One commercially available method employs removal of IgG antibody in the specimen followed by a simple immunoblot technique with visual interpretation. The sensitivity and specificity of this test in infants over 6 months of age approaches that of the EIA method in adults, while at age 3 months about half are detectable, but only a minority of HIV-1 infections are diagnosable by HIV IgA assay under 1 month of age.[289,293]

IMMUNOBLOT AND IMMUNOBINDING ANALYSIS.-- Rapid serologic methods for cost-effective diagnosis of HIV-1 and HIV-2 infection have been developed for use in places where the high cost or longer turnaround time of the EIA assay with smaller numbers of samples makes application of routine HIV testing more difficult. Both the enzyme immunobinding (dot-blot) and particle agglutination assays do not require instrumentation or trained technicians and provide a rapid turnaround time (hours). The tests utilize recombinant-expressed peptides, derived from the protein envelope of HIV. The sensitivity and specificity of these assays are good, but not to the level of EIA and Western blot, when the test is performed properly.[263,294] This form of rapid testing has been applied to forensic science, providing a rapid means for postmortem diagnosis of HIV infection.[295]

POLYMERASE CHAIN REACTION.-- The polymerase chain reaction (PCR) method can be applied to both tissues and plasma for detection of HIV. In tissues, a DNA probe is used to detect HIV-1 proviral DNA, but is much more sensitive than *in situ* hybridization because the target DNA is amplified many times to enhance sensitivity tremendously. Quantitation of the amount of HIV present is also possible. PCR can detect one copy of viral DNA in one cell out of 100 000 to 1 000 000 cells present. The disadvantage of PCR is that the tissue, either fresh or formalin-fixed paraffin-embedded, must be digested so that the exact localization of the HIV-1 within tissues cannot be determined.[296]

The PCR method has also been employed for early viral detection in serum of perinatally acquired HIV-1 infection. The sensitivity of this assay is sufficient to detect about half of infections in the first month of life. Between 30 and 60 days following birth, PCR will detect virtually all HIV infections of infants, and there should be no false negatives after 6 months, a sensitivity equivalent to HIV culture.[289,297]

HIV-1 RNA ASSAY.-- Quantitation of HIV-1 RNA in plasma or peripheral blood mononuclear cells can be performed by three methods: reverse transcriptase-polymerase chain reaction (RT-PCR), branched DNA (bDNA) testing, and nucleic acid sequence-based amplification (NASBA).[264] These assays provide a reliable means for monitoring progression of HIV infection independently of CD4 lymphocyte counts. Levels of HIV-1 are reported in viral copies per milliliter on patient plasma, and results may vary up to two-fold among these assays, so one assay should be utilized consistently for a given patient.[298] The level of HIV-1 RNA may vary up to three-fold in a single patient. However, there appears to be no diurnal variation. The HIV-1 RNA level tends to increase as the CD4 lymphocyte count declines and HIV infection

progresses.[299] However, the commercial viral load assay kits vary in their ability to quantify different HIV-1 subtypes.[300]

The levels of plasma HIV RNA detected correlate with the stages of HIV infection: a viremic "spike" following initial infection, then suppressed levels of HIV during the long "latent" phase of infection, and finally increased viremia with progression to clinical AIDS. The HIV-1 RNA correlates with plasma viremia and the level of p24 antigen, but is more sensitive, and can predict HIV disease progression independently of CD4 lymphocyte counts. This assay also has usefulness for closely monitoring patient response to antiretroviral therapy. An early response to therapy is marked by a decrease in viremia, while increasing drug resistance is indicated by increasing viremia.[301,302,303]

In neonates, qualitative HIV-1 RNA assays may be useful for diagnosing or excluding perinatal HIV infection. Sensitivity is 29% in the first week, 79% at 8 to 28 days of age, and >90% at 29 days of age and thereafter.[304] In children, presence of a high viral burden correlates with onset of disease.[297]

However, just as with CD4 lymphocyte counts, there can be variability in bDNA assays of HIV-1 RNA. Though there is no diurnal variation, the HIV-1 RNA level may have up to a 0.4 $\log_{10}$ variance. Genetic subtypes of HIV-1 may provide differences up to a factor of 1.5. The plasma levels of HIV-1 RNA have been shown to increase transiently during bacterial infections. There is lack of standardization among different methodologies. Thus, testing for HIV-1 RNA is not routinely used for diagnosis of HIV-1 infection.[305,306]

NUCLEIC ACID TESTING.-- NAT is based upon the amplification of HIV RNA in plasma. It is possible for this test to detect the presence of HIV RNA up to 11 to 12 days prior to ELISA and 3 to 6 day before the p24 antigen is detected. Thus, NAT has been proposed as a means for reducing the "window" period to only 10 to 12 days from HIV infection to serologic positivity for screening blood product donations. Such tests can potentially detect levels of HIV RNA from 5 to 40 copies/mL.[307]

IMMUNOHISTOCHEMISTRY.-- Immunohistochemical staining methods for diagnosis of HIV-1 in tissues make use of a monoclonal antibody raised against HIV-1 antigen. This is used to detect cells containing HIV-1 provirus in 10% (v/v) neutral buffered formalin-fixed, paraffin-embedded tissues. The method is similar to other immunohistochemical staining methods and can be employed by many laboratories that already use this technique. However, it is not as sensitive as methods that employ DNA probes. Immunohistochemical reagents with antibody to the gp41 component of HIV appear to be superior to those with antibody to p24. Immunohistochemistry is also limited because it requires visual interpretation, often made difficult by background staining, because cells staining for HIV-1 can often be few in number.[308]

IN SITU HYBRIDIZATION.-- In situ hybridization (ISH) makes use of molecular hybridization techniques to create a DNA probe to detect target HIV-1 proviral DNA in fresh tissues, paraformaldehyde or alcohol fixed tissues, or 10% (v/v) neutral buffered formalin-fixed paraffin-embedded tissues. Probes are labeled either with isotopes, in which case autoradiography is required, or with biotin, which requires histochemical methods, for detection. This labeling allows the specific cell type to which the probe has hybridized to be identified by light microscopy, which is useful when the exact localization of HIV-1 within tissues is desired.[309]

HIV-1 CULTURE.-- HIV-1 viral culture for diagnosis requires cultivation of HIV-1 in vitro. This can be accomplished by co-cultivating peripheral blood mononuclear cells (PBMC's) from the patient with normal uninfected PBMC's. Culture supernatants are assayed for HIV production twice weekly, typically by p24 antigen assay, for several weeks. As an alternative, plasma may be cultured to detect cell-free viremia. A whole blood coculture technique may also be used that requires smaller sample volumes.[310] HIV-1 culture can detect approximately half of perinatal HIV-1 infections at birth and about three-fourths up to 3 months of age, with a specificity of 100%. Almost all infants and children beyond 3 months of age have detectable virus.[289,291]

The drawbacks to HIV culture include cost, prolonged time for results to be reported (up to a month), considerable laboratory expertise in performing culture, considerable biohazard to those performing this assay with need for stringent precautions to prevent accidental exposure of laboratory workers, and the possibility of not detecting early infections. Assay of viral reverse transcriptase and use of electron microscopy are additional tools used to assess the growth or cytopathic effects of HIV-1 in cell culture.[288,289]

IMMUNOLOGIC SURROGATE MARKERS.-- T-cell lymphocyte subsets can be helpful in monitoring the course of HIV infection. HIV-1 infection produces quantitative abnormalities in cell populations of the immune system. The helper (inducer) lymphocytes designated as CD4 cells (T4 cells) decrease over time, for they are the prime targets of HIV. The lymphocytes with a suppressor (cytotoxic) function, designated as CD8 cells (T8 cells), are not decreased and may initially be increased. Abnormalities in numbers of CD4 and CD8 T-cell subsets and the helper/suppressor ratio (CD4/CD8) were used very early in the AIDS epidemic to help define persons affected with AIDS before a screening test for HIV-1 was available. A low number of CD4 lymphocytes alone or in combination with a decreased CD4:CD8 ratio and total lymphocyte count can be useful as a predictor of HIV-1 seropositivity and progression of disease.

The CD4 lymphocyte count is typically measured by flow cytometry. Monoclonal antibodies to the various lymphocyte subpopulations (CD3, CD4, CD8, CD45, etc.) with fluorochrome marker are utilized. Guidelines for performance of this assay have been published by the Centers for Disease Control.[311]

In persons with HIV infection 6 years of age or older, a CD4:CD8 ratio of less than 1.0, a total CD4 lymphocyte count of less than 500/μL, and a total lymphocyte count of less than 1500/μL indicate a poor prognosis (see section on *Definition of Pediatric HIV Infection and AIDS* that follows for immunologic parameters in persons <6 years of age).[160,163] A total lymphocyte count of greater than 1250/μL is nearly as good as a CD4 count of greater than 200/μL at predicting that the stage of clinical AIDS has not been reached.[312] Elevated levels of soluble CD30 activation molecule from T-lymphocytes is another factor that is associated with progression to AIDS independent of other factors.[43]

Evaluation of the immune status in HIV infection is complicated by the progressive nature of the infection with a constantly changing immunologic status. The decreases in CD4 lymphocytes and increases in CD8 lymphocytes that are observed in AIDS are also reported in other viral infections, including hepatitis B, Epstein-Barr virus, and cytomegalovirus. Patients with HIV can be infected with other viruses simultaneously at the time of exposure to HIV or as a result of increased susceptibility to additional viral infections from HIV-1-induced immunosuppression. Unlike most viral infections, the T-lymphocyte alterations in response to HIV are progressive and irreversible.[313]

The CD4 lymphocyte count can demonstrate variability, even in the same patient. There can be diurnal variations of more than 100/μL in the CD4 lymphocyte count in the same day due to diurnal variations. Additional laboratory testing factors play a role in measurement of CD4 lymphocytes and include variations in total white blood cell count, lymphocyte percentage, and CD4 percentage. Physiologic factors may include exercise as well as consumption of tobacco, alcohol, and caffeine.[314,315]

Serum beta$_2$-microglobulin (B2-M) is a polypeptide that forms the light chain of class I major histocompatibility complex antigens found on most nucleated cells, can be measured by immunoassays such as EIA. Rising levels of B2-M, which usually increases above background in serum within 6 months of seroconversion, can be used as a marker of disease progression in HIV infection. Increased levels of B2-M in cerebrospinal fluid can be helpful as a marker for HIV-related neurologic diseases such as HIV dementia. Increased levels of B2-M also predict progression to AIDS in perinatally acquired cases of HIV infection. Zidovudine therapy appears to decrease B2-M levels in serum for 2 to 3 months following initiation of therapy, but levels increase to pretreatment levels by 6 months.[163]

Neopterin is a product of macrophages and B lymphocytes stimulated with interferon gamma. It increases in a variety of inflammatory conditions. Neopterin can be measured in serum,

urine, and cerebrospinal fluid by radioimmunoassay and by chromatography. Increasing serum neopterin levels correlate with progression of HIV infection to AIDS. Within 1 to 2 months following initiation of zidovudine therapy, neopterin levels initially fall, then increase slightly and remain below pretreatment levels for about a year.[163]

STRATEGIES FOR HIV TESTING.-- The primary approach to detection of HIV infection remains use of EIA serologic tests for HIV antibody. In developed nations, EIA tests for HIV antibody must be repeatedly reactive and confirmed by Western blot (WB) confirmatory testing before reporting as positive. False negative results are extremely uncommon, and with repeat testing after 3 months to avoid the "window" of possible seronegativity following initial HIV infection, virtually eliminated. Perinatal infections can be confirmed by p24 antigen assay, HIV IgA assay, HIV-1 RNA assay, and by HIV viral culture. Disease progression and response to antiretroviral therapies can be monitored with measurement of plasma viremia by PCR or by following the CD4 lymphocyte count.

The World Health Organization (WHO) have devised a testing approach that does not require use of the WB test. Strategy I is employed in places where the prevalence of HIV infection is 10% or greater, relies on a single rapid EIA test and is recommended for blood product screening and transplantation. Strategy II, recommended where the prevalence of HIV infection is 10% or greater, or where diagnosis of HIV-related diseases is required, calls for confirmation of initial positive EIA tests with a second EIA test. Strategy III, confirmation of two previous EIA positive tests with a third EIA test, is recommended when the prevalence of HIV is less than 10% in the population.[316]

DIAGNOSTIC CRITERIA FOR AIDS IN ADOLESCENTS AND ADULTS

The Centers for Disease Control (CDC) have in the past promulgated criteria for diagnosis, reporting, and clinical staging of AIDS in the United States based upon knowledge about HIV, available laboratory testing, and clinical course.[317,318,319,320]. The 1999 CDC revised surveillance case definition for HIV infection applies to any HIV (including HIV-1 and HIV-2) infection and incorporates the reporting criteria for HIV infection and AIDS into a single case definition:[321]

I. In adults, adolescents, or children aged greater than or equal to 18 months (children aged greater than or equal to 18 months but less than 13 years are categorized as "not infected with HIV" if they meet the criteria in III), a reportable case of HIV infection must meet at least one of the following criteria:

Laboratory Criteria

- Positive result on a screening test for HIV antibody (e.g., repeatedly reactive enzyme immunoassay), followed by a positive result on a confirmatory (sensitive and more specific) test for HIV antibody (e.g., Western blot or immunofluorescence antibody test); or
- Positive result or report of a detectable quantity on any of the following HIV virologic (non antibody) tests:
    - HIV nucleic acid (DNA or RNA) detection (e.g., DNA polymerase chain reaction [PCR] or plasma HIV-1 RNA) - [in adults, adolescents, and children infected by other than perinatal exposure, plasma viral RNA nucleic acid tests should **NOT** be used in lieu of licensed HIV screening tests (e.g., repeatedly reactive enzyme immunoassay). In addition, a negative (i.e., undetectable) plasma HIV-1 RNA test result does not rule out the diagnosis of HIV infection.]
    - HIV p24 antigen test, including neutralization assay
    - HIV isolation (viral culture)

OR

Clinical or Other Criteria (if the above laboratory criteria are not met)

- Diagnosis of HIV infection, based on the laboratory criteria above, that is documented in a medical record by a physician; or
- Conditions that meet criteria included in the case definition for AIDS

II. In a child aged less than 18 months, a reportable case of HIV infection must meet at least one of the following criteria:

Laboratory Criteria:

Definitive: Positive results on two separate specimens (excluding cord blood) using one or more of the following HIV virologic (non antibody) tests:

- HIV nucleic acid (DNA or RNA) detection
- HIV p24 antigen test, including neutralization assay, in a child greater than or equal to 1 month of age
- HIV isolation (viral culture)

OR

Presumptive: Positive results on only one specimen (excluding cord blood) using the above HIV virologic tests and no subsequent negative HIV virologic or negative HIV antibody tests

OR

Clinical or Other Criteria (if the above definitive or presumptive laboratory criteria are not met)

- Diagnosis of HIV infection, based on the laboratory criteria above, that is documented in a medical record by a physician or
- Conditions that meet criteria included in the 1987 pediatric surveillance case definition for AIDS

III. A child aged less than 18 months born to an HIV-infected mother will be categorized for surveillance purposes as "not infected with HIV" if the child does not meet the criteria for HIV infection but meets the following criteria:

Laboratory Criteria

Definitive

- At least two negative HIV antibody tests from separate specimens obtained at greater than or equal to 6 months of age, or
- At least two negative HIV virologic tests from separate specimens, both of which were performed at greater than or equal to 1 month of age and one of which was performed at greater than or equal to 4 months of age

AND

- No other laboratory or clinical evidence of HIV infection (i.e., has not had any positive virologic tests, if performed, and has not had an AIDS-defining condition)

OR

Presumptive

A child who does not meet the above criteria for definitive "not infected" status but who has:

- One negative EIA HIV antibody test performed at greater than or equal to 6 months of age and NO positive HIV virologic tests, if performed, or

- One negative HIV virologic test with at least two subsequent negative virologic tests, at least one of which is at greater than or equal to 4 months of age; or negative HIV antibody test results, at least one of which is at greater than or equal to 6 months of age;

AND

- No other laboratory or clinical evidence of HIV infection (i.e., has not had any positive virologic tests, if performed, and has not had an AIDS-defining condition).

OR

Clinical or Other Criteria (if the above definitive or presumptive laboratory criteria are not met)

- Determined by a physician to be "not infected", and a physician has noted the results of the preceding HIV diagnostic tests in the medical record;

AND

- **NO** other laboratory or clinical evidence of HIV infection (i.e., has not had any positive virologic tests, if performed, and has not had an AIDS-defining condition)

NOTE: HIV nucleic acid (DNA or RNA) detection tests are the virologic methods of choice to exclude infection in children aged less than 18 months. Although HIV culture can be used for this purpose, it is more complex and expensive to perform and is less well standardized than nucleic acid detection tests. The use of p24 antigen testing to exclude infection in children aged less than 18 months is not recommended because of its lack of sensitivity.

IV. A child aged less than 18 months born to an HIV-infected mother will be categorized as having perinatal exposure to HIV infection if the child does not meet the criteria for HIV infection (II) or the criteria for "not infected with HIV" (III).

The revised classification system for HIV infection and AIDS surveillance case definition for adolescents (≥ 13 years) and adults implemented in 1993 is based upon three clinical categories, each subdivided into three CD4 lymphocyte count categories. Clinical categories for staging of HIV infection in the 1993 revised definition are:

CATEGORY A: Conditions listed in Categories B and C must not have occurred. A person is classified in Category A with one or more of the following conditions listed below with documented HIV infection:

- Asymptomatic HIV infection;
- Persistent generalized lymphadenopathy;
- Acute (primary) HIV infection with accompanying illness or a history of acute HIV infection.

CATEGORY B: For classification purposes, Category B conditions take precedence over those in Category A. Persons are included in Category B with symptomatic conditions not included among conditions listed in clinical Category C and that meet at least one of the

following criteria: (a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or (b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. Many Category B diseases are not life-threatening. Examples of conditions in clinical Category B include, but are not limited to:

- Anorectal squamous epithelial dysplasia or carcinoma;
- Bacillary angiomatosis;
- Candidiasis, oropharyngeal (oral thrush);
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy;
- Constitutional symptoms, such as fever (38.5^0 C) or diarrhea lasting >1 month;
- Hairy leukoplakia, oral;
- Varicella (herpes) zoster virus (shingles), involving at least two distinct episodes or more than one dermatome;
- Idiopathic thrombocytopenic purpura;
- Listeriosis;
- Nephropathy, HIV-related;
- Onychomycosis;
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess;
- Peripheral neuropathy

CATEGORY C: For classification purposes, once a Category C condition has occurred, the person so classified will remain in Category C. Many Category C diseases are life-threatening. Clinical conditions for inclusion of a person in Category C are:

- Candidiasis of bronchi, trachea, or lungs;
- Candidiasis, esophageal;
- Cervical cancer, invasive;
- Coccidioidomycosis, disseminated or extrapulmonary;
- Cryptococcosis, extrapulmonary;
- Cryptosporidiosis, chronic intestinal (>1 month's duration);
- Cytomegalovirus disease (other than liver, spleen, or lymph nodes);
- Cytomegalovirus retinitis (with loss of vision);
- Encephalopathy, HIV-related;
- Herpes simplex: chronic ulcer(s) (>1 month's duration); or bronchitis, pneumonitis, or esophagitis;
- Histoplasmosis, disseminated or extrapulmonary;
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma;
- Lymphoma, Burkitt (or equivalent term);
- Lymphoma, immunoblastic (or equivalent term);
- Lymphoma, primary, of brain;
- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary;
- *Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary
- *Penicilliosis marneffei* infection, disseminated
- *Pneumocystis carinii (jirovecii)* pneumonia;
- Pneumonia, recurrent;
- Progressive multifocal leukoencephalopathy;
- *Salmonella* septicemia, recurrent;
- Toxoplasmosis of brain;
- Wasting syndrome due to HIV

The subdivisions of the above categories are made according to the CD4 counts as follows:

Categories A1, B1, C1:	CD4 ≥500 cells/μL
Categories A2, B2, C2:	CD4 200 to 499 cells/μL
Categories A3, B3, C3:	CD4 <200 cells/μL, or <14% CD4 cells

DIAGNOSIS OF AIDS: All persons within Category C as well as all persons in subset 3 with a CD4 lymphocyte count <200/μL (or <14% CD4 cells) meet surveillance criteria for a definition of AIDS.

DEFINITIVE DIAGNOSTIC METHODS FOR DISEASES INDICATIVE OF AIDS

The conditions listed above under Category C may be diagnosed by a variety of methods, depending upon the nature of the disease and the diagnostic methods available. These conditions and the definitive methods are delineated below and in Table 4.

The following diseases are definitively diagnosed by microscopy (histology or cytology): cryptosporidiosis, isosporiasis, Kaposi's sarcoma, lymphoma, lymphoid pneumonia (lymphocytic interstitial pneumonitis) or hyperplasia, *Pneumocystis jirovecii (carinii)* pneumonia, progressive multifocal leukoencephalopathy, toxoplasmosis, cervical cancer.

Candidiasis is definitively diagnosed by: Gross inspection by endoscopy or autopsy, or by microscopy (histology or cytology) on a specimen obtained directly from the tissues affected (including scrapings from the mucosal surface), not from a culture.

The following diseases are definitively diagnosed by microscopy (histology or cytology), culture, or detection of antigen in a specimen obtained directly from the tissues affected or a fluid from those areas: coccidioidomycosis, cryptococcosis, cytomegalovirus, herpes simplex virus, histoplasmosis.

The following diseases are diagnosed definitively by culture: tuberculosis, other mycobacteriosis, salmonellosis, other bacterial infection.

HIV encephalopathy (AIDS dementia) is diagnosed by clinical findings of a disabling cognitive and/or motor dysfunction interfering with occupation or activities of daily living, or loss of behavioral developmental milestones affecting a child, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings. Methods to rule out such concurrent illnesses and conditions must include cerebrospinal fluid examination, and either brain imaging (computerized tomography or magnetic resonance imaging) or autopsy.

HIV wasting syndrome ("slim disease") is diagnosed by findings of profound involuntary weight loss greater than 10% of baseline body weight plus either chronic diarrhea (2 or more loose stools per day for 30 or more days) or chronic weakness and documented fever (for 30 or more days, intermittent or constant) in the absence of a concurrent illness or condition other than HIV infection that could explain the findings (such as cancer, tuberculosis, cryptosporidiosis, or other specific enteritis).

Recurrent pneumonia is diagnosed definitively by the finding of recurrence (more than one episode of pneumonia in a 1 year period), acute onset (new radiographic evidence not present earlier) of pneumonia diagnosed by both a) culture (or other organism-specific diagnostic method) obtained from a clinically reliable specimen of a pathogen that typically causes pneumonia (other than *Pneumocystis jirovecii (carinii)* or *Mycobacterium tuberculosis*), and b) radiologic evidence of pneumonia; cases that do not have laboratory confirmation of a causative organism for one of the episodes of pneumonia will be considered to be presumptively diagnosed.

DISEASES INDICATIVE OF AIDS DIAGNOSED PRESUMPTIVELY

Given the seriousness of diseases indicative of AIDS, it is important to diagnose diseases indicative of AIDS definitively, especially when the therapy used may have serious side-effects or when definitive diagnosis is needed to determine the appropriateness of antiretroviral therapy. Nonetheless, in some situations, a patient's condition may not permit the performance of definitive tests. In other situations, accepted clinical practice may be to diagnose presumptively, based on the presence of characteristic clinical and laboratory abnormalities. The complete guidelines for presumptive diagnoses are given under disease headings in the organ systems in Chapter 4.

The diseases with criteria for a presumptive clinical diagnosis of AIDS include:

- Candidiasis of the esophagus
- Cytomegalovirus retinitis with loss of vision
- Kaposi's sarcoma of skin and mucous membranes
- Lymphoid interstitial pneumonia (LIP) affecting a child younger than 13 years of age
- Mycobacteriosis
- *Pneumocystis carinii (jirovecii)* pneumonia
- Pneumonia, recurrent
- Tuberculosis, pulmonary
- Toxoplasmosis of brain

PEDIATRIC HIV INFECTION AND AIDS

The diagnosis of HIV infection and of AIDS in children under 13 years of age varies slightly from that in an adult. Significantly, children under the age of 18 months may still retain passively acquired maternal HIV antibody, while those above 18 months rarely have residual maternal antibody, so standard immunologic tests alone for HIV infection (EIA and confirmatory Western blot) cannot be used to define HIV infection in this setting. Both HIV viral culture and polymerase chain reaction (PCR) assays for HIV RNA or proviral DNA, however, can be used to detect HIV infection in infants born to HIV-infected mothers with nearly 100% sensitivity by 3 to 6 months of age.[319]

The criteria for diagnosis of human immunodeficiency virus (HIV) infection in children was redefined by the Centers for Disease Control (CDC) in 1994 (establishing new criteria beyond the 1987 AIDS surveillance case definition[318]) and superseded by the 1999 definition.[321] Classification into mutually exclusive categories is made through assessment of: a) infection status, b) clinical status, and c) immunologic status. An HIV-infected child cannot be reclassified from a more severe to a less severe category.

The clinical categories for children with HIV infection are made by the 1994 CDC definition as follows:

Category N: Not symptomatic. Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A.

Category A: Mildly symptomatic. Children with two or more of the conditions listed below but none of the conditions listed in Category B and C.

- Lymphadenopathy (≥0.5 cm at more than two sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

Category B: Moderately symptomatic. Children who have symptomatic conditions other than those listed for Category A or C that are attributed to HIV infection.

Examples of conditions in clinical Category B include but are not limited to:

- Anemia (<8 gm/dL), neutropenia (<1000/mm^3), or thrombocytopenia (<100,000/mm^3) persisting ≥30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children > 6 months of age
- Cardiomyopathy
- Cytomegalovirus infection, with onset before one month of age
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (more than 2 episodes within 1 year)
- Varicella (herpes) zoster virus (shingles) involving at least two distinct episodes of more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonitis (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis

- Persistent fever (lasting 1 month)
- Toxoplasmosis with onset before 1 month of age
- Varicella, disseminated (complicated chicken pox)

Category C: Severely symptomatic. Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome with the exception of LIP. Conditions included in clinical Category C for children infected with human immunodeficiency virus (HIV) include:

- Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhea persisting >1 month
- Cytomegalovirus disease with onset of symptoms at age >1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (for criteria, see section in Central Nervous System Pathology in AIDS)
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists for >1 month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a child >1 month of age
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi's sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved (Burkitt), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype
- *Mycobacterium tuberculosis*, disseminated or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Pneumocystis carinii (jirovecii)* pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (non typhoid) septicemia, recurrent
- Toxoplasmosis of the brain with onset at >1 month of age
- Wasting syndrome in the absence of concurrent illness other than HIV infection that could explain the following findings:

  a) persistent weight loss >10% of baseline

  or:

  b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child ≥1 year of age

  or:

c) <5th percentile on weight-for-height chart on two consecutive measurements, ≥30 days apart PLUS a) chronic diarrhea (i.e., at least two loose stools per day for ≥30 days) OR b) documented fever (for ≥30 days, intermittent or constant)

The immunologic categories for clinical classification of HIV infection in children is based on age-specific CD4 lymphocyte counts and the percent of total lymphocytes as follows:

Immunologic category 1: No evidence of suppression
Immunologic category 2: Evidence of moderate suppression
Immunologic category 3: Severe suppression

	Age of child					
	< 12 months		1-5 years		6-12 years	
Immunologic category	CD4 /μL	%	CD4 /μL	%	CD4 /μL	%
1:	≥1500	(≥25)	≥1000	(≥ 25)	≥500	(≥ 25)
2:	750-1499	(15-24)	500-999	(15-24)	200-499	(15-24)
3:	<750	(<15)	<500	(<15)	<200	(<15)

Thus, the 1994 CDC classification system for HIV infection can be summarized as follows:

N = No signs or symptoms
A = Mild signs or symptoms
B = Moderate signs or symptoms
C = Severe signs or symptoms

		Clinical Categories*			
Immunologic Categories		N	A	B	C
1.	No evidence of suppression	N1	A1	B1	C1
2.	Evidence of moderate suppression	N2	A2	B2	C2
3.	Severe suppression	N3	A3	B3	C3

* Children whose HIV infection status is not confirmed are classified by using the above grid with a letter E (for perinatally exposed) placed before the appropriate classification code (e.g., EN1, EA3, etc.)

1987 PEDIATRIC AIDS SURVEILLANCE CASE DEFINITION.-- Evidence for HIV infection in a child <18 months of age is defined as:[128]

- Demonstration of HIV in blood or tissues by culture or nucleic acid probes; or
- HIV antigen detection (p24 antigen) in serum; or repeatedly reactive serum screening test for HIV antibody (e.g., EIA) along with specific antibody identified by the use of supplemental tests (such as Western blot or immunofluorescence assay), plus increased serum immunoglobulin levels and at least one of the following abnormal immunologic test results:

- reduced absolute lymphocyte count
- depressed CD4+ T-lymphocyte count
- decreased CD4:CD8 lymphocyte ratio

and one or more findings present in staging category P-2 as defined below.

Evidence for HIV infection in a child >15 months is defined similarly to that of an adult, and demonstration of HIV antibody alone is sufficient for diagnosis of HIV infection.

The clinical categories of HIV infection in the 1987 CDC surveillance case definition (with the corresponding categories for the 1994 classification in parentheses) are as follows:[318,319]

CLASS P-0 (PREFIX "E" IN 1994) - Indeterminate infection: includes perinatally exposed infants and children up to 15 months of age who cannot be classified as definitely infected according to the above criteria but who have antibody to HIV, indicating exposure to a mother who is infected.

CLASS P-1 (N IN 1994) - Asymptomatic infection: includes patients who meet one of the above definitions for HIV infection but who have had no previous signs or symptoms that would have led to classification in Class P-2.

Subclass A - Normal immune function: includes children with no immune abnormalities associated with HIV infection.

Subclass B - Abnormal immune function: includes children with one or more immune abnormalities such as hypergammaglobulinemia, T4 lymphopenia, decreased T4:T8 ratio, and absolute lymphopenia. Other causes of these abnormalities must be excluded.

Subclass C - Not tested: includes children for whom no or incomplete (see above) immunologic testing has been done.

CLASS P-2 - Symptomatic infection: includes patients meeting the above definitions for HIV infection and having signs and symptoms of infection, with other causes excluded. Patients may be classified into more than one subclass.

Subclass A (A, B, and C in 1994) - Nonspecific findings: includes children with two or more unexplained nonspecific findings persisting for more than 2 months, including fever, failure-to-thrive or weight loss of more than 10% of baseline, hepatomegaly, splenomegaly, generalized lymphadenopathy (lymph nodes measuring at least 0.5 cm present in two or more sites, with bilateral lymph nodes counting as one site), parotitis, and diarrhea (three or more loose stools per day) that is either persistent or recurrent (defined as two or more episodes of diarrhea accompanied by dehydration within a 2-month period).

Subclass B (C in 1994) - Progressive neurologic disease: includes children with one or more of the following progressive findings:

1) loss of developmental milestones or intellectual ability,
2) impaired brain growth (acquired microcephaly and/or brain atrophy demonstrated on computed tomographic scan or magnetic resonance imaging scan), or

3) progressive symmetrical motor deficits manifested by two or more of these findings: paresis, abnormal tone, pathologic reflexes, ataxia, or gait disturbance.

Subclass C (B in 1994) - Lymphoid interstitial pneumonitis: includes children with a histologically confirmed pneumonitis characterized by diffuse interstitial and peribronchiolar infiltration of lymphocytes and plasma cells and without identifiable pathogens, or, in the absence of a histologic diagnosis, a chronic pneumonitis--characterized by bilateral reticulonodular interstitial infiltrates with or without hilar lymphadenopathy--present on chest roentgenogram for a period of at least 2 months and unresponsive to appropriate antimicrobial therapy, with other causes of interstitial infiltrates to be excluded.

Subclass D - Secondary infectious diseases: includes children with a diagnosis of an infectious disease that occurs as a result of immune deficiency caused by infection with HIV.

Category D-1 (C in 1994) - includes patients with secondary infection disease due to one of the specified infectious diseases listed in the CDC surveillance definition for adolescent and adult AIDS (as given above), except that criteria for potential congenital infections are modified as follows:

- Toxoplasmosis, disseminated, with onset after 1 month of age
- Cytomegalovirus infection with onset after 6 months of age
- Herpes simplex virus infection, chronic mucocutaneous or disseminated, with onset after 1 month of age

Category D-2 (C in 1994) - includes patients with unexplained, multiple or recurrent, serious bacterial infections (any combination of at least two within a 2-year period), of the following types in a child less than 13 years of age: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media or superficial skin or mucosal abscesses), caused by *Haemophilus*, *Streptococcus* (including pneumococcus), or other pyogenic bacteria

Category D-3 (B in 1994) - includes patients with other infectious diseases, including oral candidiasis persisting for 2 months or more, two or more episodes of herpes stomatitis within a year, or multidermatomal or disseminated varicella (herpes) zoster virus infection.

Subclass E - Secondary cancers: includes children with any cancer described below in categories E-1 and E-2.

Category E-1 (C in 1994) - includes patients with Kaposi's sarcoma, B-cell non Hodgkin lymphoma, or primary lymphoma of the brain.

Category E-2 (B in 1994) - includes patients with the diagnosis of other malignancies possibly associated with HIV infection.

Subclass F (B in 1994) - Other diseases: includes children with other conditions possibly due to HIV infection not listed in the above subclasses, such as hepatitis, cardiomyopathy, nephropathy, hematologic disorders, and dermatologic diseases.

DIAGNOSIS OF AIDS BY 1987 SURVEILLANCE CASE DEFINITION--. Children who fulfill criteria for HIV infection and who have a reliably diagnosed disease at least moderately indicative of underlying cellular immunodeficiency and no other known cause of underlying cellular immunodeficiency or any other reduced resistance reported to be associated with that disease (see Table 3) meet surveillance criteria for a definition of AIDS.

Criteria for pediatric AIDS are essentially the same as for adult AIDS except that (1) for children <15 months of age the HIV antibody test alone will not necessarily be indicative of HIV infection and further criteria must be applied, (2) the criteria for use of the indicator diseases toxoplasmosis, cytomegaloviral infection, and herpes simplex virus infection are modified, (3) HIV encephalopathy is replaced by specific criteria in children for progressive neurologic disease, (4) HIV wasting syndrome is replaced by expanded non-specific criteria in children for failure to thrive, and (5) lymphoid interstitial pneumonitis is added as an indicator disease in children.

CRITERIA FOR PERSISTANT GENERALIZED LYMPHADENOPATHY

The original criteria for inclusion of patients into the condition of persistent generalized lymphadenopathy (PGL) are given below:

- Persistent generalized lymphadenopathy involving two or more extra inguinal sites lasting 3 months or more
- Absence of an intercurrent disease or illness causing the lymphadenopathy
- Reactive pattern on tissue biopsy

CRITERIA FOR AIDS-RELATED COMPLEX

AIDS-related complex (ARC) was a category of HIV infection used early in the AIDS epidemic before more specific staging criteria were formulated. The term ARC is no longer widely used. The definition is given here for historical purposes and to allow correlation with earlier studies. AIDS-related complex is defined as a syndrome in which a person has laboratory evidence for HIV infection along with PGL, without other causes for immunodeficiency, and has at least two of the clinical and two of the laboratory findings listed below. Additional clinical disorders commonly found in patients with ARC include cutaneous and oral fungal infections, chronic diarrhea, idiopathic thrombocytopenic purpura, nephrotic syndrome, and in children failure to thrive with chronic and persistent infections. Often, further testing of the immune system is necessary before other causes of these disorders can be ruled out.

Clinical findings may include:

- Intermittent or continuous fever (greater than 38.5^{o} C) not associated with infection
- Unexplained weight loss of > 10% of body weight
- Intermittent or continuous diarrhea (more than 3 stools per day) without an identifiable pathogen
- Unexplained excessive fatigue producing decreased physical or mental ability
- Intermittent or continuous night sweats without an infection.

Laboratory findings may include:

- Neutropenia, lymphopenia, thrombocytopenia, or anemia
- Decreased absolute T-helper cells
- Decreased T-helper/suppressor ratio
- Decreased blastogenesis
- Increased serum immunoglobulin
- Anergy to skin tests.

OTHER CAUSES OF IMMUNOSUPPRESSION

Disease processes may occur in the population at risk for HIV infection that are neither caused by HIV, nor are potentiating factors, but which can lead to immunosuppression. These conditions may account for acquired immunodeficiency states. Lymphoreticular malignancies can occur in age groups in which HIV infection is prevalent, but such diseases have not been linked with AIDS by definition, except for the high grade lymphomas in persons within whom an HIV infection can be demonstrated. Among these are non-Hodgkin lymphomas, leukemias, and Hodgkin disease. Persons undergoing cancer chemotherapy may also have immune system dysfunction and clinical findings similar to patients with AIDS. Patients undergoing organ transplantation and persons with collagen vascular diseases may also be treated with immunosuppressive regimens placing them at risk for opportunistic infections. Long-term corticosteroid therapy can produce lymphopenia and immune dysfunction. The extreme debilitation accompanying malnutrition, drug abuse, and dementia can also reduce immune function, though the infections in these persons are usually bacterial.

Primary immunodeficiency states must be considered in the differential diagnosis of AIDS, particularly in infants and children. Such conditions may include severe combined immunodeficiency (SCID), partial or complete DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia, chronic granulomatous disease, and agammaglobulinemia or hypogammaglobulinemia with raised IgM. Common variable immunodeficiency (CVID) may occur at a variety of ages, including young to middle aged adults.

Appropriate laboratory testing, including tests for HIV when indicated, must be employed to distinguish immunodeficiency states. A thorough history and physical examination aids in this process. Immunodeficiency states can be multifactorial in origin. As always, to use the CDC definition for diagnosis of AIDS, it is necessary to determine HIV status with certainty. Without evidence for HIV infection, a search for other causes of immunosuppression should always be done, regardless of the age of the patient. Both inherited as well as acquired immunodeficiency states may occur.

ALTERNATIVE STAGING SYSTEMS FOR HIV INFECTION

The World Health Organization (WHO) have proposed staging criteria for HIV infection for use in places where the CDC criteria cannot be readily applied in the absence of definitive information on CD4 lymphocyte counts. These criteria, based upon both laboratory and clinical findings, define four clinical stages of persons demonstrated to have HIV infection as follows:[322]

CLINICAL STAGE 1 - asymptomatic

1. Asymptomatic
2. Persistent generalized lymphadenopathy (PGL)

Performance scale 1: asymptomatic, normal activity

CLINICAL STAGE 2 - early mild disease

3. Weight loss <10% of body weight
4. Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
5. Varicella (herpes) zoster virus infection within the last 5 years
6. Recurrent upper respiratory infections (i.e., bacterial sinusitis)

And/or Performance scale 2: symptomatic, normal activity

CLINICAL STAGE 3 - intermediate (moderate) disease

7. Weight loss >10% of body weight
8. Unexplained chronic diarrhea, >1 month
9. Unexplained prolonged fever (intermittent or constant), >1 month
10 Oral candidiasis (thrush)
11. Oral hairy leukoplakia
12. Pulmonary tuberculosis within the past year
13. Severe bacterial infections (i.e., pneumonia, pyomyositis)

And/or Performance scale 3: bed-ridden, <50% of the day during the last month

CLINICAL STAGE 4 - late (severe) disease (basically equivalent to AIDS)

14. HIV wasting syndrome, as defined by CDC
15. *Pneumocystis carinii (jirovecii)* pneumonia (PCP)
16. Toxoplasmosis of brain
17. Cryptosporidium with diarrhea, >1 month
18. Cryptococcosis, extrapulmonary
19. Cytomegalovirus (CMV) disease of an organ other than liver, spleen, or lymph nodes
20. Herpes simplex virus (HSV) infection, mucocutaneous >1 month, or visceral any duration
21. Progressive multifocal leukoencephalopathy (PML)
22. Any disseminated endemic mycosis (i.e., histoplasmosis, coccidioidomycosis)
23. Candidiasis of the esophagus, trachea, bronchus, or lungs
24. Atypical mycobacteriosis, disseminated

25. Non-typhoidal *Salmonella* septicemia
26. Extrapulmonary tuberculosis
27. Lymphoma
28. Kaposi's sarcoma (KS)
29. HIV encephalopathy, as defined by CDC

And/or Performance scale 4: bed-ridden, >50% of the day during the last month

(Note: both definitive and presumptive diagnoses are acceptable)

Several staging systems for HIV infection, in addition to those by the CDC and WHO given above, have been devised to assess prognosis, to define study groups, and to determine the selection, timing, and appropriateness of treatments. The systems define progressive stages from asymptomatic HIV infection through AIDS via laboratory testing for immunologic competence and via specific clinical signs. The Walter Reed Staging Classification (WRSC) has five stages based upon appearance of lymphadenopathy, progressive depletion of CD4 lymphocytes, appearance of skin test anergy, and presence of oral thrush. An immunologic staging system (ISS) defines four stages with the sequential appearance of: CD4:CD8 ratio less than 1.0, absolute CD4 lymphocyte count less than 500/μL, and total lymphocyte count less than 1500/μL. A simplified system has three stages: asymptomatic, CD4 lymphocytes less than 400/μL or oral disease (thrush or hairy leukoplakia) present, and both CD4+ depletion and oral disease.[323]

Cofactors of age, sex, and other underlying disease may modify HIV disease progression and survival. Use of the above systems depends upon the availability of laboratory testing, close clinical monitoring, and diagnostic acumen. Once clinical AIDS develops, survival diminishes markedly with appearance of one or more of the following: severe diarrhea, serum albumin less than 2.0 g/dl, any neurologic deficit, arterial oxygen tension greater than or equal to 50 mm Hg, hematocrit less than .30, total lymphocyte count less than 150/μL, white blood cell count less than 2500/μL, and platelet count less than 140 X 10^9/L.[323]

CHAPTER 3 - OPPORTUNISTIC INFECTIONS IN AIDS

The various infectious agents that are defined by the Centers for Disease Control (CDC) as diagnostic of AIDS when present in persons infected with HIV can produce a host of clinical and pathologic conditions. There may be regional, racial, age, or gender-associated variations in the incidences of opportunistic infections seen with AIDS. Table 5 depicts organ or organ system distribution of AIDS-defining diseases in a large metropolitan public hospital autopsy series. Table 6 indicates the extent of dissemination for those diseases. Table 7 outlines the various treatment modalities.[324]

PNEUMOCYSTIS JIROVECII (CARINII) INFECTIONS

Prior to the AIDS epidemic, *Pneumocystis carinii*. renamed to *P jirovecii* in humans, was known primarily as an opportunistic pathogen of severely debilitated or immunocompromised persons, including patients on chemotherapy, renal transplant recipients, patients with congenital immune deficiencies, and nutritionally deprived infants. Though still infecting these groups, *P carinii* today is most often seen in association with AIDS. Infection with *P carinii* is acquired via the respiratory tract and is primarily manifested as a severe pneumonia, called *Pneumocystis carinii* pneumonia (PCP). *P carinii* is widely distributed, but PCP historically complicated the course of AIDS more often in North America and Europe than in Africa and Asia. However, the numbers of cases of PCP in developed nations are dropping due to prophylaxis, while cases in developing nations are increasing, particularly in conjunction with concomitant *Mycobacterium tuberculosis* infection.[325]

Serologic evidence suggests that most humans have become exposed to *P carinii* by age 2. However, there are no defined clinical syndromes for *P carinii* infection in immunocompetent persons. Molecular typing has identified over 50 different variants of *P carinii*. Most of the variations occur in the internal transcribed spacer (ITS) regions 1 and 2 of the nuclear rRNA operon. Analysis of these genotypes reveals that patients may become reinfected with new genotypes, or that a different genotype of the organism may be detected during a single episode of pneumonia. However, the clinical severity of infection is not affected by genotype.[326] Immunocompromised persons who develop PCP probably have reinfection rather than reactivation of prior infection.[327]

P carinii is a one-celled organism with a life cycle similar to that of protozoa such as *Toxoplasma gondii*. Ultrastructurally, *P carinii* organisms lack a complex organelle system but contain intracystic bodies, which is typical of protozoa. However, both argyrophilia of the *P carinii* cyst walls as well as ribosomal RNA sequence studies suggest that *P carinii* is a fungal organism most closely related to *Saccharomyces*. There is not as yet a routine culture method available for this organism outside of research laboratories. Serologic testing is not often useful, for most people have some detectable antibodies. Diagnosis is routinely made histopathologically by obtaining tissue or cytologic specimens from the lung.[328,329]

Mature cyst forms of *P carinii* contain up to eight sporozoites. When the cysts rupture, the released sporozoites mature into trophozoites and repeat the cycle. In tissue sections the cysts are identified by cell wall stains such as Gomori methenamine silver (GMS), cresyl violet, or toluidine blue. Gomori methenamine silver staining gives the best contrast for screening of a tissue section or cytologic smear because the red cell-sized *P carinii* organisms have a dark brown-black color. The 5 to 7 micron cysts usually occur in cohesive clusters. They are round to elliptical in shape with sharp but sometimes slightly folded edges resembling crushed ping-pong balls. Folding or rupture produces crescentic (parenthesis-shaped) or cup-shaped forms. The lightly-stained folds of the *P carinii* cell membranes may appear as a central dark dot. Endothelial cell nuclei, in contrast, have a granular to stippled appearance. Red blood cells may be concave, folded, or crescentic, but they are smaller, do not typically appear clustered in alveoli, and have no central dot. Precipitated

stains are variably sized, have angular borders and are distributed haphazardly throughout the slide with no regard for tissue structures. [328]

The *P carinii* organisms are typically found within a foamy to granular pink exudate within alveoli. This foamy exudate is seen by electron microscopy to be composed of cysts and trophozoites with little or no fibrin. The organisms appear to be held together by slender membranotubular extensions growing from their surfaces. The uneven contours of the organisms lead to the formation of voids that contribute to the characteristic light microscopic appearance of the foamy exudate. *P carinii* cysts have a characteristic folded or crescentic appearance.[328]

The GMS stain is most frequently used for diagnosis of *Pneumocystis carinii*. There are a variety of methods published for the performance of this stain, and some of them employ a microwave oven or pre-treatment with oxidizers to reduce the time needed for completion to under 20 minutes and improve recognition of organisms.[330,331] Regardless of which method is chosen, it is crucial that this stain be performed as consistently as possible to avoid both false positive and false negative diagnoses.

False negative methenamine silver stains result from under stained preparations in which the *P carinii* cysts are too faint to be recognized. Over staining results in false negative results if there is so much black precipitate on the slide that it obscures the organisms. False positive preparations come from over staining so that red blood cells, endothelial cell nuclei, or precipitated stain that appear the same overall size and shape as *Pneumocystis* organisms are misinterpreted.[332]

Several additional methods are available in addition to GMS staining for identification of *P carinii* in smears. Giemsa or Diff-Quik staining identifies the small, delicate intracystic bodies, or sporozoites (up to 8), under oil immersion (1000X) arranged in a clock face to haphazard distribution within the cyst and appearing as 1 to 2 micron dark blue dots. Giemsa or Diff-Quik stains cannot demonstrate the cell wall, so contrast is poor, limiting this technique primarily to cytologic material obtained from bronchoalveolar lavage or sputum specimens. This method is preferred by some pathologists because the appearance is quite characteristic, giving a high specificity, and the method is simple and quick.[333]

The calcofluor white stain can also be utilized to detect cysts of *P carinii* in pulmonary specimens.[335] With calcofluor white, a chemofluorescent stain, cysts of *P carinii* will appear under fluorescence microscopy with light peripheral staining along with a double-parenthesis-like structure near the center of the cysts.[334] The sensitivity of this stain is as good as GMS for detection of *P carinii* cysts.[334]

Highly sensitive and specific direct fluorescence antibody (DFA) and immunohistochemical stains, as well as the polymerase chain reaction (PCR), are available that can enhance screening sensitivity for *Pneumocystis*. The direct fluorescent antibody (DFA) stains available for diagnosis of *Pneumocystis* in cytologic specimens are usually obtained from induced sputum or bronchoalveolar lavage. Sensitivity with the DFA technique is good, but specificity requires skill in interpretation. PCR for *P carinii* has a sensitivity of 100% but a specificity around 80% and should be considered in cases of atypical PCP where few organisms are present.[335,336]

Fluorescence microscopy may aid in screening of Papanicolaou stained organisms which will demonstrate a bright yellow autofluorescence (from the eosin component of the stain) of the *P carinii* cell wall. Immunofluorescence procedures are not technically difficult and allow diagnosis in less than 1 hour.[337]

All of these methods can be highly sensitive and specific when performed routinely. Immunohistochemical staining is slightly more sensitive than GMS stains in tissues and fluids.[338] The DFA is more sensitive than the calcofluor white method in cytologic preparations.[335] The Diff-Quik and DFA are the most cost-effective.[339]

The clinical, gross, and microscopic appearances of *P carinii* pneumonia (PCP) are described fully in the section on respiratory tract pathology. Dissemination of *Pneumocystis* outside of the lungs is uncommon (less than 5% of cases). The use of aerosolized pentamidine isethionate, without systemic therapy, as a prophylaxis against *Pneumocystis* pneumonia has been suggested as a possible etiologic factor for this phenomenon. Only hilar lymph nodes, or another single organ, may be involved, while in rare cases multiple organs are affected (Table 5).[340]

The extrapulmonary microscopic appearance of *Pneumocystis* is often similar to that of the alveoli, with a foamy to granular pink exudate on hematoxylin-eosin stain. However, in widely disseminated cases, *P carinii* can produce numerous small 0.1 to 0.3 cm calcified granulomas that give cut surfaces of parenchymal organs the gross appearance of rough sandpaper. These calcifications can demonstrate a stippled appearance on roentgenography, as in the pointillist style of painting. In the spleen, multiple nonenhancing, low-density masses with necrosis, hemorrhage, or peripheral to punctate calcification may be seen with computed tomographic scans. Ultrasound may reveal small echogenic foci in liver parenchyma. Microscopically, foamy to granular pink exudate may be present with extensive calcium deposition. *P carinii* may coexist with other infectious agents, particularly mycobacteria, at disseminated sites. A Gomori methenamine silver stain reveals the organisms, even in densely calcified areas, but immunoperoxidase staining with monoclonal antibody to *P carinii* can be helpful when cysts are not readily identified.[340,341]

Survival in persons with AIDS has been markedly increased through prophylaxis for PCP, primarily through use of trimethoprim-sulfamethoxazole (TMP-SMX), dapsone, or aerosolized pentamidine. Antipneumocystis medication is recommended for AIDS patients with CD4 lymphocyte counts <200/μL. Patients who receive highly active antiretroviral therapy and who have a CD4 count that remains above 200/μL for more than 3 months can safely discontinue PCP prophylaxis.[252] Pyrimethamine-sulfadoxine has also been used for PCP prophylaxis. Adverse drug reactions (skin rash, fever, leukopenia, hepatitis) occur in half of patients taking TMP-SMX, and may necessitate an alternative therapy, but the other agents are also associated with adverse reactions.[161,162,253] Patients with access to routine medical care may have multiple episodes of PCP diagnosed and treated successfully over months to years. However, patients with AIDS may still succumb to PCP in their terminal course.[342]

There is evidence that some *P carinii* strains are developing resistance to sulfa drugs. This is mediated via mutations in the dihydropteroate synthase (DHPS) gene. Resistance is more commonly demonstrated in persons who have been receiving PCP prophylaxis. In the early 21st century, however, drug regimens still remain effective.[327]

CYTOMEGALOVIRUS INFECTIONS

Cytomegalovirus (CMV) is a very frequent infection complicating AIDS. The seroprevalence of CMV is very high in patients infected with HIV. Venereal transmission appears to be the most common route of infection in adults, though CMV can also be spread through genital secretions, oropharyngeal sections, urine, breast milk, and blood. Virus can be shed by asymptomatic persons who have primary infection or reactivation of latent infection. Most patients with AIDS who develop clinical signs and symptoms of CMV infection probably have reactivation of previous infection rather than primary infection.[343]

CMV is the most widely distributed opportunistic agent seen with AIDS and, unlike *Pneumocystis carinii*, which nearly always involves only the lung, CMV can and does involve many organs. The most clinically significant sites of involvement are lung, gastrointestinal tract, brain, and eye. In a large autopsy series, CMV occurred most frequently in adrenal and respiratory tract, followed by the gastrointestinal tract, central nervous system, and eye, infrequently in spleen and genitourinary tract, and rarely in lymph node, skin, liver, bone marrow, or heart (Table 5).[343]

The diagnosis of CMV retinopathy, one of the most clinically debilitating complications of CMV infection, is made on funduscopic examination because of the inability to obtain tissue from this site. Many patients with CMV retinopathy develop partial or complete blindness. Additional clinical manifestations of CMV infection can include altered mental status, pneumonitis with non-productive cough, colitis or esophagitis with or without gastrointestinal hemorrhage, adrenal insufficiency, hepatitis, or radiculitis.

Cytomegalovirus can be detected through culture of blood, fluids, or tissues containing the virus, but culture methods are expensive and time consuming, and the presence of CMV does not always correlate with infection causing disease. Serologic titers are not very useful to detect CMV infection, since at least 30% of persons without immunosuppression also have antibodies to CMV, and the seroprevalence is very high among immunosuppressed persons. Changing titers of antibodies may aid in the detection of response to therapy in some patients with CMV.[343]

Examination of tissue biopsies obtained from pulmonary or gastrointestinal endoscopy by routine light microscopy is often the simplest means for the diagnosis of CMV, but sensitivity is decreased by sampling error, for diagnostic inclusions can be widely scattered or infrequent. Immunofluorescent antibody staining of tissues may aid diagnostic screening in some cases. Techniques to detect cytomegaloviral DNA by *in situ* hybridization or polymerase chain reaction are more sensitive than light microscopy. The presence of CMV in bronchoalveolar lavage or sputum specimens does not necessarily indicate a clinically important infection. At autopsy, diagnosis is most often made histologically by finding characteristic CMV inclusions in the adrenal gland or lung (Table 5).[344]

Cytomegalovirus is a DNA virus of the herpesvirus group. It produces an enlargement of the infected cell, and microscopically with hematoxylin-eosin staining, a large 5 to 15 micron sized violaceous to dark red intranuclear inclusion surrounded by a thin clear halo can be seen. The nucleus of the infected cell is usually eccentrically positioned. More than one inclusion body may be present. Additionally, the cytoplasm of infected cells may contain coarse dark basophilic bodies 2 to 3 microns in size representing replication of virions in the cytoplasm. The cell border is not prominent. In tissue sections the cytomegalic cells are large and distinctive (30 to 100 microns) with rounded to oblong shapes. The plane of sectioning may not always reveal the intranuclear inclusion completely, so the finding of large cells alone should prompt a careful search for diagnostic inclusions elsewhere. Vascular endothelium, epithelial surfaces, adrenal medulla, and cortex near ependymal or meningeal surfaces of the brain are particularly good places to look for inclusions.

The tissue responses to CMV are quite varied. Often when there are infrequent and/or widely scattered inclusions, there is little appreciable inflammatory reaction accompanying the inclusions. In these cases the presence of CMV may not be associated with clinical disease. In other cases, the cytomegalic cells are accompanied by the presence of small focal areas of

inflammation, hemorrhage, or necrosis. In a few cases, there are large numbers of inclusions and the surrounding tissues are markedly inflamed, hemorrhagic, or necrotic. The inflammation can range from clusters of small lymphocytes to mixed infiltrates with lymphocytes and neutrophils to diffuse neutrophilic infiltrates. A granulomatous response is not seen and calcification does not occur.[344] In persons starting highly active antiretroviral therapy (HAART) there can be an immune restoration syndrome (IRD) marked by more florid inflammation, including an immune recovery uveitis with CMV infection.[231]

Cytomegalovirus-infected cells must be distinguished from macrophages and ganglion cells, which may also be large, have prominent nucleoli, and have basophilic stippling of the cytoplasm. Nucleoli of such cells are smaller and basophilic stippling is finer than in cytomegalic cells. *Toxoplasma gondii* pseudocysts have bradyzoites that resemble the basophilic inclusions of CMV, but the pseudocyst wall is thicker than the CMV cell membrane and the basophilic inclusions of CMV are coarser and more variable than bradyzoites. Both in situ hybridization and immunoperoxidase methods are useful for detection of cytomegalovirus, particularly when classic intranuclear inclusions are not present.[345]

Cytomegalovirus infection is the immediate cause of death in only 10% of AIDS cases overall and in 20% of cases in which CMV infection is present at autopsy. Usually, CMV is an indolent infection. Deaths from CMV infection result from pulmonary involvement in two thirds of cases, central nervous system involvement in one fourth, and gastrointestinal tract involvement in one eighth. Despite the high number of cases with adrenal involvement, death from adrenal failure is rare.[344]

Ganciclovir (9-[1,3-dihydroxy-2-propoxymethyl] guanine, abbreviated DHPG), the first drug of choice, and Foscavir (foscarnet, trisodium phosphonoformate) have been used to treat patients with CMV, particularly those with retinitis. The agent, valacyclovir, is an acyclovir congener that is rapidly metabolized to acyclovir in vivo. Another agent requiring no intracellular viral activation is cidofovir, a nucleoside analogue of cytosine with potent activity against herpesviruses. Ganciclovir, foscarnet, or valacyclovir may provide symptomatic relief in AIDS patients with CMV, and the infection is often slowed or tissue destruction diminished and survival is increased. Prophylaxis with ganciclovir or cidofovir may be used in selected patients. In treated patients who later die, residual CMV infection can usually be found at autopsy in one or more organ sites.[161,344,250,346]

MYCOBACTERIAL INFECTIONS

MYCOBACTERIUM AVIUM COMPLEX.-- Mycobacterium avium complex (MAC), also known as *Mycobacterium avium-intracellulare* (MAI), is considered a non-pathogen in non-immunocompromised persons. This complex can be further sub classified, but the clinical and pathologic findings are similar in AIDS, so that it remains useful to refer to these organisms collectively as MAC. Patients probably become colonized with MAC via the gastrointestinal or respiratory tract. The organisms can penetrate the gastrointestinal mucosa and are taken up into submucosal macrophages. These macrophages are then transported to abdominal lymph nodes and from there to the bloodstream. Cases of MAC in immunocompromised persons probably represent reinfection rather than reactivation of prior infection.[347]

The risk for disseminated disease with MAC is increased with CD4 lymphocyte counts below 100/μL. Infections with MAC are common in persons with AIDS. The organ distribution of MAC is widespread, with lymph nodes, spleen and liver most frequent organs involved. Involvement of the gastrointestinal tract, bone marrow, respiratory tract, adrenal, or genitourinary tract is less frequent. *Mycobacterium avium* complex is rarely seen in the central nervous system, skin, and heart (Table 5).[348,349]

Clinical manifestations are primarily the result of cytokine elaboration. Typical features of MAC infection include persistent fever, night sweats, and anemia in about 80% of patients, diarrhea in about half, and weight loss, lymphadenopathy, abdominal pain, and nausea/vomiting in about one third of patients. *Mycobacterium avium* complex is unlikely to be an acute life-threatening infection, is often not suspected pre mortem, and most patients have a protracted course or die from another disease first. Though the number of AIDS patients with MAC is increasing with longer survival, the number of deaths from MAC has decreased significantly with the use of newer antimicrobial therapies.[342]

Blood culture is the best laboratory means of diagnosis of MAC, particularly when disseminated MAC infection is suspected.[350] Bone marrow or lymph node tissues may be cultured. The best tissue biopsy sites for histologic diagnosis of MAC are lymph node and liver. The fairly diffuse organ involvement of MAC helps to minimize the sampling error with biopsy.[348,349]

Mycobacterium avium complex does not often produce typical grossly visible granulomas with one exception--the spleen. A classic miliary pattern of granulomas is present in spleen in about half of AIDS cases with MAC. Another distinctive gross pathologic finding with MAC is a tan-yellow to lemon-yellow cut surface of involved lymph nodes in one fourth of cases. In the gastrointestinal tract, MAC involvement of the mucosa may give diffuse or slightly raised plaque-like areas of yellowish discoloration. Visceral organomegaly, especially of liver and spleen, may result from MAC infection even though there are often no grossly visible lesions.[349]

Microscopically, MAC most often demonstrates a proliferation of small nests to extensive sheets of large round to elliptical striated pale blue macrophages (histiocytes) on hematoxylin-eosin stain. These macrophages can be up to 50 microns in size. The small round to oval nuclei of these cells are often obscured by the sheer numbers of mycobacteria. The cell borders can also be indistinct because of many mycobacteria scattered in and around the cells. The cytoplasm of these cells is teeming with mycobacteria that can not only be identified by acid fast stain, but also by methenamine silver, PAS, Giemsa, or Brown-Hopps tissue gram stain. The large numbers of closely packed mycobacteria produce the striated appearance with hematoxylin-eosin staining.[348]

The large macrophages are usually not accompanied by a typical granulomatous cellular reaction. There may be occasional lymphocytes and epithelioid cells, but Langhans giant cells, fibrosis, calcification, and caseous necrosis are quite uncommon. Rarely, the macrophages may take on a spindle shape and form a mass lesion, typically in lymph nodes, known as a mycobacterial "pseudotumor".[351] In many organs, the poorly formed MAC "granulomas" consist only of single or small groups of macrophages that cannot be seen grossly and may not be noticed until special stains are performed. Significant necrosis of surrounding tissues is uncommon.[347]

Acid fast bacilli (AFB) staining, along with culture, remains the standard procedure for detection of MAC. The AFB stains commonly employed include the Ziehl-Neelsen and Kinyoun's carbolfuchsin methods. On acid fast staining, MAC organisms are not completely distinctive from other mycobacteria, though they tend to be shorter than *M tuberculosis* and they tend to be numerous. Culture is necessary for definitive identification. Diagnosis at autopsy is aided by sampling several lymph node sites and by culture of enlarged nodes.[348]

Though MAC is often widespread throughout the body, few MAC-infected AIDS patients die from this disease.[342] Organ failure from MAC leading to the immediate cause of death most likely results from pulmonary involvement. Prophylaxis for MAC in both adults and children with either azithromycin or clarithromycin may be considered when the CD4 lymphocyte count is <50/μL, though persons with active tuberculosis should be excluded because of development of resistance to rifampin from treatment with rifabutin.[250]

In persons receiving highly active antiretroviral therapy (HAART) there can be immune restoration disease (IRD) with atypical features of MAC infection. IRD with vigorous delayed-type hypersensitivity, rather than anergy, results in more localized, rather than disseminated, disease. Lesions can include lymphadenitis, pulmonary infiltrates or masses, pyomyositis, and subcutaneous abscessing inflammation. Granulomatous to suppurative inflammatory responses are present. Lesions may produce pain.[231]

Drug therapy for MAC infection may include clarithromycin, azithromycin, or rifabutin and is most effective when combined with a second agent such as ethambutol, but a clinical response may take two to eight weeks (Table 7). Combination drug therapy with additional agents such as ciprofloxacin, clofazimine, amikacin, and rifampin show some effectiveness in cases with more severe symptoms. AIDS patients infected with MAC require life-long treatment. Resolution of mycobacteremia occurs more frequently and more rapidly with a three-drug regimen of rifabutin, ethambutol, and clarithromycin. Rifabutin is also useful for prophylaxis in patients with CD4 lymphocyte counts <100/μL. Many patients can still survive for months with disseminated disease.[161,348,349,352]

MYCOBACTERIUM TUBERCULOSIS.-- *Mycobacterium tuberculosis* (MTB) occurs commonly in many persons without AIDS, but the risk for MTB is substantially higher in persons infected with HIV. The incidence of tuberculosis in persons with HIV infection is more than 500 times that of the general population, and patients dually infected with HIV and latent MTB progress to active tuberculosis at a rate of 8 to 10% per year.[353,354] Definitional criteria for AIDS require laboratory evidence for HIV infection for inclusion of MTB as a disease diagnostic of AIDS.[320] MTB is one of the most common causes of death in patients with AIDS in Africa.[325]

The incidence of tuberculosis among persons infected with HIV in the U.S. is increased with the CD4 lymphocyte count is less than 200/μL. Persons already tuberculin (PPD) positive at first testing during the course of HIV infection are much less likely to get tuberculosis than HIV-infected persons who convert to a positive PPD. HIV-infected persons who have negativity to mumps antigen by skin testing also have an increased risk for tuberculosis.[355]

Dissemination of MTB in patients with AIDS probably results from reactivation of previous infection rather than primary infection, but pulmonary involvement by MTB in AIDS is far more common than extrapulmonary spread. Not all AIDS patients have reactivation of MTB because isolated fibrotic or calcified granulomas, without evidence for active granulomatous disease, can be found in some AIDS cases at autopsy.

The incidence of MTB as well as the number of deaths from MTB began increasing in the United States in the mid-1980's, in part due to the AIDS epidemic, but leveled off and decreased in the 1990's.[353,354] Accompanying this increase in MTB was the emergence in the 1990's of MTB strains exhibiting multiple drug resistance. Emergence of multidrug-resistant TB (MDR TB) is a function of inadequate or inappropriate drug taking by patients or drug prescribing by physicians.[356] The clinical presentation is similar to non-resistant strains, though the chest roentgenographic appearance is more often an alveolar infiltrate, and cavitation is more frequent than with non-resistant MTB. These resistant strains are also likely to result in pathologic lesions

with poor granuloma formation, extensive necrosis, neutrophilic inflammation, and numerous acid fast bacilli.[357] The greatest number of reported cases of MDR TB have come from New York City, and the numbers of cases reported diminished in the late 1990's.[358]

Unlike MAC, though, striated macrophages are not a common feature with multiple drug resistant MTB. Patients with multiple drug resistant MTB have extrapulmonary dissemination in a third of cases, and their survival from the time of diagnosis is two months or less. Despite therapy with multiple agents, most patients will continue to have intermittently or persistently positive sputum cultures, indicating that such resistant MTB pose a considerable risk to other patients and to health care workers.[147]

Yearly skin test screening with 5 TU of purified protein derivative (PPD) is recommended in previously PPD-negative persons. Only 10% of persons with a CD4 lymphocyte count >500/μL are likely to exhibit anergy, though a positive test in HIV-infected persons should be defined as any area of induration >0.5 cm (or >0.2 cm for intravenous drug users). Anergy may be detected by companion testing with *Candida*, mumps, or tetanus toxoid skin tests. Patients suspected of having tuberculosis should be evaluated further with a chest roentgenogram and have at least three sputum specimens collected to detect acid fast bacilli.[161,250]

Mycobacterial infections can also be detected with tissues or cytologic material obtained via bronchoalveolar lavage, transbronchial biopsy, and fine needle aspiration. Acid fast bacilli (AFB) staining, along with culture, remains the standard procedure for detection of MTB. The AFB stains commonly employed include the Ziehl-Neelsen and Kinyoun's carbolfuchsin methods. False positive results can occur when the carbol-fuchsin stain precipitates on short segments of cellular debris. Interpret as acid fast bacilli only those structures that are uniformly and evenly stained throughout their length. Some morphologic variability exists among different species of mycobacteria. False negative results can be avoided by searching the slide carefully for many minutes. Using a positive control that does not have numerous organisms will help to avoid under staining and give an indication of how difficult the search can be.

The polymerase chain reaction (PCR) to mycobacterial DNA can be performed in selected cases. If disseminated tuberculosis is suspected, then cytologic or histologic material obtained from extrapulmonary sites should also be cultured for MTB.[161,354] Rapid, but expensive, tests for detection of MTB are available that are based upon the detection of DNA or ribosomal RNA from MTB organisms. These rapid tests yield results in less than a day, but do not replace acid fast staining, which can provide an index of contagiousness, or mycobacterial culture, which indicates drug susceptibility.[353]

The use of an auramine fluorescent stain for mycobacteria requires a microscope with fluorescence attachment. Newer epifluorescent microscopes are easier to set up and use. Most new fluorescence units employ filters that pass fluorescent light that only provides visualization for the auramine component of the stain, in contrast to the wide band filters of older units. The fluorescent stain is more sensitive than acid fast stains by light microscopy. False positive results can be avoided by careful interpretation.

In persons converting to a positive skin test, a 12 month course of isoniazid is recommended, with use of rifampin for patients unable to tolerate isoniazid. HIV-infected persons who are close contacts of persons infected with tuberculosis may begin to receive prophylactic therapy, and a decision to continue therapy can be made after skin testing and follow up. For patients with newly diagnosed tuberculosis, a four drug regimen consisting of isoniazid, rifampin, pyrazinamide, and either streptomycin or ethambutol is recommended, with therapy lasting at least 9 months (at least 6 months after sputum cultures are negative). For patients exposed to multiple-drug resistant MTB, therapy for 12 months with high dose ethambutol with pyrazinamide and ciprofloxacin is recommended. The use of bacille Calmette-Guérin (BCG) vaccine in patients with HIV infection is not recommended because of the risk for disseminated disease.[161,250,354,356]

The organ distribution of MTB in AIDS is widespread. Extrapulmonary MTB is found in 70% of patients with a CD4 lymphocyte count less than 100/μL and in 28% of those with a CD4 lymphocyte count greater than 300/μL At autopsy, the respiratory tract is involved most frequently, followed by spleen, lymph node, liver and genitourinary tract. Bone marrow, gastrointestinal tract,

and adrenal are less common sites of involvement. *Mycobacterium tuberculosis* is uncommonly identified in central nervous system, heart, and skin (Table 5).[342,354]

The clinical presentation of MTB in AIDS can resemble that of non-AIDS patients, and MTB can often be the first AIDS-defining illness, particularly in regions where the incidence of MTB is high in the general population. Tuberculosis should be suspected in patients with fever, cough, night sweats, and weight loss, regardless of chest roentgenogram findings. In patients with residual immune function, with a CD4 count >200/μL, MTB resembles reactivation tuberculosis, with cavitation and upper lobe infiltrates on chest roentgenography, and tuberculin skin tests are often positive. With severe immunosuppression and CD4 counts below 200/μL, hilar adenopathy, pleural effusions, lack of cavitation or consolidation but presence of a miliary pattern more typical of primary MTB infection appear.[353,359]

Tuberculin skin tests are frequently falsely negative. Pulmonary symptoms can also include hemoptysis, chest pain, and dyspnea. Differentiation from *P carinii* or fungal infection can be difficult, but both sputum and blood cultures are useful for diagnosis. Extrapulmonary MTB often produces fever, weight loss, and lymphadenopathy, and the yield from lymph node aspiration biopsy is high.[353,354] Clinical features that help to distinguish disseminated MTB infections from disseminated *Mycobacterium avium* complex (MAC) infections include night sweats, extra-inguinal lymphadenopathy, acid fast bacilli in sputum smears, hilar enlargement on chest radiograph, miliary lesions, and pleural effusions. Hepatosplenomegaly, elevated serum alkaline phosphatase (twice normal), and leukopenia are more likely to suggest disseminated MAC.[360]

Grossly, MTB produces recognizable discreet tan to white, firm granulomas in most involved organs. Unlike MAC, the lesions will not show bright yellow coloration. Most of the granulomas are 0.1 to 0.5 cm, but larger granulomas can occur and demonstrate central caseation. Large cavitary lesions with AIDS are not common. A classic miliary pattern is not seen frequently because the granulomas of MTB in AIDS tend to be more variably sized and more widely scattered in distribution. A pneumonic pattern may occasionally be seen.

The microscopic appearance of MTB with AIDS can be typical of that seen in MTB infecting non-AIDS patients. The granulomas contain epithelioid cells, Langhans giant cells, lymphocytes, and fibroblasts with central caseation. In many cases the inflammatory response is poor and the granulomas are ill-defined, particularly in advanced AIDS. Acid fast stains show variable numbers of mycobacteria, but usually there are more mycobacteria than are seen in non-AIDS patients. In some cases with few or small granulomas, mycobacteria are not numerous; in other cases with many larger caseating granulomas, they may be abundant. Large macrophages filled with mycobacteria similar to those seen in MAC are quite uncommon in MTB.[361]

Persons starting highly active antiretroviral therapy (HAART) can develop immune restoration disease (IRD) with a vigorous delayed-type hypersensitivity reaction and more pronounced granulomatous inflammation. There may be thoracic lymphadenitis. Extrathoracic disease is unlikely with IRD.[231]

Unlike MAC, MTB infections in patients with AIDS often do respond to antimycobacterial therapy with rifampin, isoniazid, and pyrazinamide (and ethambutol hydrochloride in cases with resistance) but death from MTB is more common than with MAC from both an increase in the numbers of infections and death rate from infection. The rise in multiple drug resistant strains of MTB has played a role in this increasing death rate.[353,357] At autopsy, about one third of AIDS patients with MTB are found to have succumbed to this infection, usually from extensive pulmonary involvement.[342] Prophylaxis against MTB infection can be considered for patients with a positive tuberculin skin test (induration >5 mm) who have never been treated for tuberculosis, and for patients with recent exposure to someone with active tuberculosis. Isoniazid plus pyridoxine, or rifampin plus pyrazinamide, administered for 9 months, are the regimens of choice.[250]

MYCOBACTERIUM FORTUITUM.—Mycobacterium fortuitum occurs less commonly than either MTB or MAC in AIDS. This organism is widely found in the environment but is an infrequent human pathogen. In culture it is a rapid grower. In persons who are immunocompetent, infections of surgical sites, soft tissues, skin, and lung can occur but are typically not life-

threatening. In immunocompromised persons, *M fortuitum* infections are more disseminated and severe, with multiple skin lesions and deep organ involvement. In persons with HIV infection, *M fortuitum* occurs late in the course, with CD4 counts typically below 100/μL. Cervical lymphadenitis is the most common initial sign. Microscopically, the lesions are characterized by a mixture of granulomatous and acute suppurative inflammation. The long, filamentous acid fast bacilli may not be numerous and may stain poorly with standard special stains such as Ziehl-Neelsen, Kinyoun, or auramine. They may be confused with *Nocardia* species, though *M fortuitum* organisms tend to have shorter, blunter branches that extend at right angles from their origin, compared to *Nocardia*. A response to antibiotic therapy with agents such as amikacin and ciprofloxacin is generally seen.[362]

MYCOBACTERIUM XENOPI.—Mycobacterium xenopi is most likely to be a colonizing agent in persons with AIDS in regions where this organism is endemic and considered to be a commensal or environmental contaminant where it can be recovered from water sources. In most cases it does not require specific antimicrobial therapy.[363] However, in some cases it can cause pneumonia and/or septicemia in persons with AIDS. *M xenopi* infection may be accompanied by cough, chronic fever, and wasting syndrome. Disseminated infections are rare. *M xenopi* demonstrates reduced susceptibility to anti-tuberculous drugs, and the response to treatment is variable.[364]

OTHER MYCOBACTERIA.-- Infections with *Mycobacterium kansasii*, *Mycobacterium scrofulaceum*, or *Mycobacterium gordonae* may also occur in AIDS. These infections both clinically and pathologically are more likely to resemble MTB infection than MAC infection.[353] The specific diagnosis depends upon culture of tissues or body fluids, but morphologically *M kansasii* organisms have a long, curved or folded, and beaded appearance (barber pole) on acid fast stain.[365] *M avium* complex (MAC) organisms are short, thick, and beaded. *M tuberculosis* organisms are not as thick or beaded as those of MAC. *Mycobacterium scrofulaceum* organisms are very short and delicate. Another pattern of infection is seen with *Mycobacterium haemophilum* which produces disseminated cutaneous erythematous macular to ulcerated lesions. Infected patients may respond to treatment with rifampin, amikacin, and ciprofloxacin. The organism is very fastidious and slow-growing in culture media.[366]

CRYPTOCOCCUS NEOFORMANS INFECTIONS

Cryptococcosis is a leading cause for fungal disease in persons infected with HIV. There are two main variants of *C neoformans*. The organism *C neoformans* var. *neoformans* is cosmopolitan, and bird droppings tend to play a major role in its distribution to urban settings. In contrast, *C neoformans* var. *gattii* tends to occur in tropical and subtropical locations. Most cases of *C neoformans* var *gattii* are seen in males past the first decade in age. About 6 to 10% of HIV-infected persons not on prophylactic therapy or highly active antiretroviral therapy have been shown to develop cryptococcal meningitis in developed nations. More than three-fourths of cases occur when the CD4 count is less than 50/μL. Most infections are acquired via the respiratory tract, where the major host defense mechanism is complement-mediated phagocytosis by macrophages, with help from both CD4 and CD8 cells to inhibit proliferation of cryptococcal organisms. Cryptococcosis may represent either primary infection or reactivation of prior infection.[367] Though cryptococcosis is a major complication in adults with advanced HIV infection, cryptococcal infections in children are relatively uncommon, with a frequency of less than 1%.[368]

Involvement of the central nervous system and lung by *Cryptococcus neoformans* in AIDS is similar to non-AIDS cases. In cases with dissemination, *C neoformans* has a wide distribution, appearing in decreasing frequency in: lymph node, spleen, genitourinary tract, liver, adrenal, and bone marrow tissue. *Cryptococcus neoformans* is infrequently identified in gastrointestinal tract and skin (Table 5).[369]

The most common clinical presentation of cryptococcosis is meningitis, seen in over 70% of infections. The onset and course of cryptococcal meningitis can be rapid and severe, though symptoms may develop over days to weeks. Sometimes only headache and altered mental status are present. One of the best clinical means of diagnosis is examination of cerebrospinal fluid (CSF) obtained from lumbar puncture with an India ink preparation that will highlight the budding nuclei. The CSF cell counts and chemistries can be abnormal, and cryptococcal antigen is positive in 90% of cases when the CSF culture is positive for *C neoformans*.[370]

In about a third to half of cryptococcal infections, there is a pneumonitis. Pulmonary involvement is usually seen with dissemination, though isolated pulmonary disease may be present. Fever, cough, and dyspnea are non-specific manifestations of pulmonary cryptococcosis. Other clinically apparent lesions may be seen on skin and in the eye. Persistent prostatic infection which is difficult to detect may serve as a reservoir that is difficult to eradicate.[370]

If large numbers of cryptococci with capsules are present, a grossly apparent mucoid exudate may be seen in the cerebral ventricles or on the meningeal surfaces of the central nervous system. Sometimes variably sized pale soft granulomas are grossly visible in the lungs or elsewhere. In a few cases, the granulomas have surrounding hemorrhage. The lungs may show patchy areas of consolidation. In some cases the only grossly identifiable pathologic change is organomegaly.

Microscopically, *C neoformans* organisms are pale narrow-based budding yeasts that average 2 to 7 microns in size with a prominent surrounding capsule. The yeast cells appear pale blue and ovoid while the capsule is round and clear with routine hematoxylin-eosin-stained tissue sections or on Papanicolaou-stained cytologic material. With the capsule, the organisms are 5 to 20 microns. Pale or clear areas at low power magnification in examined tissues may be found at high power to contain large numbers of cryptococci. Accompanying inflammation is usually scanty, with a few small scattered lymphocytes or macrophages with phagocytized organisms.

The capsule, when present, can be stained in tissue sections or cytologic smears with most mucin stains. Methenamine silver and PAS stains readily demonstrate the nuclei of the organisms. In many cryptococcal infections with AIDS, there are present only very poorly or non-encapsulated cryptococci. The presence of these poorly encapsulated forms may explain the paucity of gross pathologic findings. This appearance is similar to subcultures of cryptococci on growth media in the laboratory. Such capsule-deficient forms may be difficult to distinguish from *Candida* and *Histoplasma capsulatum*. The cellular pleomorphism of *Cryptococcus*, larger cell size, and lack of

pseudohyphae help to distinguish it from *Candida*. The football-shaped *C neoformans* yeasts are much larger than the small round cells of *H capsulatum* organisms.[371]

Cryptococcal organisms can also be distinguished by the presence of a melanin-like pigment that is identified with the Fontana-Masson stain. The Alcian blue stain will help to distinguish the capsule of *C neoformans* (if present) as well as the wall of *Blastomyces dermatitidis*. The PAS stain will highlight the cell walls of each of these latter two organisms.[372]

When highly active antiretroviral therapy (HAART) is begun, within 2 months there may be immune restoration disease (IRD), loss of anergy, and development of more florid inflammatory responses from delayed-type hypersensitivity restoration. With cryptococcal infections, IRD is most often manifested by lymphadenitis, particularly within the mediastinum.[231]

Antifungal therapies with amphotericin B, flucytosine, and triazoles (fluconazole, itraconazole), are successful in many cases. Fluconazole or itraconazole are the drugs most often used for secondary prophylaxis, since many patients with treated *C neoformans* infections will have a recurrence without continued suppressive therapy. About half of AIDS patients infected with *Cryptococcus* are found to have died of their cryptococcal disease, most often from CNS involvement.[161,250,342]

HERPESVIRUS INFECTIONS

The human herpesviruses, including herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpes virus 6 (HHV-6) may appear in the course of HIV infection and produce a variety of clinically significant manifestations either as self-limited or non-resolving opportunistic infections.[373] Cytomegalovirus produces the greatest morbidity as well as resultant mortality and has been discussed separately above. Epstein-Barr virus is thought to play a role in development of both oral hairy leukoplakia and malignant lymphomas in AIDS.[374] Although HHV-6 has been found to replicate in a variety of cell types, including CD4+ lymphocytes, and has been implicated as a cause for roseola, it has not yet been found in association with a specific infectious or neoplastic process in AIDS.[374]

Herpes simplex types I and II are sexually transmissible agents of importance in patients both with and without HIV infection. Recurrent mucocutaneous herpes simplex virus infections of more than one month's duration satisfy definitional criteria for diagnosis of AIDS in patients proven to have HIV infection.[320] Clinically, the recurrent herpetic lesions of AIDS patients are more of a chronic nuisance than a life-threatening condition. Ulcerated or excoriated lesions may subsequently become secondarily infected.

Both HSV types 1 (HSV-1) and 2 (HSV-2) primarily infect skin and mucus membranes to produce inflammation, often vesicular, progressing to sharply demarcated ulcerations. Herpes simplex type 1 involves predominantly the oral cavity while HSV-2 more often involves the genital region. However, either body region may be infected by either subtype to produce clinically and histologically indistinguishable disease.[375]

Varicella zoster virus (VZV) infections typically begin as childhood chickenpox, and the virus becomes latent in dorsal root ganglia. VZV may reactivate years later in adults who are immunocompromised, including those with AIDS. However, children with HIV infection are also at risk for VZV infection. The classic presentation in reactivation is "shingles" with painful skin vesicles appearing in a dermatomal distribution, most commonly thoracic, lumbar, or cervical. The vesicles may develop into blisters within 2 weeks to a month. VZV is not a disseminated disease involving multiple organ systems and does not cause death, but is a debilitating nuisance for persons who have it. Skin dissemination can occur in the form of multiple dermatomal distributions. Persons who have VZV involvement of the ophthalmic division of the trigeminal nerve may also have ocular involvement in the form of acute retinal necrosis, progressive outer retinal necrosis, or progressive herpetic retinal necrosis. About 8 to 15% of patients, particularly the elderly, may develop post-herpetic neuralgia. Central nervous system involvement by VZV can lead to encephalitis, ventriculitis, periventriculitis, vasculopathy, and myelitis.[376]

All herpesviruses exhibit latency following initial infection. Either HSV or VZV infection initially occurs through mucosal surfaces or through abraded skin via contact with a person who is excreting virus through active, usually ulcerative, lesions. Viral replication begins within epithelium and underlying dermis or within submucosa. From these initial sites, HSV or VZV spreads to nerve endings and is transported intra-axonally to neurons in ganglia, from which spread is then via peripheral sensory nerves back to other, usually adjacent, skin and mucosal sites.[375]

Thus, vesicular HSV or VZV lesions may later appear or recur away from the initial site of involvement. After an initial host response in which both cell-mediated and humoral mechanisms take part, the infection usually becomes latent, with HSV or VZV present but not actively replicating within ganglia. It is unclear just how reactivation of HSV, or VZV as VZV, occurs but lack of cell-mediated immunity in immunocompromised patients may be implicated.[375]

The typical patient with HSV or VZV has a grouped vesicular skin eruption that ruptures, crusts, and heals in seven to ten days. Infection may be associated with a history of severe pain, often persisting for months after the skin lesions resolve. Scarring also occurs. Chronic VZV infections may be characterized by pseudocarcinomatous hyperplasia, verrucous epidermal hyperplasia, and massive hyperkeratosis.[377] Reactivation of VSV as shingles may often occur as

an early manifestation of immune impairment with HIV infection as the CD4 cell count diminishes below 500/μL, though development of VZV does not appear to be associated with duration of HIV infection, nor does the presence of VZV predict faster progression of AIDS.[378] The incidence of VZV may increase as a consequence of immune restoration disease (IRD) in the months following the start of successful highly active antiretroviral therapy (HAART).[231]

In persons with HIV infection, as with immunocompetent individuals, recurrent lesions of HSV predominantly involve skin and mucus membranes, while the lesions of VZV are typically limited to skin. Internal organ involvement has been reported less frequently, and disseminated infections are uncommon, but the clinical course of recurrence is similar to that seen in other immunocompromised patients or even immunocompetent persons. The upper gastrointestinal tract including tongue, oropharynx, and esophagus may occasionally have herpetic lesions, and the central nervous system is less commonly involved (Table 5). Herpetic mucocutaneous lesions of immunocompromised patients, including those with AIDS, have been reported to be more extensive, more severe, and longer-lasting, with more ulceration, necrosis, and pain than in immunocompetent patients.[373,375,379]

Although cytologic or histologic diagnosis is simple and cost-effective, viral culture remains the most sensitive clinical method for HSV or VZV diagnosis; methods for antigen detection are less sensitive. Culture sensitivity is higher when the herpetic vesicular lesions first appear and before they ulcerate. Later ulcerative lesions may have no detectable virus. Serologic testing is mainly of value for detection of past infection, but not acute infection, for immunocompromised patients are unlikely to mount a significant (fourfold or greater) rise in anti-HSV titer between acute and convalescent samples.[375]

Microscopically, lesions of HSV and VZV both in tissue biopsies or from cytologic preparations (Tzanck or Pap smears) demonstrate characteristic acantholytic epithelial or discohesive parenchymal cells, often multinucleated or in clusters, with mauve to pink to steel-gray ground glass intranuclear (Cowdry type A) inclusions and nuclear chromatin margination. The cytoplasm of infected cells is not prominent and, unlike CMV, does not contain inclusion bodies of any kind. With ulceration, such cells may be infrequent or autolyzed. Epithelial cells of the skin adnexa (sweat ducts and hair follicles with sebaceous apparatus) may also be involved.[380]

On average, cells infected with herpes simplex and varicella zoster virus groups do not reach the size of those with cytomegalovirus, but the larger cells with herpes simplex or varicella zoster and the smaller cells with cytomegalovirus may be of similar size. The intranuclear inclusions of cytomegalovirus tend to be darker and larger. Also, in squamous epithelium with herpetic lesions, ballooning degeneration is common, and CMV is unlikely to be associated with vesicle formation in mucosae.

For VZV, typical cytologic features most often occur in cells between papillae and dermal adnexa. On average, cells infected with HSV or VZV do not reach the size of those with CMV, and the intranuclear inclusions of CMV tend to be darker and larger, and intracytoplasmic inclusions may accompany CMV. Immunoperoxidase staining with primary antibody against HSV-1, HSV-2, and VZV will help to exclude other viral etiologies such as CMV, EBV, and HPV.

Acyclovir has been found to be effective therapy for treating most mucocutaneous and visceral herpetic infections and may be useful prophylactically in persons with frequent recurrences.[161,250,375] However, both HSV and VZV infections that are resistant to acyclovir, and in some cases resistant to foscarnet as well, are increasing in number.[381] The cyclical nature of herpetic infections means that they may at times regress without therapy, or in spite of it.[373] Death from either herpes simplex or varicella-zoster viruses is quite rare, and usually results from central nervous system involvement.[342]

Human herpesvirus 6 (HHV-6) is highly seroprevalent, with a worldwide distribution. Most persons are infected by the age of 2; the probable mode of transmission is through saliva. In infants it may cause roseola, and a mononucleosis-like syndrome. This virus is predominantly tropic to CD4 lymphocytes. HHV-6 infection can coexist with HIV infection, and may be involved with progression to AIDS, since HHV-6 upregulates CD4 expression and can, therefore, increase HIV replication to deplete CD4 lymphocytes. Active HHV-6 infection can be present before the stage of clinical AIDS is reached.[382,383]

Human herpesvirus 7 (HHV-7) is a lymphocytotropic agent for CD4 cells that typically infects most persons during childhood and may cause skin rashes such as pityriasis rosea. Both HHV-7 and HIV use CD4 receptors and can interfere with each other. The immunosuppression accompanying HIV infection may lead to reactivation from latency and increased replication of HHV-7 in lymph nodes.[384,385]

Human herpesvirus 8 (HHV-8) is also known as Kaposi sarcoma-associated herpes virus (KSHV) is known to be associated with a variety of neoplastic and proliferative lesions seen with AIDS. The seroprevalence of HHV-8 is 5 to 10% of the general population, but 20 to 70% of homosexual populations. Risk factors for transmission of HHV-8 include sexual activity and injection drug use. The transmission of HHV-8 by needle sharing is less efficient than for HIV. HHV-8 is present in all cases of AIDS-associated Kaposi's sarcoma. It is invariably present in primary effusion lymphoma of body cavities. It has been detected in multicentric Castleman disease.[386,387]

CANDIDA INFECTIONS

Candida is so ubiquitous in both healthy and ill persons that it is often difficult to determine just how important it really is when identified in patient specimens. *Candida* organisms can be found on the skin or in the oral cavity so commonly that they are not necessarily presumed to always be pathogens at these sites. Likewise in AIDS, finding *Candida* does not always mean that a pathologic condition is present. In HIV-infected persons, binding of viral gp160 and gp41 envelope proteins enhances the virulence of *Candida*.[388]

AIDS patients often receive a clinical diagnosis of "oral candidiasis" or "oral thrush" as a result of finding white creamy patches or plaques on oral mucosal surfaces. Such mucous membrane involvement is seen in over 90% of HIV-infected persons at some point in their course, with oral candidiasis seen in over 70%.[370,389]

The progressive depletion and dysregulation of mucosal Langerhans cells from HIV infection reduces normal processing of *Candida* antigens, and this, coupled with progressive loss of CD4 lymphocytes, reduces adaptive immunity to *Candida*. However, innate immune defenses, including intraepithelial T cells, neutrophils, and calprotectin, remain so that dissemination of *Candida* is uncommon, but may appear with bone marrow suppression.[390] There are no specific clinical findings with disseminated candidiasis, and this manifestation is unlikely to be diagnosed pre mortem.[320]

The most common species isolated in microbiologic cultures include *Candida albicans*, *Candida tropicalis*, and *Candida parapsilosis*. Of these Candida albicans accounts for the most cases. *Torulopsis glabrata* may appear clinically and histologically similar to *Candida*, though they are often of very small 1 to 2 microns size. Except for epidemiologic purposes, most of these fungal species with budding cells are clinically or histologically grouped as "*Candida*" or "yeast." Patients are usually colonized with a single strain, and recurrences are usually due to the same strain.[389]

In order to fulfill the definitional criteria for diagnosis of AIDS, *Candida* must be found to satisfy specific requirements: there must be *invasive* esophageal or respiratory tract (trachea, bronchi, or lungs) candidiasis.[320] Merely finding budding yeasts upon a mucosal surface without any tissue reaction is not sufficient for diagnosis of AIDS. *Candida* is seen in the upper gastrointestinal tract, primarily the esophagus, in many cases in which it is present. The lung is often involved at autopsy. In a few cases, *Candida* may be disseminated beyond the respiratory or gastrointestinal tracts. Other organs are infrequently involved, and in bone marrow, *Candida* is rarely identified in AIDS (Table 5). Drug therapies that lead to bone marrow suppression, corticosteroid therapy, or other immunosuppressive agents may enhance dissemination of *Candida*.

There are characteristic gross findings on mucosal surfaces as seen in the oral cavity, pharynx, trachea, bronchi, esophagus, or vagina. These findings include the commonest pseudomembranous form, with white, elevated mucosal plaques that often have a cottage-cheese like appearance. Other gross findings include the erythematous (atrophic) form with flat red patches, the hyperplastic form with partially removable white plaques, and angular cheilitis with erythema and fissuring at the corners of the mouth. Other superficial forms of *Candida* involvement can be seen as paronychia or onychomycosis.[370]

If dissemination occurs to visceral organs, *Candida* is most likely to produce a pattern similar to bacterial microabscesses, with small pinpoint to 0.3 cm diameter soft yellow foci, sometimes surrounded by a small hemorrhagic zone. Organomegaly is infrequent with such lesions.

Microscopically, *Candida* microabscesses contain more polymorphonuclear leukocytes than lymphocytes or macrophages. If the degree of immunosuppression is marked, there may be little inflammatory reaction, and the pseudohyphae will grow haphazardly throughout the tissues. In fact, a typical hyphal or pseudohyphal growth pattern exhibits extension across mesothelial-lined surfaces or into blood vessel walls. Vascular invasion may lead to hemorrhage, thrombosis, or infarction.

Candida organisms are identified histologically by their 3 to 5 micron size, budding, and pseudohyphae. The pseudohyphae can be distinguished from *Aspergillus* hyphae by the lack of branching, the smaller size, and the frequent absence of true septations in the former. Sometimes *Candida* species may also have septate hyphae that can be long, but often of uneven caliber, with bulbous or pinched portions along their length. Budding cells of *Candida* are larger than *Histoplasma capsulatum* and lack a defined "capsule" with inner nucleus. *Candida* are smaller than *Cryptococcus neoformans* and generally not as pleomorphic. A mucin stain will be negative with *Candida*, since there is no surrounding capsule as in *C neoformans*. Methenamine silver and PAS stains are most helpful to identify *Candida*.

Even though *Candida* occurs in about 40 to 90% of patients with AIDS, death from *Candida* infection occurs in less than 5% of cases even when it is present, most often when the disease is widely disseminated, and usually from pulmonary involvement. In a small number of AIDS cases, *Candida* can produce a fatal septicemia. Though disseminated candidiasis and candidemia are rare in adults with HIV infection, children are more prone to develop these complications during prolonged hospitalization. Candidemia is more likely to develop as a community acquired complication in children who are receiving total parenteral nutrition and intravenous therapy via indwelling central venous lines. The prolonged presence of a central venous catheter is the most important risk factor for fungemia. Diagnosis of fungemia can be aided by use of PCR-based assays.[368]

Primary prophylaxis for candidiasis, most often involving oropharynx, esophagus, or vagina, is usually not indicated, unless recurrences are severe or frequent, since most of these infections respond well to administered topical or oral antifungal agents, including fluconazole, ketoconazole or clotrimazole. Fluconazole is more effective for curing oral candidiasis. Resistance to fluconazole therapy is more frequent when the CD4 lymphocyte count is low.[389]

In some patients, recurrences of yeast infections are common and secondary prophylaxis with topical clotrimazole troches or nystatin are used for oral candidiasis. Systemic fluconazole therapy is recommended for recurrent esophageal candidiasis, with ketoconazole therapy also available; rarely, amphotericin B therapy is required (Table 7).[161,324]

TOXOPLASMA GONDII INFECTIONS

Toxoplasmosis is an uncommon infection that, before the AIDS epidemic, was rarely seen in adults. It is more common in warm humid climates, and this distribution may influence its appearance in AIDS. Toxoplasmosis can occur perinatally as a congenital infection in the absence of HIV infection.[391] Ingestion of poorly cooked meat (usually pork) is a principle form of transmission in adults, though ingestion of food or water contaminated with *T gondii* oocysts is also an important route of infection.[392]

T gondii can invade virtually all tissues of the body, but in AIDS patients, the organ system distribution of *T gondii* infection is generally not widespread. The central nervous system is involved in most cases. Extracerebral toxoplasmosis is more likely to occur later in the course of AIDS with a greater degree of immunosuppression when the CD4 lymphocyte count is low. Extracerebral sites for *T gondii* in AIDS are most often eye and lung, with heart and gastrointestinal tract involved much less often. Other organs are infrequently involved, with reticuloendothelial tissues occasionally affected (Table 5).[393]

The clinical appearance of toxoplasmosis is typically that of altered mental status from central nervous system involvement. Headaches, fever, and focal neurologic deficits may occur. Diagnosis may be suggested by elevated serologic titers, but many persons have antibodies to *T gondii* as a result of subclinical infection. Serologic titers give no indication of dissemination. The presentation of cerebral toxoplasmosis may appear quite similar to that for non-Hodgkin lymphoma, and stereotaxic brain biopsy may be useful for diagnosis. Extracerebral toxoplasmosis may sometimes be diagnosed by bronchoalveolar lavage or endoscopic biopsy.[393]

The gross appearance of toxoplasmosis is not distinctive. In the brain, the diagnosis is suggested by finding multiple small areas of necrosis or cystic change, while in the heart, a patchy parenchymal myocarditis with tan to white irregular infiltrates may occur in severe cases. In other organs, there are no specific features and grossly visible lesions may not be apparent.

In biopsy material, diagnosis is best made by finding characteristic cysts filled with the organisms--dubbed bradyzoites in this location. The cysts may be "true" cysts formed only by the *T gondii*, or they may be "pseudocysts" that form within an existing cell and use the cell wall as a cyst wall. Cysts average 50 microns in size. Free *T gondii* organisms, called tachyzoites, are 2 to 3 microns wide and are often difficult to distinguish, with hematoxylin-eosin staining, from background cellular debris.[328] The sexual cycle of T gondii occurs in the definitive host, the cat, where oocysts form in the intestine and are excreted into the environment to be ingested by other animals or man.[392]

Encysted *T gondii* usually produce no or minimal inflammatory reaction, but serologic titers may increase. However, rupture of the cysts with release of *T gondii* as free tachyzoites does produce a host response. The tachyzoites are too small to be morphologically distinctive by hematoxylin-eosin staining in most tissue sections. Immunohistochemical staining may aid in finding not only the cysts, but also in identifying free tachyzoites.[391]

The inflammation that accompanies the cysts and free tachyzoites is usually mixed, with neutrophils, lymphocytes, macrophages, and plasma cells in varying proportions. These mixed inflammatory cell infiltrates occur in a patchy pattern within involved organs. Even though inflammation may be extensive, finding cysts is still difficult, though the greater the degree of inflammation, the greater the likelihood of finding cysts. Larger areas of inflammation are usually accompanied by some cellular necrosis.[391]

Sometimes, cysts may be difficult to distinguish from cytomegalic cells that have intracytoplasmic basophilic inclusions in which the plane of sectioning has missed the nucleus. Cytomegalovirus basophilic bodies tend to be more pleomorphic than bradyzoites, and *T gondii* cyst walls are thicker than cytomegalic cell borders. Macrophages containing *Histoplasma capsulatum* tend to be more irregular in outline with fewer yeasts than the rounded pseudocysts of toxoplasmosis with many small bradyzoites.

Patients with HIV infection who lack antibody to *Toxoplasma* may avoid infection by not eating raw or undercooked meat, by hand washing after contact with raw meat or soil, by washing raw fruits and vegetables before eating them, and by reducing or avoiding contact with cat litter boxes. In the advanced stages of AIDS when the CD4 lymphocyte count is <100/μL and when there is serologic evidence for *Toxoplasma* infection, patients may receive prophylaxis. Trimethoprim-sulfamethoxazole (TMP-SMZ) used for prophylaxis against *Pneumocystis carinii* pneumonia (PCP) is also effective for prevention of toxoplasmosis and should be considered for patients with anti-toxoplasma antibodies who have a CD4 count <100/microlier. The alternative prophylactic regimen consists of sulfadiazine plus pyrimethamine and leucovorin.[250]

Pyrimethamine-sulfadiazine with folinic acid therapy for cerebral toxoplasmosis is often successful for treating diagnosed infections. A response to therapy occurs in about two thirds of cases.[393] Death from toxoplasmosis occurs in slightly less than half of AIDS patients infected with *T gondii* at autopsy. Of these, central nervous system involvement is responsible for death in virtually all instances. *Toxoplasma* myocarditis causing patient demise occurs sporadically.[324,392]

HISTOPLASMA CAPSULATUM INFECTIONS

Histoplasmosis is an infection traditionally seen in areas in which this particular dimorphic fungus is endemic--mainly the Mississippi and Ohio river valleys of the United States. Infections may also occur over a wider geographic area encompassing the St. Lawrence river valley to the north and Florida and Central America to the south. Infections reported in non-endemic areas are probably the result of reactivation of infections acquired earlier in endemic areas. HIV-infected persons who have lived or traveled in endemic areas may have reactivation of long latent *Histoplasma capsulatum* infection with the onset of clinical AIDS. *H capsulatum* grows in a mycelial form in soils, particularly those enriched by bird or bat excrement. Persons infected with HIV should avoid bird roosting sites (particularly chicken coops) and caves in regions where *H capsulatum* is endemic. Inhalation of sporulating mycelial fragments into lung is followed by rapid conversion to the yeast form. Histoplasmosis tends to be a widely disseminated infection involving multiple organs, particularly reticuloendothelial tissues (Table 5).[370]

Widespread organ involvement with histoplasmosis, seen in 95% of cases in patients with AIDS, results in protean manifestations. Fever, sepsis, hepatosplenomegaly, lymphadenopathy, weight loss, and respiratory complaints including shortness of breath and cough are common. Clinically, bone marrow biopsy and culture, along with elevated complement fixation titers of anti-*H Capsulatum*, can establish the diagnosis in most cases.[394]

There are several methods for diagnosis. Skin testing with histoplasmin is not predictive of histoplasmosis, because of anergy in the majority of patients with HIV infection. The use of complement fixation serologic testing may be useful in identifying persons at risk. Regardless of immune status, persons infected or reinfected with *H capsulatum* will seroconvert within 4 weeks, with seroreversion within 5 years. A CD4 lymphocyte count <300/μL also indicates an increased risk for infection. Cultures of bone marrow and blood are positive in up to 90% of cases, but *H capsulatum* can be slow growing, requiring from 1 to 6 weeks for positive culture results. Serologic testing will demonstrate antibodies in 50 to 70% of cases. Antigen can be detected in urine, serum, fluid from bronchoalveolar lavage, and in cerebrospinal fluid in most cases.[250,370,395]

Infections with *H capsulatum* in AIDS typically involve multiple organs in a diffuse pattern. There are no specific gross pathologic findings. Sometimes histoplasmosis will produce visible granulomas that are variably sized, discreet, white to tan, firm, and indistinguishable from those of other dimorphic fungi or *Mycobacterium tuberculosis*.

The organisms are small 2 to 4 micron yeasts that may show budding. The yeasts are usually found within the cytoplasm of macrophages that tend to have irregular outlines with indistinct cell membranes on hematoxylin-eosin staining. These macrophages may cluster to form small granulomas that rarely have an accompanying pronounced or distinctive inflammatory response. The yeasts of *H capsulatum* are difficult to see with routine hematoxylin-eosin staining, appearing only as small faint bluish dots or circles.

Special stains should be used to identify the presence of *H capsulatum* in tissue biopsies or cytologic material. Methenamine silver staining provides the best contrast and is the easiest to screen, but the yeasts may be confused with the slightly larger budding cells of *Candida* when pseudohyphae are lacking in the latter. In regions with prevalent *Leishmania* infections, there may be difficulty in distinguishing *H capsulatum* by hematoxylin-eosin staining alone.

A PAS stain helps to define the thin cell membrane or "capsule" of *H capsulatum* and the central dot-like cell contents that form with artifactual shrinkage during fixation. Clusters of such organisms are quite characteristic of *H capsulatum*. However, immunoglobulin inclusions (Russell bodies) within plasma cells (Mott cells) must be distinguished from yeasts on PAS staining by the homogeneity of staining, greater pleomorphism, and lack of a capsule in the former. Immunohistochemical staining for *H capsulatum* will aid in diagnosing difficult cases. Microbiologic culture will provide a definitive--though delayed--answer.[394]

Prophylaxis for *H capsulatum* using antifungal agents has not been shown to prevent histoplasmosis. Treatment resulting in prolonged survival may include induction with amphotericin B followed by long term maintenance on itraconazole or fluconazole. Histoplasmosis responds well to therapy, but relapses in the absence of chronic suppressive antifungal therapy. When death occurs from histoplasmosis, organ involvement is frequently so widespread that it is difficult to determine a specific organ failure as a cause of death.[161,394,395]

COCCIDIOIDES IMMITIS INFECTIONS

Coccidioidomycosis is included in the definitional criteria for AIDS because it may appear in HIV-infected persons who have lived in endemic areas--arid plains of the Southwestern United States, Mexico, and Central and South America.[320] *C immitis* exists in a mycelial form (septated alternating arthrospores) in soils and is released into the air as arthroconidia that are inhaled.[370] *C immitis* grows as a yeast form in tissues. In areas endemic for *C immitis*, HIV-infected persons may prevent infection by avoiding exposure to dusty environments or areas where soil is disturbed.[250] Coccidioidomycosis in AIDS probably represents a reactivation of a previous infection rather than recent infection.[396]

Coccidioidomycosis in association with AIDS tends to be a widely disseminated infection involving numerous organs (Table 5). The lung serves as the portal of entry for *Coccidioides immitis* . There are several clinical patterns of involvement, including focal pulmonary disease, diffuse pulmonary disease, cutaneous disease, meningitis, and wide dissemination. Grossly visible granulomas similar to other dimorphic fungi and to *Mycobacterium tuberculosis* may be present in lung, but often are not seen in other organs. Serologic tests for antibody to *C immitis* are positive in about two thirds of cases.[370,396]

The most frequent symptoms are fever with chills, weight loss, and night sweats. The clinical presentation is most often as pulmonary disease in 80%, followed by meningitis in 15% of cases. A fourth of patients have lymphadenopathy. A chest radiograph will demonstrate a diffuse reticulonodular infiltrate in over half of cases, but negative findings may occur in 16% of cases.[396] Diagnosis can be made by several methods. In general, skin testing is not useful, since few HIV-infected persons with coccidioidomycosis will have a positive result. Most of the false negative serologic tests are found when diffuse pulmonary disease is present. Blood cultures will be positive in about 12% of cases. Cultures of cerebrospinal fluid are positive in over half of cases of *C immitis* meningitis.[370]

Microscopic diagnosis is made by finding clusters of large 10 to 80 micron thick-walled spherules containing endospores in tissue biopsies. Spherules may also be identified in sputum and bronchoalveolar lavage fluid. Ruptured spherules may be partially collapsed with small 2 to 5 micron endospores close by. Once the endospores are released, they begin to grow into spherules with endospores, completing the life-cycle. Thus, variably sized spherules are often present and only the larger ones will have well-defined endospores. Both Gomori methenamine silver (GMS) and periodic acid-Schiff (PAS) stains are helpful in identifying the organisms. An inflammatory reaction accompanying *C immitis* spherules tends to be quite sparse, consisting of only scattered lymphocytes, neutrophils, and macrophages.

Treatment with amphotericin B may be useful for acute and/or chronic infections. Secondary prophylaxis with itraconazole, fluconazole, or ketoconazole may be employed. Death occurs from coccidioidomycosis in two thirds of patients who have *C immitis* infection at autopsy. The mortality rate is highest when diffuse pulmonary disease is present and/or the CD4 lymphocyte count is $<50/\mu L$. One important etiologic differential diagnosis in disseminated coccidioidomycosis should be made: a disseminated form of this infection can also occur in anabolic steroid abusers or corticosteroid users, who may also be young males. Thus, testing to confirm or exclude HIV status is essential.[324,396]

GASTROINTESTINAL PROTOZOAL INFECTIONS

These infections occur from such organisms as *Entamoeba histolytica*, *Entamoeba coli*, *Giardia lamblia*, *Cryptosporidium* sp, *Microsporidium* sp, and *Isospora belli*. Only *Cryptosporidium* and *Isospora* are part of definitional criteria for AIDS, though one or more of these agents may be identified in the GI tract by stool examination at some point in the course of AIDS.[320] *Cryptosporidium* is far more frequently identified than *Microsporidium* or *Isospora*, at least in developed nations, while the others are more sporadic in occurrence. In the U.S. less than 5% of HIV infected persons develop cryptosporidiosis, with an increased risk for infection when the CD4 lymphocyte count is less than 100/μL.[397] Appearance of these protozoa may explain clinically significant diarrheas, though patients with such organisms diagnosed may be asymptomatic. *Cryptosporidium* and *Isospora* are more common in patients in developing nations than in the U.S.[328,398,399,400] Acid fast staining is useful for identification of *Cryptosporidium* and *Microsporidium* in stool specimens.[401]

Cryptosporidiosis in immunocompromised hosts can be the cause for diarrhea that is refractory to therapy. The species affecting humans has been designated *Cryptosporidium parvum*. There are no specific gross pathologic features and it is usually diagnosed from stool specimen examination. Cryptosporidial infection is usually unaccompanied by inflammation, hemorrhage, or ulceration. After ingesting infective oocysts, there is asexual multiplication of the organisms in host intestinal epithelial cells within a vacuole so that the organisms are intracellular but extra cytoplasmic located on the brush border. Gametogeny follows next, leading to production of oocysts that are either thin-walled and auto infective or thick-walled and passed in feces to become infective to others. More thin-walled oocysts are present in immunocompromised hosts, leading to the persistence with greater severity of the disease. The incubation period is 2 to 14 days.[328,398]

The cryptosporidia appear histologically as quite small 2 micron uniform rounded shapes; they develop outside of human cells but within a vacuole derived from the host cell. Thus, in tissue sections stained with hematoxylin-eosin, these organisms are small pale blue dots found lined along the mucosal brush border of the intestine. They can be highlighted with acid fast staining. Unfortunately, they may also resemble tissue fragments or karyorrhectic nuclei in tissue biopsies, so care must be taken in diagnosis. They are recognizable as 4-6 micron oocysts that are most distinctive from background in stool specimens with an acid fast stain. Cryptosporidia are more easily recovered from diarrheal stools than from formed stools.[328] Cryptosporidia may rarely be found outside of the GI tract in the biliary tree or respiratory tract.[342] An immunohistochemical stain may aid in detecting them.[402]

Since the major route for infection with Cryptosporidium is through fecal-oral contamination and through contaminated water, HIV-infected persons should avoid drinking untreated water, avoid contact with either human or animal feces, and wash hands after contact with pets, soils, and fecal material.[250] Death from cryptosporidiosis may occur rarely in AIDS patients because of intractable diarrhea with fluid loss and electrolyte imbalance. The cachectic state and concomitant infection with other opportunistic agents in many AIDS patients potentiates the effects of the severe diarrhea. Therapy with spiramycin or eflornithine has shown very limited success.[324]

Isospora belli infections occur less frequently than cryptosporidial infections in AIDS, but produce an indistinguishable clinical appearance. Immunocompetent persons have mild symptoms lasting only days to weeks, but AIDS patients have a chronic intermittent diarrhea lasting for months. After ingestion, infective oocysts release sporozoites that invade intestinal epithelium where they develop into trophozoites, then schizonts. The schizonts may then release merozoites which invade other epithelial cells and become either schizonts or gametocytes which form zygotes and transform into infective oocysts passed with feces. By light microscopy, the small intestinal mucosa (less frequently the colon in severe infections) shows shortening and flattening of the villi with acute and chronic inflammation. *Isospora* organisms develop within vacuoles 3-15 microns in

size on histologic section in the intestinal epithelial cells, and sometimes merozoites are visible. The infective oocysts of *Isospora* average 20-30 microns and can be seen easily in concentrated stool specimens with acid fast staining.[328,398]

Microsporidiosis is produced by spore-forming intracellular protozoan parasites identified in two genuses: *Enterocytozoon* and *Encephalitozoon* (*Septata).* In the genus *Enterocytozoon* several species have been identified in persons with AIDS: *E bieneusi*, *E cuniculi*, and *E hellum. Encephalitozoon* (*Septata) intestinalis* has also been identified.[399,403,404] When diagnostic techniques are available, microsporidia may be even more frequent than cryptosporidia as a cause for chronic diarrhea in AIDS patients. The clinical features of GI infection with microsporidiosis mimic cryptosporidiosis. Microsporidia may also be found outside of the intestine in biliary tract, urinary tract, and eye, while more uncommon locations for involvement include nasal sinuses, respiratory tract, and central nervous system.[405,406,407]

Microsporidial infection in man occurs when spores are ingested and invade intestinal epithelial cells where they proliferate by fission to produce meronts. From meronts, sporonts develop and divide into sporoblasts which then undergo metamorphosis to spores that are passed into feces.[328,398] Diagnosis is made by small intestinal biopsy with characteristic transmission electron microscopic appearance in villous epithelial cells of clusters of supranuclear intracytoplasmic 4 to 5 micron sized meronts and sporonts or 1 to 2 micron acid fast spores.[408] Microsporidiosis can also be diagnosed by light microscopy in tissue sections with Giemsa stain, modified trichome, or fluorescence staining of direct smears of unconcentrated stool or duodenal aspirate specimens fixed with formalin.[398,399,400]

A modified trichrome stain can be useful for diagnosis of microsporidia in direct smears of stool and duodenal aspirates that are unconcentrated and have been formalin-fixed.[404] In addition, fluorescence methods can be utilized for detection of microsporidia (*Enterocytozoon* and *Septata* species). The Fungifluor, Calcofluor white, and Fungiqual A fluorochrome stains can be applied to stool specimens, enteric fluids, and tissue biopsies. Spores of these organisms are best detected either in unfixed or in formalin-fixed specimens. These methods can be applied to paraffin-embedded tissues.[409] Use of immunoperoxidase staining and the polymerase chain reaction can also aid in identification of microsporidial organisms.[410,411]

Another organism that can cause a diarrhea lasting for weeks to months leading to fatigue and weight loss similar clinically to cryptosporidial diarrhea is *Cyclospora cayetanensis*.[412] Cyclosporiasis is a cause for traveler's diarrhea in both immunocompetent as well as immunocompromised persons. The causative agent is a small coccidian protozoa, originally described as a blue-green algae or cyanobacterium, that can be detected in stool by acid fast staining. The acid fast stained organisms demonstrate orange autofluorescence with blue (450 to 490 nm) fluorescent light microscopy. The organisms resemble a large cryptosporidium; they are 8 to 10 microns in size, with a double cyst wall and a central morula.[328,413] Small intestinal biopsy reveals mild to moderate acute and chronic inflammation of lamina propria with prominent plasma cells along with focal vacuolization of the brush border and mild to moderate partial villous atrophy and crypt hyperplasia.[414]

Giardia lamblia is the most common intestinal protozoan infection diagnosed in the United States, and it is common in many parts of the world. It is occasionally seen in persons with AIDS and can produce bloating, diarrhea, and malabsorption. The organisms are found tightly adherent to the duodenal mucosa and appear either as 10 micron round to oval, pale-staining trophozoites or as cysts that are slightly larger and darker staining with long axonemes and curved median bodies. These organisms may be difficult to recover in stool and require duodenal aspirate and biopsy for diagnosis.[328]

BACTERIAL INFECTIONS SEEN WITH AIDS

Bacterial infections can be frequent and clinically significant in persons with HIV infection because of the defects in both humoral as well as cell-mediated immunity late in the course of AIDS. Recurrent bacterial infections in children and recurrent pneumonia in adults may be used to define AIDS by CDC criteria.[317,318,319,320] The chronically debilitating course of AIDS along with multiple drug therapies, including the use of indwelling catheters, and the potential for superinfection of existing lesions all enhance susceptibility to bacterial infection. In fact, during the course of infection with HIV, bacterial infections can be more common than parasitic, viral, or fungal infections. Bacterial bronchopneumonia is second only to *Pneumocystis carinii* pneumonia in frequency as a cause of death from pulmonary infections in persons with AIDS.[342] The neutropenia that may occur with AIDS, either as a consequence of HIV infection or as a complication of drug therapy, significantly increases the risk for bacterial infections when the absolute neutrophil count diminishes below 750/μL, and particularly when the count is below 500/μL.[415]

The bacterial species most often responsible for pulmonary infections are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus* species--particularly *Streptococcus pneumoniae*, *Haemophilus influenzae*, and enteric bacterial species. Prophylactic vaccination for *S pneumoniae* and *H influenzae* can reduce the incidence of these infections significantly. The host response to infection with these agents is mainly neutrophilic, but is blunted late in the course of AIDS by the generalized failure of the immune system. Diagnosis is made by gram stain and culture of body fluids and tissues.[416,417,418]

Bacterial organisms in persons with AIDS most often produce respiratory disease, particularly bronchopneumonia that can be life-threatening, but such infections can become disseminated as well, and recurrence is common. The bronchopneumonias seen with AIDS can be extensive and bilateral. Mortality is higher than in non-HIV-infected patients. Bacterial septicemias are the immediate cause of death in about 5% of AIDS patients.[342] Indwelling catheters may predispose to infection, particularly with *Staphylococcus* organisms.[416,417] Nosocomial infections are more common in patients with AIDS from immunosuppression, prior antibiotic treatment, and greater exposure to invasive devices such as indwelling catheters. The incidence of nosocomial infection seen with AIDS ranges from 7.9 to 15 per 100 admissions, with bloodstream infections the most frequent, mainly due to intravascular catheters, followed by urinary and respiratory tract infections.[419]

Two bacterial agents found in soils that can infect patients with HIV infection are *Listeria* and *Rhodococcus*. *Listeria monocytogenes*, which appears as a short gram positive bacillus, occurs occasionally in HIV-infected patients, usually as meningitis, septicemia, or gastrointestinal infection. Listeriosis may not be frequent because *Listeria* is inhibited in vivo by tumor necrosis factor (TNF), and patients with AIDS typically have increased levels of TNF. However, the incidence of listeriosis in persons with HIV infection and with AIDS is about 10 and 100 times respectively that of the population as a whole. *Rhodococcus equi* is a weakly acid fast pleomorphic gram positive coccobacillary agent. The persistence of *Rhodococcus* in macrophages makes its eradication in patients with a poor cellular immune response difficult and leads to chronic relapsing infections, typically pneumonias and septicemias.[418,420,421] This persistence can also manifest in malakoplakia, or the appearance of macrophages containing target-like calcospherites called Michaelis-Gutman bodies.[422] *Legionella pneumophila* infections seen with HIV infection are more severe with higher mortality rate than in patients without HIV.[423]

Vaccination against *Pneumococcus* in adults and *H influenzae* type b in children (and possibly adults) is a useful prevention strategy against these bacterial infections in adults with HIV infection. Trimethoprim-sulfamethoxazole used for *Pneumocystis carinii* pneumonia prophylaxis has been shown to also reduce the risk for bacterial infections. In children, the use of intravenous IgG can help to prevent recurrent bacterial infections.[161,250]

Gastrointestinal bacterial infections can include *Salmonella*, *Campylobacter*, and enteropathogenic *E. coli* involving the small intestine or *Shigella*, *Campylobacter*, *Clostridium difficile*, *Vibrio parahaemolyticus*, *Yersinia*, and *Aeromonas hydrophilia* involving the colon. Small intestinal infections are generally associated with large volumes of watery stool, malabsorption, and wasting syndrome but no fever, occult blood, or fecal leukocytosis. Colonic infections are characterized by frequent but small volume stools that may contain blood, have abundant leukocytes, and be associated with painful bowel movements. Diagnosis is made via microbiologic culture of stool or blood.[424]

OTHER INFECTIONS

BARTONELLA (ROCHALIMAEA).-- Bacillary angiomatosis (epithelioid angiomatosis), peliosis of liver and spleen, osteolytic bone lesions, and persistent fever with bacteremia in HIV-infected persons are caused by fastidious gram negative organisms known as *Bartonella henselae* (formerly *Rochalimaea henselae*) or as *Bartonella quintana*. This agent appears to be rickettsia-like and can be identified in tissue sections with Warthin-Starry staining, by immunocytochemical methods, or by culture with confirmation via polymerase chain reaction. This organism has appeared in many geographic areas. Epidemiologic evidence suggests that bacillary angiomatosis is a zoonosis associated with traumatic exposure to cats, poor living conditions, and infection with *Bartonella*.[425,426,427]

LEISHMANIA INFECTIONS.-- Visceral leishmaniasis, known also as kala azar, has been reported in persons with HIV infection from endemic areas for *Leishmania donovani*., but these infections may also be seen outside of endemic areas because of increased travel. Increasing numbers of cases have been observed in Southern Europe, where 25 to 70% of adults with leishmaniasis are coinfected with HIV and 1.5 to 9% of persons with HIV infection develop leishmaniasis. The CD4 count is <200/μL in 90% of cases. The major surface molecule of *L donovani* is lipophosphoglycan which induces HIV transcription in CD4 cells; thus, leishmaniasis may promote HIV infection.[428]

L donovani is a protozoan parasite transmitted via sand fly bite. The bite introduces promastigotes into the skin, where they are then engulfed by macrophages. The organisms become amastigotes and, after proliferating, peripheral blood mononuclear cells can become infected and spread the infection through tissues of the mononuclear phagocyte system and elsewhere. Clinical manifestations include fever, hepatosplenomegaly, and pancytopenia. In some cases, leishmaniasis is the first severe infectious disease complicating HIV infection. Serologic titers indicative of *L donovani* infection are present in only a third of cases. Antimonial therapy may show an initial response followed by a chronic course with relapses, but a complete response is observed in a minority of cases. The presence of additional opportunistic infections during active leishmanial infections complicates diagnosis. In most cases, the stage of AIDS is late and the prognosis poor.[429]

Diagnosis has been made primarily through bone marrow biopsy with culture or by identification of typical amastigotes in smears. The use of PCR to detect leishmaniasis in peripheral blood may be useful and may also help to determine relapse following treatment.[430] Histologically, the amastigotes appear as round to oval 2 to 5 micron basophilic structures in the cytoplasm of macrophages with H&E stain. The organisms are positive with Giemsa stain. In some cases, the organisms can appear extracellularly in connective tissues or in vascular lumens. The macrophages may demonstrate organisms with a “double dot” appearance due to staining of both amastigote nucleus and kinetoplast with hematoxylin-eosin and Giemsa stains. Accompanying inflammation is typically minimal. By electron microscopy, the amastigotes are characterized by the presence within a cell membrane of a kinetoplast, large vacuole, microtubules, flagellar root, and eccentric nucleus with clumped chromatin.[431]

The mononuclear phagocyte system, including liver, spleen, lymph nodes, and bone marrow, are most often involved, but the gastrointestinal tract and respiratory tract may also be affected in immunocompromised hosts, and unusual sites of involvement such as the heart, skin, and adrenal may occur, particularly when the CD4 count is less than 50/μL. In the small bowel, biopsies will demonstrate mucosal infiltration by macrophages that lead to shortening and widening of villi. Liver biopsies will reveal the amastigotes in Kupffer cells, macrophages, or vessels accompanied by a portal chronic inflammatory cell infiltrate. Bone marrow biopsies show organisms within macrophages or in vessels. Skin biopsies show the amastigotes in dermal macrophages, connective tissue, or vessels.[431,432]

CHAGAS' DISEASE.-- In endemic locations for Chagas' disease, caused by the protozoan parasite *Trypanosoma cruzi* spread via the reduviid bug. Patients with AIDS may also be at risk for infection with *T cruzi* or reactivation of remote *T cruzi* infections. Such infections associated with AIDS are marked in most cases by a severe diffuse or multifocal meningoencephalitis which often presents with clinical features resembling an intracranial neoplasm. The pathologic lesions demonstrate hemorrhage and necrosis with numerous organisms. In about a third of cases there is myocardial involvement with acute and/or chronic myocarditis.[433]

PARACOCCIDIOIDOMYCOSIS.-- The dimorphic fungus *Paracoccidioides brasiliensis* is endemic to South America, where it is found in the mycelial form in soil. It is acquired as an infection by inhalation of mycelial conidia. Estrogen in women past puberty has a protective effect in preventing transformation to the invasive yeast form of this fungus. Infected persons may become asymptomatic carriers. In some cases, there is an acute disease with dissemination of the organism into the mononuclear phagocyte system, leading to lymphadenopathy, hepatosplenomegaly, osseous involvement, and cutaneous lesions. A more chronic form of this disease is characterized by mucosal involvement of the oral cavity and respiratory tract.[434]

Persons infected with HIV are more likely to have reactivation of an infection, rather than a new infection. The CD4 lymphocyte count is typically low. HIV infected persons are likely to develop a form of the disease that has elements of both acute and chronic paracoccidioidomycosis. In particular, they are more likely than HIV negative persons to develop cutaneous lesions, particularly ulcerated papular lesions that may have a necrotic center. They also have respiratory tract involvement, particularly of the lungs, with interstitial infiltrates. Ulcerated oral lesions can be present as well. Seronegativity for the fungus occurs in about half of cases, making identification of the yeast in tissue biopsies and sputum samples the best diagnostic method. Tissue involvement is characterized by poorly formed granulomas with prominent necrosis and numerous yeasts. Amphotericin B appears to be the most efficacious pharmacologic therapy for infections with acute features, while itraconazole may have usefulness in more chronic forms of this disease.[434]

STRONGYLOIDIASIS.-- The parasite *Strongyloides stercoralis* has a worldwide distribution and is transmitted when infective larvae in contaminated soil penetrate the skin, but fecal-oral and sexual transmission are also possible. In immunocompromised hosts, it is possible for an uncontrolled autoinfection cycle to occur in which rhabditiform larvae in the intestine molt into filariform larvae that invade the intestinal wall and disseminate, producing a hyperinfection syndrome called disseminated strongyloidiasis which has high morbidity and mortality. The enteropathy that can occur with HIV infection may predispose to strongyloidiasis. Clinical findings include fever, cachexia, diarrhea, melena, abdominal pain, cough, and dyspnea. A complication is sepsis with enteric organisms. Chest radiographs often reveal bilateral interstitial infiltrates. Diagnosis is best made by identifying the larvae on stool examination, or by finding larvae in sputum or bronchoalveolar lavage specimens. Serologic testing by enzyme immunoassay can also be performed, and can be useful in patients with unexplained eosinophilia, though eosinophilia is often absent in AIDS patients. A prolonged course of thiabendazole may be useful therapy, but treatment failures are common. Hyperinfection may respond to ivermectin therapy.[435,436]

MYCOPLASMA INFECTIONS AND AIDS.-- In vitro, several *Mycoplasma* species have been observed to act synergistically with HIV to increase single-cell lysis of HIV-infected cells. It is not clear what role *Mycoplasma* infections play in vivo to produce pathogenic effects. Urogenital *Mycoplasma* infections may contribute to the mucosal disruption that facilitates sexual transmission of HIV. Both *M fermentans* and *M pirium* have been found in the peripheral blood of HIV-infected persons. Both *M fermentans* and *M penetrans* have been found in the urine of patients with AIDS, and *M fermentans* has been found in association with HIV nephropathy. The strain of *M fermentans* associated with HIV infection has sometimes been labeled the *incognitus* strain. In addition, *M fermentans* has been detected in tissues of the mononuclear phagocyte system (thymus, liver, spleen, lymph node) and in brain. Some cases of respiratory failure have been linked to *M fermentans*. Detection of mycoplasmas is made primarily with molecular probes to DNA.[437]

ZYGOMYCOSIS (MUCORMYCOSIS) AND AIDS.-- Infections with the Zygomycetes, more commonly seen patients with diabetes mellitus, are infrequent in association with AIDS, though they can be the initial opportunistic infection. This infection is usually acquired through inhalation of spores, though direct inoculation via injection drug use is possible, particularly in cases of dissemination . Sites of involvement are typically the skin, respiratory tract, and intracranial cavity. One of the most common forms of involvement is rhinocerebral. Most reported cases have occurred in AIDS patients whose risk factor is injection drug use. The predisposing factor for zygomycosis of ketoacidosis seen in patients with diabetes mellitus is absent with AIDS, but the predisposing factor of neutropenia seen in other immunocompromised patients may be present with AIDS. The CD4 count is usually low. The clinical course can range from acute fulminant progression over days to an insidious infection persisting for years. Diagnosis is best made by biopsy to identify the broad, short, branching non-septate hyphae that stain poorly with special stains such as Periodic acid-Schiff (PAS) and Gomori methenamine silver (GMS). Culture can be performed, but the yield is not as great, and speciation does not influence therapy. Treatment includes surgical debridement of involved areas where accessible and amphotericin B.[438]

PENICILLIOSIS.-- Infections with *Penicillium marneffei* are seen in HIV-infected persons living in Southeast Asia and the southern part of China. Most infected persons will have a CD4 lymphocyte count below 100/μL. Infections tend to be disseminated. Clinical findings may include intermittent fever with or without chills, skin lesions, chronic productive cough, pulmonary infiltrates, anemia, hepatosplenomegaly, generalized lymphadenopathy, and weight loss. About two-thirds of patients will have skin lesions that may be the first sign of infection. The lesions are most frequent on the face, upper trunk, and extremities. The lesions may occur as papules, a generalized papular rash, necrotic papules, or nodules. Papules with central necrotic umbilication may resemble lesions of molluscum contagiosum. The skin lesions may resemble those of disseminated myxobacterial or fungal diseases.[368,439]

Diagnosis can be made via culture of tissues from affected sites, with the best yield from bone marrow and skin, but liver and lymph node biopsy cultures are useful as well. Culture of blood, stool, and cerebrospinal fluid can also be done. About half of patients will have a septicemia. At autopsy, the most common sites of involvement are lymph nodes, liver, lung, kidney, and bone marrow.[439,440]

P marneffei is found in the mycelial form in the environment, but it grows as a small spherical to oval 3 to 8 micron yeast form in tissues and appears very similar to, but slightly larger than, *H capsulatum* , and slightly smaller than *P carinii* in size with the Gomori methenamine silver (GMS) and periodic acid-Schiff (PAS) stains. Organisms are often abundant both intracellularly and extracellularly. Microscopically in immunocompetent hosts, there is typically a granulomatous reaction or a localized abscess. However, in immunocompromised hosts the tissue reaction includes necrosis without granuloma formation, and the predominant cell present is a macrophage engorged with the yeasts. Treatment may consist of itraconazole, ketoconazole, flucytosine, or amphotericin B. Most patients respond to initial therapy, but relapse can occur.[370,439,439]

SPOROTRICHOSIS.-- Infection with the dimorphic fungus *Sporothrix schenckii*, which has a worldwide distribution, is most commonly cutaneous, with lesions that appear most often on the face, trunk, and extremities as indurated, fixed plaques or small erythematous to violaceous papules. These lesions commonly become ulcerated and crusted. Dissemination is uncommon, except in the setting of immunosuppression. Persons with AIDS can have widespread dissemination with more severe forms of sporotrichosis that include lymphocutaneous, pulmonary, meningeal, and osteoarticular involvement that is difficult to eradicate, even with antifungal therapy with amphotericin B.[441]

UNUSUAL YEAST PATHOGENS.-- Adult patients with HIV infection may present with a variety of uncommon yeast infections including *Trichosporon beigelii*, *Saccharomyces cerevisiae*, *Rhodotorula rubra*, *Hansenula anomala*, and *Malassezia furfur*. *T beigelii* infections may start in

the gastrointestinal tract or at sites of vascular catheters and may cause fatal disseminated infections in immunocompromised patients, with findings of renal failure, pulmonary infiltrates, multiple cutaneous lesions, and chorioretinitis. *T beigelii* is typically resistant to amphotericin B but not to fluconazole. *M furfur* can produce tinea versicolor, infectious folliculitis, and catheter-associated fungemia. A fungemia most often develops in children receiving total parenteral nutrition via indwelling central venous catheters.[368]

ACANTHAMEBIASIS.-- Disseminated infections with free-living ameba found in water have been rarely seen in association with AIDS. Ameba of the *Acanthamoeba* and *Leptomyxida* forms have been identified. Ordinarily in non-immunocompromised persons, such organisms can produce a slowly progressive granulomatous encephalitis that is nearly always fatal. However, only about half of such infections seen in AIDS patients have had neurologic manifestations. Instead, the most striking finding is skin involvement with pustules, indurated papules and plaques, cellulitis, and ulcers, most often on extremities and less frequently on the face (nose) or torso. Involvement of the nose and nasal sinuses in many cases suggests that these sites may be portals of entry. Histologically, granulomatous, suppurative, or vasculitis-like inflammation may be present, but the similarity of ameba to macrophages makes diagnosis difficult. The organisms show vacuolated cytoplasm, an eccentric nucleus, and karyosome. Other organs may be involved, though less frequently. Skin involvement in patients with AIDS may be the only manifestation of acanthamebiasis, or it may precede additional organ involvement by weeks or months.[442]

MALARIA AND AIDS.-- Malaria is endemic to parts of Africa and Asia where the prevalence of HIV infection is 1% or more of the population. The presence of HIV infection appears to increase the incidence of parasitemia with *Plasmodium falciparum* infection, which can lead to severe malaria.[443]

ZOONOTIC DISEASE AND AIDS.-- There are a number of infections that occur in patients with HIV that can potentially be transmitted from animal sources. The agents include *Cryptosporidium*, *Microsporidium*, *Campylobacter jejuni*, *Giardia lamblia*, *Salmonella* species (not *typhi*), *Rhodococcus equi*, *Bartonella henselae*, and *Listeria monocytogenes*. Of these, only *Bartonella* appears to be acquired in patients with HIV infection mainly from an animal source (cat). Even so, the risk for zoonotic transmission of any infection to an HIV-infected person is small. The benefits of animal companionship outweigh the risks to patients and prohibition of pet ownership by HIV-infected persons is not warranted.[444]

CHAPTER 4 - NEOPLASMS ASSOCIATED WITH AIDS

KAPOSI'S SARCOMA

Several forms of Kaposi's sarcoma (KS) exist: classic, endemic, immunosuppression or transplantation-associated, and epidemic. The classic form of KS most often appears in persons of Eastern European or Mediterranean ancestry, has a male: female ratio of 15:1, and has a median age of 64 years. Classic KS typically appears on skin of hands and feet and progresses up arms and legs. Lymphedema occurs in some cases. Visceral or mucosal involvement appears in 10% of cases. The endemic form of KS is seen in Africa and typically appears on the skin of limbs in adults, though an aggressive lymphadenopathic form can be seen in children. The immunosuppressive or transplantation-associated form of KS is most likely to be seen in persons with ancestry from areas in which classic KS occurs. It appears on average 2.5 years after transplantation. The male: female ratio is 2 to 4:1. In half of cases there is mucosal, nodal, or visceral involvement. The epidemic form of KS is associated with HIV infection.[445]

Kaposi's sarcoma (KS) was rarely seen prior to the AIDS epidemic but became one of the most common diagnostic diseases seen with AIDS (Table 5). The risk for KS is approximately 178-fold for persons with AIDS.[446] with a relative risk of >10,000.[447] Kaposi's sarcoma has been seen most frequently in homosexual and bisexual males, who had a 10-fold risk compared with intravenous drug users, though the incidence of KS with AIDS has decreased over time in this population. It was noted that heterosexuals had a 2 to 3-fold risk for KS compared with intravenous drug users. Kaposi's sarcoma was infrequently seen in persons whose risk for AIDS was parenteral exposure to HIV, or in blacks and children. Kaposi's sarcoma remains less common in women than men, with a male: female ratio of 6:1 in the United States, though in Africa the ratio is 2:1.[167, 448,449]

The incidence of KS appears to have declined by 10% per year in the U.S. in the decade of the 1990's. The increasing use of antiretroviral therapy, and particularly aggressive highly active antiretroviral therapy (HAART) regimens, appears to have made the greatest difference. Persons on a single antiretroviral agent showed a 13% reduction in the development of KS, while those persons receiving triple agent therapy had a 59% reduction.[450,451]

A gamma human herpesvirus (human herpesvirus 8, or HHV-8) has been identified in skin and visceral lesions in 90% of all forms of KS, including classical, iatrogenic, endemic, and AIDS-associated forms. Thus, it has been called Kaposi's sarcoma-associated herpes virus (KSHV). HHV-8 appears to be restricted to infection of cord blood mononuclear cells, adult CD19 positive B cells, macrophages, and endothelial cells.[452]

This virus contains many genes that alter cellular growth, including BCL-2 and cyclin analogs. In addition, HHV-8 produces proteins that induce angiogenesis.[453] The mitogenic effect of HIV tat gene protein may act synergistically with KSHV to induce spindle cell growth.[450] KSHV has also been detected in the KS lesions of HIV negative homosexual males. It is phylogenetically similar to human herpesviruses 6 and 7.[454] The HHV-8 agent can be identified in the progressive stages of KS as well, but it can also be found in about a third of tissues of AIDS patients without KS, suggesting that it is disseminated and plays a permissive role in development of KS. This agent may rarely be found in tissues of patients with AIDS who do not yet have a diagnosis of KS.[455]

KS is an angioproliferative disorder resulting from immune dysregulation. The early lesions of KS are thought to be reactive and, theoretically, reversible. However, the immune system activation, with a TH1 response and cytokine production, that continues with HHV-8 infection, drives the process to true neoplasia, with evolution from polyclonal proliferation to monoclonal tumor. The HIV Tat protein also appears to play a role by stimulating growth and angiogenesis.[456]

In developed nations the HHV-8 agent (KSHV) is seen as a sexually transmissible disease that can occur independently of HIV infection, and it accounts for the increased incidence of KS in

homosexual males. The prevalence of HHV-8 is 30-40% among homosexual males and correlates with the number of sexual partners. In Africa, KSHV is also spread as a congenital infection and in childhood. Primary infection with KSHV is asymptomatic.[445] The HHV-8 agent can be identified in peripheral blood mononuclear cells with a higher frequency in persons with KS than without KS. It can be detected in saliva and semen. This agent can still be detected despite therapy with anti-herpesvirus drugs. However, the incidence of KS decreases with antiretroviral therapy.[457]

Neither cytomegalovirus (CMV) nor human herpesvirus-6 (HHV-6) infection appears to be associated with development of KS.[458] The increased prevalence of KS in men, typical those whose risk factor for HIV infection is sexual intercourse with other males, over women is explained by the lower prevalence of HHV-8 seropositivity in HIV-infected women.[459]

Though the skin is involved in over three fourths of cases and is often the site of initial clinical presentation, skin is usually not the sole site of involvement. Visceral KS (involving one or more internal organs sites) is also present in three fourths of cases, but may not be diagnosed prior to autopsy. Visceral involvement frequently includes the lung, lymph nodes, and gastrointestinal tract. In fewer cases, KS appears in the liver or genitourinary system. Kaposi's sarcoma is infrequent in adrenal, heart, and spleen; KS is rare elsewhere (Table 5). Though multifocal, KS appears to be monoclonal in origin, typical of a true neoplasm.[460]

Bronchoscopic and gastrointestinal endoscopic biopsy may yield a diagnosis of KS, but these methods are hampered by sampling error from the focal nature of KS lesions. Though it is common for KS to become widely disseminated, some patients may have only one site or focus of involvement, not necessarily skin. The natural history of KS, however, is progression over time to involve multiple sites in multiple organs.

A complete description of gross and microscopic appearances of KS is given in the section of organ system pathology on skin. To summarize, KS lesions grossly are red to red-purple. The lesions range from a flat patch to slightly raised plaques to nodules. Lesions larger than 0.5 cm are usually nodular. Microscopically, KS is characterized by atypical large spindle to fusiform cells that line slit-like vascular spaces. Red blood cell extravasation, hemosiderin pigmentation, and hyaline globules usually accompany the spindle cell proliferation. The lesions have irregular, infiltrating margins. Sometimes the vascular spaces are dilated and sometimes sheets of KS spindle cells have inapparent vascularity. Kaposi's sarcoma has a propensity to infiltrate around large vascular structures, near epithelial or mesothelial surfaces, or near the capsules of organs.[448]

Small, early KS lesions or KS that is ulcerated or inflamed can be difficult to diagnose. Granulation tissue can have a strikingly similar appearance. Hemangiomas may grossly--and sometimes microscopically--resemble KS. When uncertain of the diagnosis, it is best to be conservative. If the lesions really are KS, they will progress over time.

A variety of single agent or combination chemotherapeutic regimens have been employed against KS, including Adriamycin, doxorubicin, vinblastine, vincristine, vindesine, etoposide, and bleomycin, as well as alpha interferon therapy. Radiation therapy has also been employed for localized, bulky or painful KS lesions. A combination of doxorubicin, bleomycin, and vindesine has shown partial or complete remission in most cases. The combination of Adriamycin, vincristine, and bleomycin has shown effectiveness in treating pulmonary KS. Survival, however, may not always increase because of concomitant AIDS-related diseases, and granulocytopenia and toxicity is common. At autopsy the response to therapy for skin lesions is demonstrated to be greater than that for visceral lesions.[445,450,461]

Treated KS lesions may show absence of atypical spindle cells with only a focus of collagenous connective tissue remaining. More often, treatment leads to only partial regression, with decreased numbers of atypical spindle or epithelioid cells, along with fibrosis, round cell infiltrates, hemosiderin, and irregular vascular spaces. Diagnosis of such lesions is difficult and is suggested at low power by the presence of a localized nodule or infiltrate.

The presence of KS appears to accelerate the clinical course of HIV infection. Opportunistic infections develop earlier and more often in patients with KS, with significantly shorter survival. However, death directly related to lesions of KS occurs in a minority of persons with AIDS carrying a diagnosis of KS, usually as a result of massive pulmonary involvement

(Table 5).[462,342] KS exhibits a less aggressive presentation in patients already receiving highly active antiretroviral therapy (HAART) compared to patients who are not receiving HAART at the time KS is diagnosed. The natural history and outcome do not appear to be influenced by the initiation of HAART before the development of KS.[463]

MALIGNANT LYMPHOMAS

As in other immunodeficiency diseases, the risk for malignant lymphoma is increased with AIDS. The incidence of non-Hodgkin lymphoma (NHL) with AIDS is 72.8-fold (relative risk >100), while the risk for Hodgkin disease (HD) is 11.5 fold (relative risk 8).[446,447] There appears to be a 5-fold risk for multiple myeloma with AIDS.[447] The organ system involvement of AIDS-associated malignant lymphomas occurs in two major patterns: (1) systemic lymphomas comprising a heterogenous group of cell types and organ involvement and (2) central nervous system lymphomas. In the former group, more than one organ may be involved at a time, and extranodal involvement is common (Table 5). The typical variety of lymphomatous neoplasm seen with AIDS is an intermediate to high grade non-Hodgkin lymphoma of B-cell origin.[320,464] High grade non-Hodgkin lymphomas of T-cell derivation with AIDS have been reported in association with Epstein-Barr virus infection in oral cavity and elsewhere. Some have a Ki-1 phenotype.[465,466]

HODGKIN DISEASE.-- Hodgkin disease (HD) may be seen with increased frequency in persons infected with HIV, but HD is not part of definitional criteria for diagnosis of AIDS. The relative risk for HD for men with HIV infection is reported from 5.0 to 18.3. HD tends to have a more aggressive course in patients infected with HIV. Intravenous drug users constitute the risk group most frequently affected. Hodgkin disease with HIV infection is more likely to be stage III or IV at presentation (82%), to have a mixed cellularity subtype, to have bone marrow involvement, to have noncontiguous spread of tumor, to have numerous Reed-Sternberg cells, and to show an association with Epstein-Barr virus infection. There is often a prominent fibrohistiocytoid stromal cell proliferation in the involved lymph nodes. Patients with HIV-associated HD are more likely (70 to 96%) to have "B" symptoms including fever, night sweats, and/or weight loss >10% of normal body weight. HD in HIV infected persons is more likely to be accompanied by anemia, leukopenia, or thrombocytopenia. Extranodal involvement, including bone marrow, liver and spleen, is more likely to occur.[467]

HD in HIV infected persons is more likely to present earlier in the course of infection, when the CD4 lymphocyte count is higher, than in persons with non-Hodgkin lymphomas. However, HD tends to occur in the later stages of AIDS. Generalized lymphadenopathy is likely to be present, and the clinical picture may resemble persistent generalized lymphadenopathy (PGL). However, mediastinal lymphadenopathy is less frequent in HIV infected patients with HD. Response to therapy and survival with HD is lessened when HIV infection is present. Predictors of longer survival with HD in HIV infected persons include absence of prior AIDS diagnosis (20 versus 7 months) and a CD4 count >250/μL (38 versus 11 months). The use of highly active antiretroviral therapy (HAART) can improve control of infection and allow for more aggressive chemotherapy.[467,468

NON-HODGKIN LYMPHOMAS.-- Persons infected with HIV develop non-Hodgkin lymphoma (NHL) more frequently than the general population. The presence of the chemokine receptor variant CCR5 delta32 appears to significantly lower the risk for development of HD in persons with HIV-1 infection while presence of the SDF1-3'A chemokine receptor variant doubled the risk when heterozygous and led to a fourfold increase in HD in persons homozygotes.[469] The use of highly active antiretroviral therapy (HAART) results in a reduction in the incidence of NHL in HIV infected persons.[451]

AIDS-related lymphomas are thought to arise when a variety of predisposing factors promote polyclonal B-cell proliferation. These factors include: diminished immunosurveillance with decreasing CD4 lymphocyte counts, destruction of follicular dendritic cells leading to interference with apoptosis and allowing B-cell clonal proliferation, chronic antigen stimulation marked by polyclonal hypergammaglobulinemia, Epstein-Barr virus (EBV) infection, and cytokine deregulation. This B-cell proliferation is best characterized clinically as persistent generalized

lymphadenopathy (PGL). Over time, B-cell oligoclonal expansions arise within this PGL pattern. A monoclonal proliferation eventually arises from a single clone that has accumulated sufficient genetic abnormalities.[464,470]

The clinical characteristics of non-Hodgkin lymphomas vary somewhat. About 80% of NHL's in AIDS arise systemically, either nodally or extra nodally, while 20% arise in the central nervous system. AIDS patients with systemic lymphomas are likely to have had previous opportunistic infections and be severely immunosuppressed with low CD4 lymphocyte counts at the time of presentation. For persons with CNS lymphomas, presenting symptoms are often non-localizing and include confusion, lethargy, and memory loss. Less frequent findings include hemiparesis, aphasia, seizures, cranial nerve palsies, and headache. Radiographic findings with either magnetic resonance imaging (MRI) or computed tomographic (CT) scans include single or multiple discrete ring-enhancing lesions very similar to those seen with toxoplasmosis. In contrast, patients presenting with systemic lymphomas are generally not as immunosuppressed, but typically have widespread extranodal disease.[464,470]

Grossly, non-Hodgkin lymphomas with AIDS may appear as small infiltrates, focal nodular lesions, or larger tumor masses. Multicentric lesions may appear in the same organ. Smaller lymphomatous lesions appear white to tan with irregular borders, while larger masses with definable margins are accompanied by necrosis and hemorrhage leading to appearance of a variegated (red to brown-black to white) cut surface resembling a strawberry or chocolate sundae.

Microscopically, systemic non-Hodgkin lymphomas seen with AIDS fall into two broad categories, both of B-cell origin. About 30% are high-grade B-cell (small non-cleaved) Burkitt-like lymphomas (in the REAL classification), called intermediate grade and classified as small noncleaved-cell (SNCLL) lymphomas (Burkitt or Burkitt-like lymphomas) in working formulation classification, and called Burkitt's lymphoma with or without plasmablastic differentiation (in Kiel classification). They may also be called AIDS-related Burkitt's lymphomas. These NHL's consist of cells having round nuclei with one or more prominent nucleoli and scant cytoplasm. The cells comprise diffuse sheets that form a discreet mass or irregularly intersect and infiltrate normal tissues without significant necrosis. Within the sheets of lymphomatous cells, uniformly distributed macrophages containing phagocytosed debris are present, and occasional mitoses are seen. Plasmablastic features including eccentric nuclei and well-defined Golgi zone may occur.[464,471]

The second broad category of non-Hodgkin lymphoma, comprising virtually all of primary CNS lymphomas seen with AIDS and about 70% of systemic lymphomas in AIDS, is composed of large cells that are best described as diffuse large B cell lymphoma (in the REAL classification), which can be either large cell immunoblastic lymphomas in working formulation classification (immunoblastic with or without plasmacytic differentiation in Kiel classification) or large noncleaved-cell lymphomas in working formulation classification (centroblastic diffuse in Kiel classification). The immunoblastic types consist of cells having moderate to large amounts of cytoplasm with or without plasmacytic features of eccentric nuclei and basophilic cytoplasm, large round to oval nuclei, and prominent single nucleoli. The large cell types have less cytoplasm and one or more peripheral nucleoli in a nucleus with finely dispersed chromatin. Necrosis is often a prominent feature, and mitoses are frequent.[464,471]

The molecular biology and biologic behavior of non-Hodgkin lymphomas with AIDS shows some variation. The intermediate grade AIDS-related Burkitt's lymphomas can occur when the CD4 lymphocyte count is low but sustained and can even be the initial manifestation of AIDS. Virtually all of them demonstrate activation of the c-*myc* proto-oncogene. Mutations of the p53 tumor suppressor occur in 60% of them, while about 30% of these lymphomas demonstrate Epstein-Barr virus (EBV). Though none demonstrate bcl-6 gene rearrangements, small mutations in of the bcl-6 gene can be found in 60% of cases. These intermediate grade lymphomas tend to occur at a younger age than the high grade lymphomas.[464]

In contrast, the high grade AIDS-related diffuse large cell lymphomas typically occur later in the course of AIDS, and the risk increases markedly as the immune system fails and the CD4 count is low and declining. Infection with EBV can be demonstrated in 70 to 80% of cases. Many have molecular alterations of the bcl-6 proto-oncogene, including mutations of the 5' regulatory

sequences. Rearrangements of the c-myc proto-oncogene may be seen in about 20% of AIDS-related DLCL's, when mutations of p53 are rarely seen.[464,470]

The 20% of NHL's seen in the central nervous system are of the high grade diffuse large cell variety. They typically occur late in the course of AIDS when the CD4 count is low and declining. Virtually all of them arise in the setting of EBV infection and they are essentially an expansion of EBV-infected B-lymphocytes. Mutations in bcl-6 regulatory regions may also be present.[464,470]

The high grade nature of most AIDS associated lymphomas helps in diagnosis, which can be difficult because of routinely employed biopsy procedures that may yield a small amount of tissue. Whether the tissue is obtained by stereotaxic brain biopsy, bronchoscopic lung biopsy, or endoscopic gastrointestinal biopsy, small tissue samples are usually obtained. Immunohistochemical staining may aid in defining a monoclonal cell population consistent with a neoplastic proliferation. Staining with common leukocyte antigen (CLA) may be useful in identifying the nature of lymphomatous infiltrates when necrosis is extensive.

Malignant non-Hodgkin lymphomas lead to the death of adult AIDS patients in over half of cases when this neoplasm is present at autopsy. Organ involvement leading to death is divided almost evenly among the central nervous system, gastrointestinal tract, and respiratory system. Chemotherapy protocols usually do not significantly alter the course of malignant lymphomas in patients with AIDS. There may be a short initial response, but virtually all lymphomas relapse, with an average time from diagnosis to death of less than a year.[342,471]

PRIMARY BODY CAVITY-BASED LYMPHOMAS.-- A small number of AIDS-associated NHL's may appear only as malignant cells within body cavity effusions without evidence for a mass lesion, organomegaly, or lymphadenopathy. These primary body cavity-based lymphomas (BCBLs), also known as primary effusion lymphoma (PEL), have occurred in either pleural effusions or ascites. The prognosis is poor.[472,473] They are associated with the same herpesvirus-like agent, known as human herpesvirus 8 (HHV-8), as lesions of Kaposi's sarcoma. There is frequent presence of the Epstein-Barr virus and no associated c-*myc* gene rearrangement, similar to the high grade non-Hodgkin lymphomas seen elsewhere.[474] The primary body-cavity based lymphomas are of a large cell variety with an immunophenotype that includes the following markers: CD30, CD38, CD45, and EMA.[336] Some high grade B cell non-Hodgkin lymphomas that are HHV-8 positive occur as solid masses, and their morphologic and immunophenotypic characteristics and prognosis are similar to PEL. They may be termed extracavitary PELs.[475]

MALT LESIONS.-- Mucosa-associated lymphoid tissue (MALT) lesions are lymphoid proliferations that typically occur at extranodal sites such as the gastrointestinal tract, bronchi, and salivary glands. Such MALT lesions have been described in association with both adult and pediatric AIDS. The spectrum of lesions have included myoepithelial sialadenitis (MESA) with low-grade MALT lymphoma, low-grade MALT lymphoma, diffuse large cell lymphoma, and atypical pulmonary lymphoid hyperplasia and lymphoid interstitial pneumonitis complex. These lesions appear to follow an indolent course in children. Unlike the MALT lesions seen in other immunocompromised adults that regress when immune suppression is reduced, as in transplant recipients, those in adults with AIDS have an aggressive course with poor prognosis.[476,477]

CUTANEOUS LYMPHOMAS.-- Cutaneous non-Hodgkin lymphomas may be seen in patients with AIDS. Though mycosis fungoides is the most common primary cutaneous lymphoma in immunocompetent persons, such lesions are rarely seen in association with AIDS. Two types of cutaneous lymphoma are seen with AIDS: CD30+ T-cell lymphomas and high grade B-cell lymphomas. The cutaneous T-cell lymphomas with AIDS are similar to those in non-HIV-infected persons and frequently present as localized nodules that demonstrate occasional spontaneous regression. The diffuse large B-cell cutaneous lymphomas with AIDS may remain localized for months without extra cutaneous spread, but do not regress. AIDS patients present with either T- or B-cell cutaneous lymphomas at an advanced stage and typically die from opportunistic infections.[478]

PLASMABLASTIC LYMPHOMA OF THE ORAL CAVITY.-- There is a distinctive type of non-Hodgkin lymphoma called plasmablastic lymphoma that is found in the oral cavity and jaw of persons infected with HIV. The lesions typically involve the mucosa or gingiva and may spread to underlying structures. This is a high-grade diffuse large cell lymphoma with plasmacellular differentiation as indicated by immunohistochemical staining for CD20, CD79a, and VS38c. In over half of cases, there is an association with Epstein-Barr virus infection. In some cases, other organ sites are involved.[479]

DIFFUSE INFILTRATIVE LYMPHOCYTOSIS SYNDROME.-- Although not a lymphoma, about 3% of HIV positive patients have visceral organ lymphocytic infiltrates that may mimic lymphoma. This condition, called diffuse infiltrative lymphocytosis syndrome (DILS) is seen more frequently in Blacks and in persons with risk factor of homosexuality. DILS is characterized by a persistent CD8 lymphocytosis and multivisceral CD8 lymphocyte infiltration. The most common site of involvement is the parotid gland, leading to bilateral facial swelling and xerostomia. Less commonly involved are lung, muscle, and liver. Some patients may also manifest either a peripheral neuropathy or polymyositis.[480,481,482]

MULTIPLE MYELOMA.-- Although hypergammaglobulinemia is a common finding in persons with AIDS, monoclonal gammopathy is not. Both transient and persistent paraproteinemias have been observed in HIV-infected patients. The paraproteins have high-titer anti-HIV activity. The same molecular mechanisms that give rise to non-Hodgkin lymphomas of B-cell lineage can also give rise to myelomas, though the reduced T-cell function with HIV infection may diminish the stimulus to plasma cell differentiation.[483] There is a 5-fold risk for myeloma with AIDS (relative risk of 5).[446,447]

OTHER NEOPLASMS

In adults, the only neoplasms that are part of definitional criteria for AIDS are Kaposi's sarcoma, non-Hodgkin lymphomas, and cervical squamous cell carcinomas.[320] Overall, the incidence for other malignant neoplasms with AIDS is 2.7 times that of the general population.[446] Persons who are HIV infected have a younger age at diagnosis (47 years) for malignant neoplasms that are not AIDS-defining, compared with non-HIV infected persons with the same neoplasms (60 years), and immunosuppression with loss of immune regulation may play a role in this phenomenon.[484] Smooth muscle tumors, including leiomyomas and leiomyosarcomas, are not common but are seen with increased frequency in children with HIV infection, where they form the second most frequent type of neoplasm.[485,486] In children, leiomyosarcomas are part of definitional criteria for AIDS.[319] The relative risk for leiomyosarcoma in children with AIDS is 10,000.[447] Leiomyosarcomas have also rarely been reported in adolescent and adult AIDS patients. These tumors may be associated with Epstein-Barr virus (EBV) infection of smooth muscle cells.[487]

Squamous epithelial lesions including dysplasias and carcinomas can be observed in persons with HIV infection. The relative risk for cervical cancer is 3 and for anal cancer 30 with AIDS.[447] One in five HIV-infected women without evidence for cervical lesions may develop SIL within three years, which emphasizes the importance of Pap smear screening in this population.[488] Cervical dysplasias in women with HIV infection are more common than in non-HIV-infected women. Particularly among males having anal intercourse, there is an increased incidence of anorectal epithelial dysplasias and anorectal squamous carcinomas. Penile cancer is more frequent in AIDS, but the association is not strong.[446] Human papillomavirus (HPV) infection plays a major role in development of these lesions in males and females. Squamous epithelial carcinomas in AIDS are more likely to be multifocal and extensive and more difficult to treat.[489]

The risk for development of skin cancers appears to be increased in HIV-infected individuals. Persons with AIDS tend to have a higher risk for development of basal cell carcinoma than the general population, and basal cell carcinoma is the second most common skin cancer in AIDS patients, with an incidence of 1.8%, compared to an overall incidence of cutaneous Kaposi’s sarcoma of 6.2%. In HIV-infected persons, basal cell carcinomas tend to be superficial, multicentric, and located on the trunk. The degree of immunosuppression does not appear to play a role in the appearance of this neoplasm.[489,490]

Dysplastic nevi and melanoma have been reported in HIV-infected patients with no prior family history of melanocytic lesions. The median age appears to be lower, and there is a greater tendency for thicker lesions with early metastasis, compared to non-HIV-infected persons, particularly when the CD4 lymphocyte count is lower.[489,490]

Lung cancers are seen with increased frequency in association with HIV infection, with a 4.5 fold relative risk.[446] HIV-infected persons get lung cancers at a younger median age, and they are most likely to have an adenocarcinoma, while small cell anaplastic carcinomas in this population are much less common than in the general population. Over 80% of HIV-infected patients with lung cancer present with advanced stage III or IV lesions that are inoperable. There may not be a strong a link with immunosuppression, since most reported cases of such lung cancers have occurred when HIV infection was asymptomatic or mildly symptomatic.[490]

The relative preponderance of young males infected with HIV increases the likelihood for appearance of testicular neoplasms, since this is the most common solid malignant neoplasm in young males. There is a relative risk of 2 in HIV-infected males compared with matched controls.[446] Most cases of testicular cancer occur before the stage of clinical AIDS has been reached. The stage at diagnosis is similar to non-HIV-infected persons, and response to therapy is also similar.[490,491].

Patients with a risk factor of intravenous drug use are often infected with viral hepatitis, putting them at increased risk for hepatocellular carcinoma. Other malignancies seen in association

with HIV infection are likely to be coincidental, and longer survival of HIV-infected patients increases the likelihood for appearance of neoplasms. Benign neoplasms are not seen with increased frequency in patients with AIDS. The overall incidence of non-AIDS-defining neoplasms (those not part of criteria for AIDS) does not appear to be high, with 51 such cases observed in 4041 patients in one study over a decade ending in 1998, but the survival of AIDS patients with such tumors appears to be decreased.[492]

CHAPTER 5 - ORGAN SYSTEM PATHOLOGY IN AIDS

RESPIRATORY TRACT PATHOLOGY IN AIDS

Patients with HIV infection frequently present with a wide spectrum of pulmonary complications from opportunistic infections and neoplasms that may be associated with a high mortality rate. Diseases of the respiratory tract account for many deaths from AIDS.[342] The response to therapy in AIDS can be slower and complicated by a greater number of adverse reactions to therapeutic agents than with other immunocompromised states. Cigarette smoking increases the risk for colonization by infectious agents, and smoke decreases alveolar macrophage function, leading to increased numbers of infections or more severe infections.[493]

The clinical features of many pulmonary diseases in AIDS are similar, necessitating serologic, culture, tissue, or cytologic diagnosis. Table 5 indicates the distribution of AIDS-diagnostic diseases in the respiratory tract seen at autopsy. Table 8 details the typical patterns of involvement.

PNEUMOCYSTIS CARINII (JIROVECII) PNEUMONIA.-- *Pneumocystis carinii (jirovecii)* pneumonia (PCP) is one of the most frequent and severe opportunistic infections in patients with AIDS.[329] Many AIDS patients will have at least one episode of PCP at some point during their clinical course, with mortality from a single episode ranging from 10 to 30%. However, use of antipneumocystis therapy and prophylaxis, either with trimethoprim-sulfamethoxazole, dapsone, or aerosolized pentamidine, can greatly diminish the incidence of PCP and increase survival.[162] The more extensive use of these therapies has increased survival for AIDS patients in places where it has been applied, both in the short term following a bout of PCP and in the first two years following diagnosis of AIDS.[494]

Clinical features that suggest a high risk for PCP include oral thrush or unexplained fever. Clinical features with PCP that predict a poor prognosis include long duration of symptoms (weeks), prior episodes of PCP, prior therapy with antibiotics other than trimethoprim-sulfamethoxazole, older age, and presence of cytomegalovirus.[495,496]

Clinical features of PCP typically include the classic triad of fever, non-productive cough, and dyspnea.[329] A pleuritic type of chest pain may also be present. A pleural effusion may accompany PCP. Spontaneous pneumothorax is an uncommon complication that can recur and be difficult to treat.[497] In general, the duration of these symptoms in a patient with AIDS is longer than that for patients without AIDS. Elevation of the serum lactate dehydrogenase (LDH) is highly sensitive for the diagnosis of PCP, but not specific because other pulmonary diseases such as tuberculosis and bacterial pneumonia may also have an elevated LDH, as well as extrapulmonary disorders.[498]

Pneumocystis carinii typically produces a pneumonia that is widespread throughout the lungs. *Pneumocystis carinii* pneumonia is a chronic disease that often responds well to drug treatment. However, there can also be rapid progression leading to adult respiratory distress syndrome (ARDS). *Pneumocystis carinii* pneumonia can be a presumptive clinical diagnosis to define AIDS using the following suggested guidelines:[320]

- A history of dyspnea on exertion or nonproductive cough with onset in the previous three months; AND
- Chest roentgenogram evidence of diffuse bilateral interstitial infiltrates or gallium scan evidence of diffuse bilateral pulmonary disease; AND
- Arterial blood gas analysis showing an arterial pO2 of less than 70 mm Hg or a low respiratory diffusing capacity (less than 80% of predicted values or an increase in the alveolar-arterial oxygen tension gradient; AND
- No evidence of a bacterial pneumonia

Radiographically, the findings with PCP are quite variable. Early in the course of the disease, the chest roentgenographic findings may be normal in 10 to 39% of patients. The presence of ground glass opacifications on high resolution CT imaging has a sensitivity of 100% for early PCP.[499] As PCP progresses there may be interstitial or reticulonodular infiltrates, nodules, or even patchy areas of consolidation. Use of aerosolized pentamidine for prophylaxis against PCP may lead to the appearance of localized upper lobe disease because this drug is preferentially deposited in middle and lower lobes.[495] In children, PCP may manifest radiographically as a rapidly progressive increase in air space opacity with air bronchograms.[500]

Therapies can include trimethoprim-sulfamethoxazole (oral or parenteral), pentamidine isethionate (parenteral or in aerosolized form), prednisone, trimethoprim-dapsone, dapsone, trimetrexate, pyrimethamine-sulfadoxine, or clindamycin-primaquine. Prednisone may be added as an adjunctive agent to lessen hypoxemia.[161,251] Trimethoprim-sulfamethoxazole (TMP-SMZ), if tolerated, is the first choice for either prophylaxis or therapy in both adults and children. If TMP-SMZ cannot be tolerated, then alternative therapy for prophylaxis may consist of dapsone, a combination of dapsone with pyrimethamine and leucovorin, or aerosolized pentamidine. Regimens containing dapsone and pyrimethamine are also effective prophylaxis against toxoplasmosis. Prophylactic therapy to prevent PCP is also recommended in pregnancy.[250]

Drug allergy or toxicity may develop in over half of treated patients and may also interfere with concomitant zidovudine therapy. Adverse reactions with trimethoprim-sulfamethoxazole occur in half of patients and include fever, skin rash (rarely Stevens-Johnson syndrome), nausea, vomiting, nephritis, leukopenia, hepatitis with elevated liver enzymes, and bone marrow suppression. Adverse reactions with pentamidine may include nausea, vomiting, rash, hypotension, alterations in serum glucose, pancreatitis, hepatotoxicity, nephrotoxicity, and leukopenia. Aerosolized pentamidine, which is preferentially deposited in middle and lower lobes, is often accompanied by bronchoconstriction that must be alleviated with concomitant use of an inhaled beta-adrenergic agent. Dapsone may cause rash, nausea, and hemolysis. Untreated, or with poor response to therapy, the terminal hospital course with PCP can be as short as a few days.[161,162,253,501]

Pneumocystis is more likely to have a diffuse involvement of lung than other opportunistic infectious agents or neoplasms with AIDS. *Pneumocystis* typically involves alveolar spaces, giving the gross appearance of pneumonic consolidation. *Pneumocystis carinii* pneumonia tends to be more confluent throughout the lungs than bacterial pneumonias. Cut surfaces of lung with early PCP show a prominent "poached salmon" or pale pink appearance when in the fresh state, and the markedly consolidated lung is firm to friable with a definable lobular pattern. There may be scattered areas of hemorrhage or congestion. The weight of each lung can exceed 1 kg.[495] Laboratory diagnosis is accomplished by staining of the organisms in fluids and tissues recovered from the patient.[502]

An uncommon gross appearance of PCP is a "granulomatous" pattern resembling *Mycobacterium tuberculosis* infection. This pattern is more likely to be present when a chest radiograph demonstrates one or more parenchymal nodules. The granulomas are typically less than 1 cm in size, are firm, and tan-white. Microscopically, occasional epithelioid cells and Langhans giant cells may be seen around a central zone of necrosis mixed with foamy exudate. A "pneumocystoma" pattern with one or more ill-defined pale pink to tan masses is also uncommonly seen.[503,504]

As PCP progresses, the lung texture becomes rubbery and the cut surfaces are often slimy, typical of diffuse alveolar damage (clinically defined as adult respiratory distress syndrome or "shock" lung). Severe infections poorly responsive to therapy may go on to produce diffuse alveolar damage that can organize to "honeycomb" lung with type II pneumonocyte hyperplasia and interstitial fibrosis. Lymphocytic or plasma cell interstitial infiltrates can be prominent, though this is more common with PCP in children than in adults. A pattern of bronchiolitis obliterans may be apparent. The greater the degree of organization, the fewer and smaller the alveolar exudates become, and the harder the organisms are to identify within the tissue histologically. Concomitant therapy of PCP with intubation and ventilation utilizing high oxygen tensions may lead to oxygen toxicity that also promotes diffuse alveolar damage.[495]

In hematoxylin-eosin-stained transbronchial biopsy specimens, PCP is suggested by the presence of a characteristic intra-alveolar exudate consisting of refractile, foamy to granular to honeycomb eosinophilic material composed mainly of the *Pneumocystis* organisms (both trophozoites and cysts) held together by intertwined slender membranotubular extensions. The exudate contains little fibrin, and scanty admixed cellular elements or debris may consist of lymphocytes, macrophages, pneumonocytes.[328] Early infections may lack the foamy exudate, though *P carinii* cysts and trophozoites can be demonstrated on alveolar septae. An inflammatory component is not a striking feature in most cases, though in some cases macrophages, polymorphonuclear leukocytes, or lymphocytes may be seen. Diagnosis is made by finding the 5 to 7 micron cysts with special stains in biopsy or cytologic specimens.[495]

Most PCP cases are "typical" in that pink foamy to granular alveolar exudate is present and interstitial or inflammatory changes are minimal to absent. This exudate is found in most alveoli throughout the lung, though it may be more pronounced in some. A patchy pattern of alveolar involvement is seen in a few cases. However, one or more "atypical" features may be found in over half of PCP cases and can include: a plasma cell interstitial pneumonitis with round cells--including many plasma cells; a necrotizing granulomatous pattern of inflammation with giant cells, epithelioid macrophages, and caseation; prominent microcalcifications; absence of foamy exudate; interstitial or intraluminal fibrosis; bronchiolitis obliterans; or desquamation of type II pneumonocytes. A "pneumocystoma" may develop and consist of a localized mass lesion containing sheets of foamy to granular pink exudate without an intervening alveolar framework.[496,501,503,504]

Pulmonary cavitation may occur in association with PCP in less than 5% of cases, either alone or within an area of pulmonary consolidation, mass, or nodule. Patients with cavitation may present with hemoptysis. Cavitation may be promoted by vascular invasion by *P carinii* and subsequent vasculitis and necrosis or by alveolar septal invasion and necrosis.[495,505]

Extrapulmonary spread of *P carinii* occurs in less than 5% of cases of AIDS in which *P carinii* infection is diagnosed. The most common site is hilar lymph nodes, followed by spleen and liver.[342] The microscopic appearance is often similar to that of the alveoli, but in widely disseminated cases, *P carinii* can produce numerous small 0.1 to 0.3 cm calcified granulomas that give cut surfaces of parenchymal organs the gross appearance of rough sandpaper. A GMS stain reveals the organisms, even in densely calcified areas. Immunohistochemical staining for *P carinii* in extrapulmonary sites is very useful.[340] In the rare cases of PCP accompanied by pleural effusion, typically in association with aerosolized pentamidine therapy, pleural fluid cytologic examination with GMS stain helps to reveal the organisms.[506]

CYTOMEGALOVIRUS.-- Cytomegalovirus (CMV) involvement of lung varies from an insignificant and incidental microscopic finding without extensive gross or microscopic changes to a florid pneumonitis with numerous inclusion bodies. Cytomegalovirus may not always be diagnosed pre mortem either because a long latent incubation period is present without characteristic morphologic changes, infection develops agonally, or there is sampling error with tissue biopsy or cytologic methods caused by the patchy distribution of cells with characteristic CMV inclusions.[507]

The finding of CMV in bronchoalveolar lavage or sputum specimens or by culture may not necessarily indicate that a pneumonitis is present.[343] Cytomegalovirus can frequently be detected in bronchoalveolar lavage fluid from HIV-infected patients and does not necessarily correlate with pulmonary symptoms nor predict outcome.[508] Cytomegalovirus inclusions in tissue biopsy specimens, along with the absence of other pathogens, may represent pneumonitis that can be treated with ganciclovir. Though CMV is the most common viral infection of lung in AIDS, it occurs frequently in conjunction with other opportunistic infections, so CMV is rarely the sole cause for a symptomatic pneumonitis.

In cases of CMV pneumonitis, the most frequent clinical findings are fever, dyspnea, and non-productive cough. Radiographic findings are present in two thirds of cases and include ground glass, reticular, or nodular opacities, consolidation, or pleural effusion. Concomitant extrapulmonary evidence for CMV accompanies half of cases. Hypoxemia suggests a poor

prognosis, and the overall mortality is about 40%. Treatment with ganciclovir may be useful in the setting of a diffuse interstitial pneumonia with hypoxemia and histologic evidence for CMV in the absence of other pathogens.[343,509]

There are no specific gross pathologic changes attributable to CMV. The distribution of CMV in the lung may be alveolar, interstitial, or tracheobronchial. Characteristic inclusion bodies are more often seen within epithelial cells of the lung. Occasionally, inclusions are seen in vascular endothelium, more often in the tracheobronchial tree. The patterns of involvement include focal interstitial pneumonitis and acute necrotizing tracheobronchitis, though vasculitis may also be seen. More florid cases of CMV pneumonitis may present with areas of patchy to confluent red or tan consolidation. This can progress to diffuse alveolar damage. Areas of hemorrhage may be present.[509,510]

Microscopic presence of cytomegalic cells with intranuclear inclusions is necessary for light microscopic diagnosis with hematoxylin-eosin staining. Inclusions may be scant to numerous. Cytomegalic cells may line alveolar spaces, appear within the lumina of air spaces, or involve endothelium. When CMV infection is florid, two or more inclusions may be seen within a cytomegalic cell. Since inclusions may be difficult to find in tissue biopsy or cytologic material, direct fluorescence antibody staining, culture, and use of immunohistochemistry or *in situ* hybridization may be very helpful ancillary techniques. Accompanying inflammation may not always be present, but in florid cases consists of many polymorphonuclear leukocytes and/or lymphocytes. Inflammatory infiltrates are primarily within interstitium, but can be alveolar in florid cases. A search should be made for additional opportunistic infectious agents, particularly *P carinii*.[510]

CRYPTOCOCCAL PNEUMONITIS.-- Infection with *Cryptococcus neoformans* probably occurs after inhalation of an aerosol containing the unencapsulated yeast, but there is no known environmental factor that consistently increases the risk for infection. *C neoformans* can be found throughout the world. Colonization of the tracheobronchial tree, followed by pulmonary infection, whether silent or symptomatic, probably precedes dissemination to other organs.

There are no specific clinical signs or symptoms of cryptococcal pneumonia; patients may have fever, night sweats, fatigue, and headache for days to months. About a third of patients with cryptococcosis have respiratory symptoms including cough and dyspnea. Diagnosis of cryptococcal infection can be made by the sensitive and specific cryptococcal antigen test that can be run on serum, cerebrospinal fluid, or pleural fluid. Radiographically, cryptococcal pneumonia appears most often as a diffuse interstitial pneumonia with interstitial infiltrates, though focal or widespread consolidation, ground-glass shadowing, miliary nodules, cavitation, pleural effusion, and hilar lymphadenopathy can also be seen.[511, 512]

Pulmonary involvement by *C neoformans* is second only to central nervous system involvement in frequency in AIDS (Table 5). Cryptococcosis tends to be a disseminated disease, though death with *C neoformans* often results from pulmonary involvement. The gross patterns of *C neoformans* involvement within the pulmonary parenchyma include a bronchopneumonia-like pattern with either diffuse or patchy consolidation, interstitial infiltrates, or a mixture of these two patterns. Solitary or multiple nodules, which are granulomas, may appear similar to those seen with mycobacterial infection or other fungi, and they typically have a soft, mucoid appearance. When well-defined masses or nodules are seen, they are often gelatinous because numerous organisms with minimal inflammatory infiltrates are present.[369,371]

Microscopically, the 4 to 7 micron pale cryptococci are found infiltrating the alveolar septae. Often, poorly encapsulated or non-encapsulated cryptococci are present that are smaller, only 2 to 5 microns in size, that may be difficult to distinguish from *Candida* and *Histoplasma capsulatum*.[370] Granulomas, if present, tend to be small and poorly formed. The interstitium or alveoli may show only a minimal inflammatory response consisting mainly of scattered macrophages with few lymphocytes or neutrophils. The more common pattern of involvement consists of focal small lesions. A pneumonic pattern of numerous cryptococci in alveolar spaces along with mixed inflammatory infiltrates is seen less frequently.[371]

The cellular pleomorphism of *C neoformans* and lack of hyphae help to distinguish it from *Candida*. Gomori methenamine silver (GMS) and PAS stains readily demonstrate the organisms. Cryptococci can also be distinguished from other fungi from the presence in *C neoformans* of a melanin-like pigment seen with Fontana-Masson staining.[372]

HISTOPLASMOSIS.-- *Histoplasma capsulatum* infection with AIDS often produces a disseminated infection, and pulmonary involvement is frequent. Clinically, the onset of disease is insidious, with weight loss and fever the most common symptoms. A chest roentgenogram shows diffuse interstitial infiltrates in about half of all patients, and in these patients, cough and dyspnea are often present as well, but only one-sixth of AIDS patients with histoplasmosis present with respiratory problems. Blood culture or tissue biopsy with culture are the main means for diagnosis.[394,511]

The initial response to infection is neutrophilic, but soon shifts to mononuclear phagocytes. Grossly visible small tan to white granulomas may be present in lung tissue, but often they are not. The organisms consist of small, oval 2 to 4 micron budding yeasts that are most often identified within macrophages in the interstitium, but they may also be free in the alveolar spaces. Intracellular organisms may be seen in routine hematoxylin-eosin-stained sections due to a small artifactual clear zone surrounding them, though they are best seen by either Gomori methenamine silver (GMS) or periodic acid-Schiff (PAS) stains. In older fibrotic or calcified granulomas, *H capsulatum* may be visible only with methenamine silver stain.

Histological confirmation of *H capsulatum* infection can sometimes be difficult, since the yeasts are small and can sometimes resemble *Candida*, *Pneumocystis carinii*, *Leishmania*, or poorly encapsulated *Cryptococcus neoformans* organisms. Immunohistochemical staining of smears and tissue sections with anti-histoplasma antibody can be utilized to specifically diagnose pulmonary histoplasmosis. Microbiologic culture can aid in confirming the diagnosis of *Histoplasma* pneumonitis.

CANDIDIASIS.-- *Candida* infections in the respiratory tract with AIDS primarily involve the trachea and bronchi.[511] Infection can be either mucocutaneous or invasive. Only the invasive form is included in the definitional criteria for diagnosis of AIDS.[320] In bronchoalveolar lavage and sputum specimens, the recovery of *Candida* in the absence of tissue invasion is frequent and supports the diagnosis of mucocutaneous infection, but oropharyngeal contamination must be excluded.

Large numbers of budding yeasts with pseudohyphae can often be found growing on mucous membranes of the oral cavity, pharynx, larynx, and tracheobronchial tree, but in histologic sections of these sites, the organism is also often identified on the mucosal surfaces without invasion into deeper tissues. With invasion, there can be acute ulceration with underlying submucosal chronic inflammation. The clinical appearance of oral candidiasis in patients with declining CD4 lymphocyte counts may herald the progression of HIV infection to AIDS.[511]

Invasive pulmonary parenchymal *Candida* infections occur infrequently in terminally ill patients, with the diagnosis sometimes recognized only at autopsy. The lungs grossly may show areas ranging from small microabscesses to focal consolidation, sometimes with hemorrhage and necrosis. Granuloma formation is uncommon. Microscopically, budding yeasts measuring 3 to 4 microns in size, with pseudohyphae that invade bronchial walls, blood vessels, and pulmonary parenchyma. These yeasts typically produce necrotizing microabscesses with prominent polymorphonuclear leukocytic infiltrates. The pseudohyphae can produce aggregates which must be differentiated from the mycelial forms of *Aspergillus* species that have branching, septated hyphae. *Aspergillus* hyphae are usually broader than *Candida* pseudohyphae and are septate.

MYCOBACTERIOSIS.-- Mycobacterial pulmonary infections in AIDS are most commonly caused by *Mycobacterium tuberculosis*, followed by *Mycobacterium avium* complex (MAC). Other mycobacteria, including *Mycobacterium kansasii* and *Mycobacterium fortuitum*, are seen infrequently. A specific diagnosis with speciation and antibiotic sensitivity determination for mycobacterial infections depends upon culture. Tissue or cytologic diagnosis can be made quickly,

but speciation is not exact because morphologic appearances on acid fast stain are not completely distinctive.[148] The radiographic appearance of MTB typically consists of bilateral medium to coarse reticulonodular opacities often associated with hilar lymphadenopathy. Since most patients will improve with antitubercular therapy, a worsening chest radiograph suggests the presence of another pulmonary disease.[513,514]

A presumptive diagnosis of pulmonary tuberculosis to satisfy definitional criteria for AIDS can be made as follows:[320]

> When bacteriologic confirmation is not available, other reports may be considered to be verified cases of pulmonary tuberculosis if the criteria of the Division of Tuberculosis Elimination, National Center for Prevention Services, CDC, are used. These criteria include both clinical and laboratory findings. A clinical case is defined when the following criteria are met:
>
> - A positive tuberculin skin test
> - Other signs and symptoms compatible with tuberculosis, such as an abnormal, unstable (worsening or improving) chest roentgenogram, or clinical evidence of current disease
> - Treatment with two or more antituberculous medications
> - Completed diagnostic criteria
>
> Laboratory criteria for diagnosis include:
>
> - Isolation of *M tuberculosis* from a clinical specimen, or
> - Demonstration of *M tuberculosis* from a clinical specimen by DNA probe or mycolic acid pattern on high-pressure liquid chromatography, or
> - Demonstration of acid-fast bacilli in a clinical specimen when a culture has not been or cannot be obtained

Laboratory diagnosis of pulmonary tuberculosis in HIV-infected persons can be most easily made with sputum samples and detection of acid fast bacilli under fluorescence microscopy with the auramine stain. Most such infections can be detected with a single specimen, and virtually all infections can be detected with two samples.[515] Other specimens may include bronchoalveolar lavage fluid, bronchial brushings, and biopsies. The auramine stain can also be applied to tissue sections and viewed with fluorescence microscopy and is more sensitive than the standard Ziehl-Neelsen acid fast stain viewed by light microscopy. Fine needle aspiration cytology can be employed and can detect MTB in half of cases.[336]

Radiographically, the findings of tuberculosis in AIDS patients with CD4 lymphocyte counts above 350/μL are often similar to those of non-immunocompromised patients, with predominantly pulmonary involvement with nodular densities and cavitation of larger nodules, mainly in upper lobes. Pulmonary involvement can be seen at all stages of HIV infection, but with progression of HIV disease, extrapulmonary involvement increases. In advanced stages of HIV infection, the radiographic features of tuberculosis are most likely to include intrathoracic adenopathy, focal lower or middle lobe infiltrates, and diffuse miliary or nodular infiltrates.[516] Even in the absence of pulmonary symptoms, the presence of nodular infiltrates and adenopathy should raise suspicion for mycobacterial disease.[517] Cavitation is uncommon in the late stages of AIDS.[499]

Mycobacterium tuberculosis will usually produce grossly recognizable tan to white firm granulomas, often with caseation. Sometimes, the granulomas involve the pleura and are associated with a hemorrhagic exudate or effusion. Microscopically, the classical features of caseation with Langhans giant cells, fibrosis, and lymphocytic infiltration are present but not pronounced. On acid fast stains, mycobacteria are scattered singly or in small clusters and can be numerous and easy to demonstrate.[353,354]

In contrast, MAC rarely produces pronounced radiographic findings, but if present are most likely to resemble those of MTB with areas of airspace consolidation and mediastinal

lymphadenopathy. In immune restoration following highly active antiretroviral therapy, mediastinal lymphadenopathy may become prominent.[499] Grossly visible granulomas are uncommon. The organisms are often found in an interstitial distribution. Microscopically, granulomas are ill-defined and consist primarily of a single macrophage or small macrophage clusters. The macrophages have cytoplasm with a striated pale blue appearance with hematoxylin-eosin staining. Acid fast stains demonstrate abundant mycobacteria within these macrophages.[348]

Mycobacterium kansasii and *M fortuitum* produce gross and microscopic patterns of pulmonary involvement similar to *M tuberculosis*. Infections with *M kansasii* tend to occur late in the course of AIDS, and radiographic findings include interstitial and/or lobar infiltrates, with cavitation present in about 20% of cases. Most patients present with fever, cough, chills, chest pain, weight loss, and dyspnea. Pulmonary disease occurs in over 90% of cases, while disseminated disease is seen in a fifth of cases. Thoracic lymph node involvement is common. Characteristic microscopic findings include the long, folded, beaded rod-shaped organisms with acid fast stain, and the propensity of the organisms to appear within macrophages.[365,518] Most patients respond to therapy.[514] *Mycobacterium xenopi* infections are not common but may produce significant pulmonary disease late in the course of HIV infection.[364]

COCCIDIOIDOMYCOSIS.-- *Coccidioides immitis* infection of the lungs is due to inhalation of infective arthrospores with the subsequent development of proliferating thick-walled spherules containing endospores. In AIDS, coccidioidomycosis is a rare cause of pulmonary disease, even in endemic areas of the Southwestern United States. Pulmonary infection in these patients probably results from reactivation of a previous, latent infection rather than a *de novo* opportunistic infection. Clinical features are non-specific and include fever and weight loss. An abnormal chest radiograph with diffuse infiltrates, single or multiple nodules, cavitation, or hilar lymphadenopathy can be seen in about three-fourths of cases. Diagnosis requires histologic examination with culture of bronchoalveolar lavage or lung biopsy.[511]

Grossly, small granulomas or patchy pneumonic consolidation may be seen. Microscopically, the organisms are found in focal areas of interstitium. Large, thick-walled, variably sized spherules measuring 50 to 100 microns contain numerous refractile endospores from 2 to 5 microns in size. The inflammatory response is poor. Occasionally, persons taking anabolic steroids or corticosteroids can develop disseminated coccidioidomycosis almost identical to that seen in AIDS.[396]

TOXOPLASMOSIS.-- In AIDS, toxoplasmosis is usually associated with disseminated infection and secondary pulmonary involvement. The most common clinical finding is a cough, either productive or non-productive. An abnormal chest roentgenogram marked by bilateral interstitial infiltrates may appear in only half of cases. Diagnosis can be made by bronchoalveolar lavage in most cases.[393]

Histologically, there may be focal necrosis with vague granuloma formation and/or diffuse interstitial mixed inflammatory cell infiltrates with alveolar lining cell hyperplasia. Diagnosis depends upon finding *Toxoplasma gondii* pseudocysts filled with bradyzoites, but these are infrequent--even in severe infections. Free tachyzoites are small and difficult to distinguish from debris or cell fragments with hematoxylin-eosin staining. *T gondii* pseudocysts must be distinguished from cytomegalovirus cells lacking a visible nucleus but containing intracytoplasmic virions. Cytomegalovirus tends to have a thinner wall, and the cytoplasmic basophilic bodies of CMV are coarser than bradyzoites.[391]

ASPERGILLOSIS.-- Pulmonary aspergillosis does not occur commonly with AIDS, but may appear late in the course when the CD4 lymphocyte count is <100/μL. Aspergillosis may often occur in association with other infections such as cytomegalovirus and *P carinii* (in over half of cases), bacterial, or fungal pneumonias. Over 80% of cases are accompanied by neutropenia (which can complicate antiretroviral therapy). In 15% of cases there is a history of corticosteroid therapy or broad-spectrum antibiotic therapy.[519,520] Marijuana smoking may also be a risk because marijuana is an excellent fungal growth medium.

The major clinical findings with pulmonary aspergillosis in AIDS are fever, cough, and dyspnea in over half of cases. Other findings may include pleuritic chest pain, malaise, and weight loss. The two clinical patterns of pulmonary aspergillosis in AIDS are: (1) acute invasive pulmonary aspergillosis with prolonged cough and fever, and (2) obstructing-bronchial aspergillosis with dyspnea, cough (sometimes productive of bronchial casts containing the fungal hyphae), and chest pain.[511] Dissemination of infection occurs in a few cases, with the central nervous system, kidney, and heart most likely to be affected. Bronchoalveolar lavage may yield a diagnosis in 67% of cases, though finding *Aspergillus* in BAL specimens does not always indicate a true infection, but rather upper respiratory tract colonization. A transbronchial biopsy is diagnostic in 27% of cases.[520]

Radiographically, there may be unilateral or bilateral infiltrates in 73%, cavitation in 34%, or nodular and pleural-based densities in 14% of cases on chest radiograph. Cavitary upper lobe disease may be complicated by fatal hemoptysis. On computed tomographic scans, parenchymal nodules with surrounding halo and variable cavitation from focal infarction may be seen. A rare variant known as obstructing bronchial aspergillosis may bilateral diffuse lower lobe consolidation on chest radiograph as a result of post-obstructive atelectasis.[511,516]

Histologically, the hyphae of *Aspergillus* are best identified in bronchoalveolar lavage specimens, but they can also be readily identified in biopsied tissues. The lungs grossly may show either focal or diffuse involvement, with geographic areas of firm orange to yellow-tan necrosis, hemorrhage, and edema. *Aspergillus* is readily demonstrated in Gomori methenamine silver (GMS) and periodic acid-Schiff (PAS) stains by the appearance of 3 to 5 micron diameter branching Y-shaped septate hyphae of fairly uniform caliber which commonly invade bronchial walls and blood vessels. Vascular invasion can produce thrombosis and infarction. A poorly formed granulomatous response at the periphery of the lesions is uncommon.

Aspergillus fungal hyphae can be readily distinguished from *Candida* by the absence of budding cells and pseudohyphae in the latter. *Aspergillus* can be distinguished from Zygomycetes such as *Mucor* by the smaller diameter of hyphae and presence of septation in the former. Hyphae of *Mucor* are non-septate, short, broad, and have irregular shapes, while pseudohyphae of *Candida* are smaller than the branching, finger-like hyphae of *Aspergillus*. The various species of *Aspergillus* can be distinguished by culture, but they all have similar morphologic appearances in tissue sections as well as similar clinical courses. Amphotericin B and/or itraconazole are variably effective treatments.[511,520]

NOCARDIOSIS.-- *Nocardia*, a genus of aerobic actinomycetes, can produce both localized and disseminated disease, usually late in the course of AIDS. The lung is the most common site for infection and *N asteroides* is the most frequent species isolated. There are no specific clinical findings, though fever, productive cough, and weight loss are the most frequent findings. On chest radiograph, an alveolar pattern of pulmonary infiltrates is the most common feature, with reticulonodular patterns seen in fewer patients. The nodules may be spiculated and cavitated on chest CT, with an associated pleural reaction. Gross pathologic features may include pneumonic consolidation, abscess formation, cavitation, and pleural effusions. Microscopically, *Nocardia* produces an acute inflammatory response in which the gram positive filamentous organisms can be identified. The disease may remain localized or become disseminated to involve such sites as subcutaneous tissues, central nervous system, and kidney, with resultant high mortality rate. Early diagnosis from culture and treatment with sulfonamides or minocycline leads to better response and outcome.[499,521,522]

BLASTOMYCOSIS.-- *Blastomyces dermatitidis* is an uncommon opportunistic infectious agent, even in endemic areas of the midwestern and south-central United States and southern Canada. Infection occurs from inhalation of infective conidia derived from the mycelial form of the organism that grows in soils with high organic content in humid climates. Blastomycosis is most often seen when the CD4 lymphocyte count is less than 200/μL. Infection usually involves the lung. Blastomycosis with HIV infection can manifest as localized pulmonary disease, but disseminated infection occurs just as frequently and most often involves the central nervous system,

though a wide variety of tissue sites can be affected. Cutaneous involvement with deep ulcers is less frequent in association with HIV infection than in non-immunocompromised hosts.[370]

Patients have usually developed a prior AIDS-defining illness, and blastomycosis occurs as a late or terminal event. Typical presenting symptoms include fever, cough, pleuritic chest pain, dyspnea, and weight loss. Radiographs are often abnormal with lobar infiltrates, nodules, miliary pattern, or diffuse interstitial changes. Diagnosis can be made by finding thick-walled, double-contoured 8 to 20 micron sized yeasts with single broad-based buds in cytologic specimens or tissue biopsies and by confirmatory culture. Serologic tests are not useful. Cultures of bronchopulmonary lavage material, skin, cerebrospinal fluid, and blood are positive in 90% of cases. Initial therapy with amphotericin B can be curative or can prolong survival, with ketoconazole or itraconazole administered for the remainder of life, but half of infected AIDS patients die.[370,523,524]

BACTERIAL PNEUMONITIS.-- Bacterial pneumonias in AIDS can lead to significant morbidity and mortality and are second only to *Pneumocystis carinii* pneumonia as an immediate cause of death.[342] Overall, bacterial organisms account for more pulmonary infections than other infectious agents in persons with AIDS.[525] The defects in B-cell as well as T-cell mediated immunity in with HIV infection result in pneumonia caused by any of a large group of bacterial organisms, both gram positive and gram negative. Bacterial pneumonias are more frequent in persons infected with HIV than in seronegative persons. The risk for HIV-infected persons is highest when the CD4 lymphocyte count is <200/μL. Among risk groups, injection-drug users are most likely to develop bacterial pneumonias.[526]

Acute bronchopneumonia may be suggested by bronchoalveolar lavage or transbronchial biopsies in which neutrophilic exudate is present and gram stain reveals bacteria. The clinical signs and symptoms may be subtle, and a peripheral blood neutrophilia may not be present or prominent. Tissues or fluids should be sent for routine microbiologic culture. When microbiologic cultures are performed, the most common etiologic agents for bacterial pneumonias are *Staphylococcus aureus, Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and enteric gram negative organisms. Bacterial bronchopneumonias may also be present along with other opportunistic infections.[527]

Recurrent pneumonia as a criterion for AIDS may be diagnosed presumptively as follows:[320]

> Recurrent (more than one episode in a 1-year period), acute (new symptoms, signs, or roentgenographic evidence not present earlier) pneumonia diagnosed on clinical or radiologic grounds by the patient's physician.

Grossly and radiographically bacterial pneumonias in patients with AIDS resemble those seen in other patients. Focal or multifocal areas of consolidation appear on chest x-ray, in either a lobar or segmental pattern, which helps in distinguishing bacterial pneumonia from PCP. Complications of sepsis, cavitation, and abscess formation are frequent.[499] The most common pattern, particularly in hospitalized and terminally ill patients, is that of bronchopneumonia with patchy bilateral infiltrates. Accompanying the areas of patchy consolidation can be seen changes in small airways. Best observed with computed tomographic scans, small airway disease may consist of dilation and thickening of bronchial walls or bronchiolitis marked by small 3 mm densities.[516]

Microscopically, alveolar neutrophilic exudates with accompanying parenchymal congestion and edema are seen in varying amounts. These bronchopneumonias can be bilateral and extensive. Staphylococcal pneumonias can be abscessing and/or hemorrhagic. Pneumococcal pneumonia, the most common community acquired bacterial pneumonia with HIV infection, may present with a lobar pattern that produces a disease clinically indistinguishable from that in HIV negative patients, including complications of abscess, empyema, and pleural effusions.[528] Also seen frequently is *Pseudomonas aeruginosa*, which is important to recognize because in rare cases it can produce a granulomatous response that grossly mimics *Mycobacterium tuberculosis* infection.[416]

Persons with HIV infection are at increased risk for *Streptococcus pneumoniae* and *Haemophilus influenzae* pulmonary infections. It is recommended that vaccination against pneumococcus be given in patients newly diagnosed with HIV infection.[493] In children, and possibly adults, the vaccine for *H influenzae* type b can help reduce *Haemophilus* infections, though the variety of serotypes may mitigate somewhat against effectiveness of *H influenzae* type b vaccination.[161,250,527]

Recurrent infections with these and other bacterial agents, principally *Pseudomonas* and *Staphylococcus* species, increase the risk for chronic bronchitis. In patients with increased survival, chronic bronchitis can lead to bronchiectasis. Such complications typically are manifested in patients with CD4 lymphocyte counts below 200/μL.[529]

Other streptococcal species and enteric bacterial organisms such as *E. coli* and Enterobacteriaceae are seen with AIDS. Less frequent organisms reported in association with AIDS include *Legionella* and *Moraxella*. With *Legionella pneumophila* infection, Dieterle or fluorescent antibody staining of sputum or bronchoscopic specimens can be helpful for diagnosis; serologic titers are helpful less often.[417,418]

Rhodococcus equi has been recognized as a pathogen in persons with HIV infection, and it can be missed because it sometimes stains weakly acid fast or resembles contaminant diphtheroids on gram stain. Three fourths of HIV-infected patients with *R equi* have a CD4 lymphocyte count <200/μL. This organism most often produces a cavitary pneumonia. The most common symptoms are fever and cough in over 80% of cases. A third of patients may have chest pain, while hemoptysis or dyspnea occur in one sixth of cases. Radiologic findings most often include a localized pneumonia with consolidation and cavitation. A single cavity may be seen in over half of cases, usually an upper lobe, often with a fluid level, but multiple cavities may appear in 13% of cases. Non-cavitary infiltrates are seen in a third of cases, and pleural effusions appear in only 8% of cases. There may be associated septicemia (sometimes without concomitant pneumonia) or extrapulmonary abscesses. Diagnosis is made by sputum, pleural fluid, or blood culture. Blood and sputum cultures are positive in over half of cases. Continued antibiotic therapy is necessary because of frequent relapse. Death may occur in 15% of cases. The persistence of *R equi* in macrophages can also lead to the appearance of pulmonary malakoplakia. Malakoplakia is a form of granulomatous inflammation marked by the appearance of Michaelis-Gutman bodies, which are target-like calcospherites, within macrophage cytoplasm. [417,418,499,530]

Septic emboli involving the lungs are typically caused by bacterial organisms. The radiographic appearance includes a peripheral or subpleural distribution of 1 to 2 cm nodules. Cavitation within nodules or wedge-shaped opacifications from infarction can occur.[499]

VIRAL PNEUMONITIS.-- Aside from cytomegalovirus, other viral infections of lung are less frequently diagnosed, though the true incidence remains unknown. Viruses may be recovered from bronchoalveolar lavage fluid. Viral pneumonitis may be difficult to distinguish from non-specific interstitial pneumonitis or lymphoid interstitial pneumonitis without specific viral cultures or serologies. Bacterial infections often complicate viral pneumonitis and may be indistinguishable clinically, though a viral pathogen may be the only infectious agent present in some cases. Viral pneumonias most frequently are due to herpes simplex, rhinovirus, influenza, parainfluenza, and adenovirus in adults, with respiratory syncytial virus more frequent in children. *Mycoplasma* species, though not viruses, can produce a similar clinical picture with infection, and can also be recovered with bronchoalveolar lavage.[531] Vaccination against influenza is recommended for all HIV-infected persons.[161,532]

Human herpesvirus 6 (HHV-6) infects at least 90% of all persons by two years of age and can reactivate in immunocompromised hosts to produce a severe pneumonitis. Such reactivation of latent infection in persons with AIDS may be the cause for a fatal pneumonitis. HHV-6 can be found in other tissues as well, and lymphoid tissues are the reservoir for HHV-6 infection. HHV-6 can be demonstrated in tissues by immunohistochemical staining.[533]

KAPOSI'S SARCOMA.-- The clinical diagnosis of pulmonary Kaposi's sarcoma (KS) can be difficult because KS is difficult to distinguish from opportunistic infections. The diagnosis is

made more likely when a previous skin biopsy has demonstrated KS. Most patients with pulmonary KS will present with fever, non-productive cough, and dyspnea. Hemoptysis and chest pain are additional common findings. Hoarseness and stridor may suggest upper airway involvement of larynx and trachea.[450]

Radiographic findings are not specific and may include bilateral reticulonodular, interstitial, or alveolar infiltrates in over half of cases. The presence on chest radiograph of abnormal hilar densities with perivascular or peribronchial extension into adjacent pulmonary parenchyma is suggestive of KS. Hilar lymphadenopathy tends to be seen as a late finding. Also, bronchial wall thickening, nodules, Kerley B lines, and pleural effusion can be additional findings seen in association with pulmonary KS. Chest CT scans can demonstrate bronchial wall thickening and spiculated lesions, with poorly marginated nodular infiltrates radiating out from the hilum and from bronchovascular structures into interlobular septae. Gallium scans may help to distinguish KS from infections.[450]

A diagnosis of KS is suggested by the finding on fiberoptic bronchoscopy of raised, cherry-red to violaceous macular to papular endobronchial lesions averaging several millimeters in size. This finding is often regarded by experienced bronchoscopists as diagnostic, even in the absence of histological support, and the vascular nature of KS can produce copious bleeding with biopsy. Transbronchial biopsy is often nondiagnostic, because of the focal distribution of the lesions, lack of endobronchial lesions, distal lesions, and the predominantly submucosal location with subsequent sampling error, and because of the sparse amount of tissue obtained. Pleural biopsy and pleural fluid cytology have a very poor yield for diagnosis of KS. The non-specific finding of increased hemosiderin-laden macrophages in bronchoalveolar lavage fluid is suggestive of KS. Open lung biopsy has a diagnostic yield of only 50% and is rarely performed due to potential complications.[450,507]

Grossly at autopsy, KS lesions of lung appear as firm dark red to purple nodular areas, most often surrounding large bronchi or blood vessels for a distance of 1 to 5 mm, or as subpleural nodules. Up to 10% of lesions can be white or tan rather than red or purple. With extensive involvement, the lesions may become almost confluent. Nodules of KS may also appear on bronchial or tracheal mucosal surfaces.

Microscopically, KS in lung shows infiltrates of atypical spindle cells with endothelial-lined, slit-like spaces containing red blood cells. The pattern of KS is infiltrative into the lung parenchyma, and the lesions of KS also tend to surround blood vessels and bronchioles or form subpleural nodules. Extravasated red blood cells, hemosiderin, plasma cells, and lymphocytes may also be present. When accompanied by organizing pneumonia or diffuse alveolar damage, KS may be difficult to diagnose, and cellular atypia helps to distinguish the lesions of KS from inflammatory or reparative changes.

MALIGNANT LYMPHOMAS.-- Pulmonary non-Hodgkin lymphoma (NHL) in patients with AIDS will have a similar gross and microscopic appearance as elsewhere. In most cases, the lung is secondarily involved due to widespread dissemination. NHL limited to the lung in AIDS is very uncommon and diagnosed when there is absence of mediastinal and/or hilar lymphadenopathy and absence of extrathoracic extension. Such primary NHL's of lung are typically of a high grade B cell histologic type with demonstratable Epstein-Barr virus in tumor cells. They are not usually accompanied by pleural effusions, but they may cavitate.[534] Thus, in the absence of an infectious cause, the presence of multiple peripheral pulmonary nodules and/or masses without hilar or mediastinal adenopathy and without pleural effusion suggests a primary pulmonary NHL. The best diagnostic yield comes from use of percutaneous transthoracic needle biopsy.[535]

Malignant lymphomas can have a bronchovascular distribution (where lymphatic vessels are found), or less commonly they may present as one or more definable mass lesions. Rarely, they may appear only as malignant effusions (primary body cavity-based lymphomas), without a definable mass lesion.[472,473] Radiographically, they can appear as patchy and nodular opacities or as solitary, well-delineated masses. Hilar adenopathy is not common, but a pleural effusion may be present along with parenchymal involvement.[497] Gallium scans may help to distinguish non-Hodgkin lymphomas from infections and Kaposi's sarcoma.[450]

Microscopically, they are high grade diffuse large cell (immunoblastic sarcoma) or intermediate grade small noncleaved (Burkitt or Burkitt-like) lymphomas. Concomitant infection with opportunistic agents may obscure lymphomatous infiltrates or be admixed with them. Enlarged hilar lymph nodes may also be involved with malignant lymphoma.[536]

LYMPHOID INTERSTITIAL PNEUMONITIS.-- Lymphoid interstitial pneumonitis (LIP) can be used as a diagnostic criterion for AIDS in childhood.[319,320] LIP is neither diagnostic of, nor frequently seen with, AIDS in the adult. It must be differentiated from other infiltrative and interstitial pulmonary diseases. Tissue diagnosis of LIP is usually made with an open lung biopsy, because bronchoscopic biopsies are frequently nondiagnostic. Peripheral blood may show plasmacytosis and eosinophilia. A presumptive clinical diagnosis of LIP for definition of AIDS requires that bilateral reticulonodular interstitial pulmonary infiltrates must be present on chest roentgenogram for ≥2 months with no pathogen identified and no response to antibiotic treatment.[537]

Lymphoid interstitial pneumonitis may present with progressive dyspnea and dry cough, along with systemic symptoms such as fever, night sweats, and weight loss. LIP cannot be distinguished grossly. The radiographic pattern in children as seen on plain radiographs and with computed tomography most often reveals a diffuse, symmetric, reticulonodular or nodular pattern that is occasionally associated with mediastinal or hilar adenopathy. There may be diffusely increased interstitial markings on CT scan with 3 mm interstitial nodules, mainly in a centrilobular distribution.[500,516] The radiographic appearance in adults, best seen with high-resolution CT imaging, can resemble *Pneumocystis carinii* pneumonia and include thickened bronchovascular bundles, variably sized nodules in either centrilobular or subpleural locations, cysts ranging from 1 to 30 mm, and bilateral ground glass opacities.[538]

The earliest microscopic pathologic finding is hyperplasia of bronchial associated lymphoid tissue with aggregates of lymphocytes and plasma cells in a bronchovascular distribution with minimal intersitial inflammation. In more advanced lesions, all lung fields demonstrate a diffuse interstitial infiltrate of lymphocytes, plasma cells, and macrophages. Additional features can include lymphoid aggregates with germinal centers, intraluminal fibrosis, increased alveolar macrophages, and type II pneumonocyte hyperplasia. Advanced cases may demonstrate confluent pulmonary nodules several centimeters in size. Rarely, poorly formed granulomas may be present.[495,539]

Unlike chronic or nonspecific interstitial pneumonitis, LIP is more florid and extensive and has a tendency to infiltrate alveolar septae. LIP, unlike malignant lymphomas, has a predominance of small lymphocytes along with a mixture of inflammatory cell types. Immunohistochemical staining of questionable infiltrates will demonstrate a polyclonal cellular proliferation with LIP.[537] Lymphoid interstitial pneumonitis rarely results in progressive pulmonary interstitial fibrosis.[495,539] Progression to lymphoma is possible but not common. Many cases of LIP are accompanied by detectable Epstein-Barr virus (EBV) in lung tissue.[538] There is a variable response to corticosteroid therapy. From a third to half of patients with LIP die within 5 years of diagnosis and about 5% transform to lymphoma.[538]

Accompanying LIP may be a pattern of pulmonary lymphoid hyperplasia (PLH) that is characterized by lymphoid follicles with or without germinal centers that often surround bronchioles. The most florid form of lymphoid hyperplasia involving lung is seen in HIV-infected children and is known as polyclonal B-cell lymphoproliferative disorder (PBLD). With PBLD there are nodular infiltrates of polyclonal B-lymphocytes and CD8+ T-lymphocytes. Other organs may also be involved by PBLD.[540]

NONSPECIFIC INTERSTITIAL PNEUMONITIS.-- About 1 in 10 bronchoscopic biopsies in adult AIDS patients reveals the presence of an interstitial pneumonitis with lymphocytic infiltrates, but no identifiable organisms. It may represent a *Mycoplasma* or viral pneumonitis, such as influenza, without diagnostic pathologic features. A careful search for viral inclusions should be made, in addition to performance of histologic stains for fungi, mycobacteria, and *Pneumocystis carinii*. Sometimes, only multinucleated cells suggestive of viral effect are found. Multiple viral serologic studies are often not useful. Clinically, non-specific interstitial pneumonitis mimics

Pneumocystis pneumonia or lymphocytic interstitial pneumonitis. Thus, not all cases of pneumonitis in AIDS have a definable cause despite an extensive search for etiologies. Though lymphoid aggregates may be present, the lymphocytic infiltrates of nonspecific, or chronic, interstitial pneumonitis tend to be less extensive than those of lymphoid interstitial pneumonitis and restricted to peribronchiolar, perivascular, paraseptal, and pleural regions. Clinically, patients with nonspecific interstitial pneumonitis often have a normal chest roentgenogram.[539]

MISCELLANEOUS PULMONARY LESIONS IN AIDS.-- The pulmonary interstitium may show small foreign body granulomata with needle-shaped crystalline material that is birefringent under polarized light in patients with a history of intravenous drug use. Only rarely are these granulomata visible as 0.1 to 0.3 cm pale tan nodules. Rarely are they accompanied by extensive interstitial fibrosis.

When patients with AIDS receive antiretroviral therapy and are diagnosed and treated for opportunistic infections of the lungs, their survival is increased. However, increasing survival with multiple, recurrent, and prolonged bouts of infections results in a greater incidence of bronchiectasis. Bronchiectasis in association with AIDS is most often seen following recurrent pyogenic infections.[516,541]

Pulmonary hypertension is not common but appears with increased frequency in association with HIV infection and AIDS. Clinically it resembles cases of primary pulmonary hypertension in non-HIV-infected patients. There is a slight male preponderance and a wide age range for this condition. The time from onset of symptoms to diagnosis ranges from 6 to 30 months. Histologically, the patterns of disease range from plexogenic pulmonary angiopathy (sometimes in association with lymphoplasmacytic pulmonary infiltrates), to thrombotic pulmonary arteriopathy, to pulmonary veno-occlusive disease. There does not appear to be an association with either CD4 lymphocyte counts or with the existence of pulmonary infections. Acute response to epoprostenol therapy is similar to that for non-HIV infected patients. The course is slightly more fulminant than in patients with primary pulmonary hypertension, with half of patients dying in a year.[542,543]

Pleural effusions are relatively common in association with a variety of infectious pulmonary complications of HIV infection. The most common infectious cause of AIDS-associated pleural effusions is bacterial pneumonia. Sometimes, the pneumonia may be severe enough to result in empyema. *Mycobacterium tuberculosis* is another frequent cause for pleural effusion. Of neoplasms seen with AIDS, Kaposi's sarcoma is most likely to result in the finding of pleural effusion, particularly with bilateral effusions. Though *P carinii* is frequent in AIDS, it is less likely to result in effusions; however, it is the most likely cause for spontaneous pneumothorax, which complicates the course in 1 to 2% of hospitalized patients with HIV infection. Radiographic evidence for cysts, bullae, or pneumatoceles suggests a risk for pneumothorax. A third of these patients may die.[544,545]

UPPER RESPIRATORY TRACT IN AIDS.-- The epiglottis, pharynx, larynx, and trachea can also be affected by AIDS-diagnostic diseases. The commonest are invasive candidiasis and Kaposi's sarcoma. Kaposi's sarcoma has a predilection for the epiglottis. Clinical findings of stridor and hoarseness may suggest KS involvement of the upper airway. Biopsy can be done, but granulation tissue formed with long-standing intubation or ulceration from infectious agents may be difficult to distinguish from KS. In order for the presence of *Candida* to be diagnostic of AIDS, it must be demonstratably invasive (most commonly in trachea) and not be found just in secretions.[450]

CLINICAL DIAGNOSTIC TECHNIQUES.-- Roentgenographic imaging with Gallium scintigraphy may be performed to aid pulmonary diagnosis. Diffuse bilateral parenchymal uptake is most often associated with PCP, particularly if uptake is intense and heterogenous. A negative Gallium scan in a patient with Kaposi's sarcoma and an abnormal chest radiograph suggests respiratory disease due to Kaposi's sarcoma. Lymph node uptake of Gallium is typically

associated with mycobacterial infection (MAC or MTB) and lymphoma. Gallium positive with thallium negative studies suggest mycobacterial disease.[546]

The alveolar exudate of PCP is generally adherent to alveolar walls so that routine sputum samples are insensitive for diagnosis. Use of induced sputum can increase sensitivity to 55.5% and specificity to 98.6% for PCP, and sensitivity can be increased to 67.1% by employing immunofluorescence detection.[547] However, bronchoalveolar lavage (BAL) is a useful technique that can detect PCP in 90% of cases, compared with a tissue biopsy yield of 56%. The diagnostic yield can be increased to 95% with multiple lung lobe sampling, particularly the upper lobes. BAL is the most useful technique for diagnosis of opportunistic pulmonary infections in AIDS, particularly cytomegalovirus and cryptococcosis.[336]

Fiberoptic bronchoscopy is an excellent method for diagnosis of pulmonary complications and enables sampling by transbronchial biopsy (TBB), bronchial brushings (BB), and bronchoalveolar lavage (BAL). With TBB, obtaining a larger number and/or size of specimens provides a greater chance of making a specific diagnosis through reduction of sampling error. The greatest diagnostic sensitivity (when the biopsy contains alveoli) is for *Pneumocystis carinii*, between 60% to 100% for most reported series. Overall, the diagnostic yield of TBB in AIDS is good. The complication rate for TBB is low.[548]

Fine needle aspiration (FNA) cytology can be useful for diagnosis. In cases of Mycobacterium tuberculosis, FNA has a sensitivity of 46% with a specificity of 100%. Use of PCR can increase the sensitivity to 84%.[336]

Bronchoscopy with BAL samples a large number of alveoli and the diagnostic sensitivity exceeds that for induced sputum or TBB for diagnosis of PCP. Thus, BAL is the procedure of choice for diagnosis of PCP.[549] Yield can be enhanced by sampling two areas of the lung and/or by directing lavage to the area of lung with the most radiographic infiltrate, particularly upper lobes. The overall diagnostic yield of BAL in patients with AIDS that present with respiratory symptoms is greater than 50%. The most common agent found with BAL in this setting is *P carinii*. Culture of BAL material for *Mycobacterium tuberculosis* (MTB) can be useful, with a yield of 95%. Direct fluorescence antigen detection with culture for CMV can be done, but a positive result does not always correlate with the presence of CMV pneumonia, and CMV may be identified by BAL in half of HIV-infected persons. A BAL procedure is useful when biopsy is contraindicated in patients with a coagulopathy or on mechanical ventilators.[532,548]

By combining TBB and BAL, the diagnostic sensitivity for PCP and MTB approaches 100%, when adequate samples are collected. The high diagnostic sensitivity of TBB and/or BAL for PCP has virtually eliminated the need for open lung biopsy. The sensitivity of BAL for PCP in patients receiving aerosolized pentamidine is increased when BAL includes upper lobes.[501]

Unfortunately, TBB or BAL is less sensitive for diagnosing other pulmonary complications of AIDS. Organisms such as *Aspergillus*, and *Candida* may be frequently identified in BAL specimens, but may not necessarily be pathogens in some cases.[511,532,548] The diagnostic yield of BAL is also reduced in HIV-infected patients who have received empiric treatments for suspected infections prior to the performance of bronchoscopy with BAL, and the results of BAL may lead to a change in treatment following definitive diagnosis.[550]

Kaposi's sarcoma (KS) may be difficult to identify on bronchoscopy because the bulk of the tumor mass is below the mucosa. The low yield coupled with the risk for bleeding from highly vascular KS lesions often precludes a biopsy diagnosis by bronchoscopy. A high grade lymphoma may involve the lungs in AIDS, but open lung biopsy is required for diagnosis. Interstitial pneumonitis, either non-specific interstitial pneumonitis or lymphoid interstitial pneumonitis, requires open lung biopsy for histologic diagnosis, but these conditions are more often diagnosed on clinical features.[548]

Routine hematoxylin-eosin, methenamine silver, and acid fast stains should be performed on histologic sections or smears of samples obtained.

GASTROINTESTINAL TRACT PATHOLOGY IN AIDS

The gastrointestinal (GI) tract is the second most common organ system site for opportunistic infections or neoplasms associated with AIDS. The most frequent clinical symptom resulting from GI involvement is diarrhea, and the etiologies for this are numerous. Diarrhea may appear with acute HIV infection, but typically it is manifested in patients with clinical AIDS.[399,551] In a few cases this diarrhea may be life-threatening. In patients receiving highly active antiretroviral therapy (HAART), the frequency of gastrointestinal involvement with opportunistic infections is greatly diminished.[552]

In general, pathogens that involve the small intestine produce signs and symptoms that include large volume watery stools (up to 10L/day), abdominal cramping, bloating, gas, and weight loss with wasting syndrome. Malabsorption can lead to vitamin and other nutrient deficiencies. Bacterial pathogens involving the colon most often produce frequent but small volume stools with painful defecation. Fever is often present. The stools can be bloody or mucoid with leukocytosis, typical for a colitis. Stool culture provides a definitive diagnosis. Septicemias in association with infections of the gastrointestinal tract are uncommon.[418]

In many cases, examination of stool for ova and parasites, stool culture, and tissues from endoscopic biopsy procedures may reveal an etiologic agent for the diarrhea. Sometimes no specific cause can be identified, and only chronic nonspecific inflammation with small intestinal villous atrophy and crypt hyperplasia is seen on biopsy.[551] A cost-effective strategy for clinical management of diarrhea employs initial use of stool culture and direct microscopy of stool specimens, with additional diagnostic testing for non respondents to symptomatic treatment. Esophagogastroduodenoscopy (EGD) or colonoscopy with biopsy comprise the second phase of this evaluation. The use of EGD in cases where esophageal symptoms are refractory to antifungal therapy or when gastrointestinal bleeding is present is more likely to generate findings that influence patient management, while EGD is less useful for evaluation of abdominal pain, nausea, and vomiting. Small intestinal biopsies, particularly those from the jejunum, are useful for diagnosis, but small intestinal aspirates are of little value.[399,553] The distribution of AIDS-diagnostic diseases in GI tract is shown in Table 5. About 7% of deaths in AIDS patients result from diseases at this site.[342]

FUNGAL INFECTIONS.-- Oral candidiasis in the form of thrush is a frequent finding in patients with HIV infection that presages development of clinical AIDS or occurs in association with AIDS.[389] The risk for development of oral thrush is increased with smoking.[169] Persons who have a T-helper 2 (HT-2) type of cytokine response to HIV infection have an increased susceptibility to mucosal candidiasis.[554] *Candida* esophagitis is one of the most common GI tract manifestation of AIDS in both adults and children, and patients with oral and esophageal candidiasis usually present with odynophagia and/or dysphagia. For use of candidiasis as a presumptive clinical diagnosis for definition of AIDS, there must be:[320]

a. Recent onset of retrosternal pain on swallowing; AND
b. Oral candidiasis diagnosed by the gross appearance of white patches or plaques on an erythematous base or by the microscopic appearance of fungal mycelial filaments in an uncultured specimen scraped from the oral mucosa.

Oral candidiasis can appear in multiple sites or on large areas of oral mucosa. There are several clinical variants. Thrush, or pseudomembranous candidiasis (PC), is characterized by yellow-white plaques that can be removed by scraping. Removal leaves an erythematous and slightly hemorrhagic surface. This variant most often affects the tongue. Erythematous candidiasis (EC) is marked by erythematous macular mucosal patches due to increased vascularity with or without epithelial atrophy. The number of CD4 cells in the inflammatory response appears diminished in both PC and EC. Hyperplastic candidiasis (HC) is marked by white plaques that

cannot be removed by scraping, and it is located most often on the buccal mucosa. These variants have no significance in terms of patient prognosis.[555,556]

Diagnosis of oral candidiasis may be made microscopically by finding typical budding yeasts with pseudohyphae. A scraping with smear stained with potassium hydroxide (KOH) may aid in finding the organisms. Acute inflammatory cells are often present. On biopsy, the organisms may invade superficially. Though visible with routine H&E staining, a periodic acid-Schiff (PAS) stain aids in demonstrating the organisms, particularly when extensive inflammation and necrosis is present. An overlying pseudomembrane of neutrophils, fibrin, and parakeratotic debris can be present. The squamous epithelium often shows acanthosis, though in the hyperplastic pattern there may also be hyperkeratosis with dysplastic changes.[557]

The esophageal plaques of *Candida* are often adherent to the underlying mucosa and may bleed when removed. Biopsy (or scraping of oral mucosa for cytologic examination) may show budding yeasts and pseudohyphae on the epithelial surface. There may be superficial invasion of the submucosa. Invasive, inflamed lesions may have irregular ulceration, but deeply invasive lesions with perforation do not occur. *Candida* is typically not a cause for diarrhea in persons with AIDS.[399,555]

Radiologic findings in association with esophageal candidiasis include discreet linear or irregular longitudinally oriented filling defects that represent the heaped-up mucosal plaques. Esophagography may reveal a markedly irregular, shaggy mucosal appearance with more advanced esophageal disease.[341]

Though no primary prophylaxis is indicated, persons with frequent oral candidiasis may benefit from clotrimazole troches or topical nystatin to prevent progression to esophageal infection. For further treatment of recurrent oral or for esophageal candidiasis, fluconazole or ketoconazole are given.[161] Treatment of dental caries may be useful to help control oral candidiasis, since dentinal carious lesions provide a location for candidal colonization.[558]

The dimorphic fungi *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Coccidioides immitis* may produce focal inflammation. The GI tract is usually involved only when there is widespread dissemination. These organisms are most likely to be found in the submucosa or on the mucosa. Grossly visible features of gastrointestinal histoplasmosis include mucosal ulceration, nodules, and hemorrhage. Obstructing masses are not common. The mucosa can appear normal even when involved. Microscopic findings include diffuse lymphohistiocytic infiltration and ulceration. Often a minimal inflammatory reaction is present. Well-formed granulomas are not common.[559] Radiographic features of colonic histoplasmosis include segmental colonic inflammation, apple-core lesions that may mimic primary adenocarcinomas, and stricture.[341]

MALIGNANT LYMPHOMAS AND LYMPHOID LESIONS.-- The GI tract is one of the most common sites of involvement by non-Hodgkin lymphomas (NHL) in patients with AIDS. These lymphomas occur most frequently in the stomach, small intestine, and colon (Table 5). Unlike Kaposi's sarcoma, gastrointestinal lymphomas may be symptomatic from complications of obstruction, perforation, or bleeding.[560] The high grade NHL's seen in the anorectal region, particularly when the risk factor for HIV infection is sex with other males, are typically associated with Epstein-Barr virus (EBV) infection, which promotes clonal proliferation of lymphoid cells.[561]

They usually appear grossly as irregular areas of nodularity of the mucosa that on sectioning have a firm white appearance extending into the submucosa. Superficial ulceration can occur. Large masses that can obstruct the lumen of small intestine or colon are not common. One pattern of abdominal involvement with NHL in AIDS is marked omental and/or mesenteric infiltration, often with a malignant effusion. Rarely, NHL may appear only as malignant cells in an effusion, without a definable mass lesion (a primary body cavity-based lymphoma).[472,473]

Radiographically, gastric NHL features include circumferential or focal thickening of the gastric wall and mural masses with or without ulceration. In the small intestine, features include diffuse or focal bowel wall thickening and excavated masses.[341]

Microscopically, the bulk of most lymphomatous infiltrates are submucosal, but small infiltrates of neoplastic lymphocytes may extend into the lamina propria or mucosa, making endoscopic biopsy diagnosis possible. The appearance of a monomorphous population of large cells, aided by identification of monoclonality by immunohistochemical staining, helps to distinguish malignant lymphomas from chronic inflammatory infiltrates.[464,471] The most common types are diffuse large cell and immunoblastic, with a smaller number of small non-cleaved lymphomas.

Most AIDS patients with gastrointestinal lymphomas will respond to chemotherapy, but toxicity is common and requires dose reduction. Intestinal perforation may occur. Median survival is only about six months, even with treatment.[562]

Other common lymphoid lesions of the GI tract include chronic non-specific colitis with or without an identifiable infectious agent. These lesions are characterized by diffuse or focal mucosal and submucosal collections of small lymphocytes, with minimal or no accompanying necrosis. More pronounced lymphoid collections characterized as nodular lymphoid hyperplasia may be related to persistent generalized lymphadenopathy (PGL) in persons at this stage of HIV infection. Mucosa-associated lymphoid tissue (MALT) lesions are lymphoid proliferations that may occur at extranodal sites such as the gastrointestinal tract.[476,477]

KAPOSI'S SARCOMA.-- The gastrointestinal tract is the second most common site for KS following skin, and the commonest visceral site, for KS in AIDS patients. In most cases, the GI tract is involved in addition to the skin and/or lymph nodes. Lesions may occur anywhere from the oral cavity to the anus. Grossly, the lesions are raised dark red nodules averaging 0.5 to 1.5 cm in diameter. They are often widely scattered, but they may also involve large areas of the mucosal surface. Though the lesions are quite vascular, large hemorrhages are uncommon. The lesions are usually asymptomatic, but occasional problems may include diarrhea, obstruction, or protein losing enteropathy. Perforation is an uncommon complication. Radiographically, KS most often produces multiple submucosal masses, with or without central ulceration that gives a target-like lesion, though plaque-like lesions or small nodules may also be seen. The microscopic appearance is similar to that seen elsewhere, but diagnosis can sometimes be difficult due to: a submucosal distribution pattern, the microscopic similarity to granulation tissue, or the small amount of tissue available from endoscopic biopsies.[341,560]

PROTOZOAL INFECTIONS.-- Gastrointestinal protozoal infections in patients with AIDS are not rare. They can be asymptomatic, but the most common symptom is diarrhea. They are transmitted via a fecal-oral route, typically from contaminated food or water containing the infective spores (oocysts), from person to person. Infection from inhalation of spores has also been postulated. In persons who remain relatively healthy, the diarrhea is usually self-limited, but in the later stages of AIDS, particularly when the CD4 count is <100/μL, protozoal infections are more frequent and patients can have protracted diarrhea, though death from protozoal infections alone is not common.[400] Combination antiretroviral therapy, including a protease inhibitor, has been shown to be effective in improving immune function to lessen the effects of these pathogens.[563]

Cryptosporidium can produce an enteritis with significant diarrhea in patients with AIDS. Cryptosporidiosis can occur in both immunocompetent and immunocompromised hosts, but in the former it is mainly a cause for self-limited diarrhea of 1 to 2 weeks duration in children. In immunocompromised hosts cryptosporidiosis can be the cause for a life-long, protracted diarrhea that is refractory to therapy. Cryptosporidiosis is a chronic infection in about half of affected AIDS patients, while it is transient in about one fourth, and fulminant in less than 10%. It is estimated to afflict 10 to 20% of patients with AIDS and diarrhea in the U.S., and half of such patients in developing nations. Cryptosporidiosis produces a voluminous, watery diarrhea with 6 to 25 bowel movements per day with a maximum stool volume of 1 to 17 liters.[398] It is often accompanied by abdominal cramps, low-grade fever, anorexia, electrolyte imbalance, dehydration, and weight loss, though it rarely leads to death.[342,399] No effective treatment has been developed. *Cryptosporidium* organisms may also be found in biliary tract, pancreas, and lung.[398,400,564,565,566]

Radiographic features of cryptosporidiosis in the small intestine include thickened mucosal folds when inflammation is present, or effacement of folds with villous atrophy. There can also be blunting, fusion, or loss of villi. Increased fluid secretion can lead to dilution of barium.[341]

Cryptosporidium does not usually produce grossly visible lesions such as erosions, ulcers, or masses, though there may be mild erythema and granularity. Microscopically on small intestinal biopsy samples, cryptosporidia are small 2 to 4 micron sized round organisms that occur singly or in rows along the mucosal brush border from villi to crypts, sometimes accompanied by acute inflammation and crypt abscesses. They are best diagnosed by examination of stool specimens with acid fast stain under oil immersion.[328] Giemsa and PAS stains may also demonstrate these organisms. On electron microscopy the organisms appear embedded in a cytoplasmic vacuole on the microvillous border.[398,557] Postmortem diagnosis is usually precluded by autolysis. Therapy for chronic *Cryptosporidium* infection consists of paromomycin.[400]

Isospora belli is more common in tropical regions than in temperate climates. It may produce a protracted watery diarrhea lasting for months, along with steatorrhea and abdominal pain, similar to *Cryptosporidium* in patients with AIDS, and extraintestinal dissemination has been documented. Diagnosis is typically made by finding large 20 to 30 micron oval oocysts in stool, aided by acid fast staining. Eosinophilia may be present, and this suggests additional helminthic infection. Biopsy of small intestine may show *Isospora* organisms within the intestinal lumen or within cytoplasmic vacuoles in mucosal cells in mucosa with mild inflammation and atrophy.[328,398,399,567] *Isospora* can be treated with trimethoprim-sulfamethoxazole.[400]

Microsporidial infections (caused by *Enterocytozoon* species including *E bieneusi*, *E cuniculi*, and *E hellum*, and by *Encephalitozoon (Septata) intestinalis*) have a similar clinical presentation to *Cryptosporidium*. However, microsporidiosis is characterized by fewer watery stools per day, a more gradual weight loss, maintenance of appetite, and lack of fever. Microsporidial infections can be more frequent than cryptosporidial infections in AIDS when diagnostic techniques are available and can best be diagnosed on small intestinal biopsy samples using light microscopy with Giemsa staining or by transmission electron microscopy. Stool examination can be more sensitive than intestinal biopsy for diagnosis. The organisms are most numerous in the jejunum, but they have also been reported as a cause for cholangitis. [398,399,557]

Grossly, microsporidial infections do not produce striking changes, though mucosal erythema and granularity may be seen on endoscopy. By light microscopy there may be partial villous atrophy with blunted villous tips from mucosal cell destruction. Crypt hyperplasia and lamina propria inflammation are variable. The 4 to 5 micron meronts and sporonts are clustered in the supranuclear intracytoplasmic region of villous mucosal cells. The 1 to 2 micron spores are acid fast, and can also be seen by light microscopy in smears of stool or duodenal aspirates by use of a modified trichrome stain.[404,412,557] Treatment with albendazole has been recommended for *Septata* infections, while no effective therapy exists for *Enterocytozoon* infections.[400]

Infection with the small coccidian organism *Cyclospora cayetansis* produces an appearance clinically similar to cryptosporidiosis.[412] Stool examination provides the diagnosis with acid fast staining for organisms that resemble a large cryptosporidium; they are 8 to 10 micron with a double cyst wall and a central morula.[398,413] On small intestinal biopsy there can be mild to moderate acute and chronic inflammation of lamina propria with prominent plasma cells along with focal vacuolization of the brush border and mild to moderate partial villous atrophy and crypt hyperplasia.[414] Cyclosporiasis has a high recurrence rate. Treatment with trimethoprim-sulfamethoxazole appears to be effective both for acute infections as well as for prophylaxis.[400,412]

Giardia lamblia infections may occur with or without diarrhea, casting doubt about the pathogenicity of this organism. By endoscopy, the small intestinal mucosa may appear mildly erythematous. On biopsy, the mucosa demonstrates no significant changes, and the organisms are mainly intraluminal, appearing as 3 by 8 micron amphophilic to eosinophilic pear-shaped trophozoites with two indistinct nuclei. Stool examination can demonstrate cysts of *G lamblia* for diagnosis.[557]

Infections with other intestinal protozoa, such as *Entamoeba histolytica*, *Blastocystis hominis*, and *Chlamydia* species, have also occurred in patients with AIDS, but not to a significant

degree. They may cause diarrhea, often mild and similar to that seen in immunocompetent hosts, but they are usually enteric commensals.[399,413,414,551,568] Visceral leishmaniasis, caused by *L donovani*, may affect the gastrointestinal tract, and the amastigotes may be seen in macrophages scattered in the lamina propria with hematoxylin-eosin or Giemsa stains.[431]

BACTERIAL ENTERIC INFECTIONS.-- Besides the usual opportunistic infections, bacterial infections can occur in association with HIV infection. Enteric bacterial infections usually produce stools that do not contain occult blood or leukocytes. Definitive diagnosis is made by stool culture.[418]

Salmonella species (not *typhi*) can occur in persons at risk for HIV infection, but most often after clinical AIDS is apparent. Gastrointestinal *Salmonella* infections have a propensity to result in septicemia and to relapse, particularly when CD4 lymphocyte counts are low. Recurrent *Salmonella* infection is a criterion for diagnosis of AIDS in adults and children, and when suspected blood culture should be performed.[319,320] Fever is common. Recurrence or failure to respond to antibiotic therapy may occur, though amoxicillin, trimethoprim-sulfamethoxazole, or ciprofloxacin appear to be appropriate therapeutic choices for *Salmonella* or *Shigella* infections. Patients taking zidovudine have a lower risk for development of salmonellosis. Typhoid fever has been infrequently reported in male homosexuals and in association with AIDS.[418,551,569]

Campylobacter jejuni infections often appear after development of clinical AIDS and are more frequent and severe than in patients without AIDS. Campylobacter jejuni infections are best treated with either erythromycin or ciprofloxacin.[551] *E*nteropathogenic *E. coli* are seen with HIV infection, most often in association with persistent diarrhea in children of developing nations.[418,551,569] *Helicobacter pylori* infection can appear in about one-sixth of HIV-infected persons with chronic gastritis, a lower incidence than that for non-HIV-infected persons, but with a similar histologic appearance of inflammation, erosions, or ulcers.[570] HIV-infected patients with *H. pylori* have a higher mean CD4 count than persons infected with HIV who do not have *H. pylori*. The gastritis associated with *H. pylori* is more severe in persons with HIV infection.[571] Occasionally, a low-grade small intestinal bacterial overgrowth of mostly aerobic bacteria may lead to malabsorption and diarrhea.[551]

Shigella infections tend to occur early with HIV infection, and half may be accompanied by a bacteremia. *Campylobacter jejuni* can produce a proctocolitis, and patients often do not have fever. *Clostridium difficile* infection may occur in AIDS patients treated with broad spectrum antibiotics, may produce pseudomembranous colitis, and may not respond promptly to therapy. *Vibrio parahaemolyticus*, which can lead to colitis following ingestion of poorly cooked seafood, should be considered in the differential diagnosis. Other bacterial pathogens to be considered in cases of colitis include: enteropathogenic *E. coli*, *Yersinia*, and *Aeromonas hydrophila*.[418,569]

Diarrheagenic (enteropathogenic) strains of *E. coli* are important worldwide as causes for diarrhea in travelers and in infants, but also can cause diarrhea in immunocompromised patients. Such strains can most often be identified by assay specifically for enteropathogenic *E. coli*. They may also be known as enteroadherent bacteria. Histopathologic findings are those of "non-specific" colitis with little crypt distortion or cryptitis, but with focal epithelial cell necrosis or degeneration, breaks or gaps in the surface epithelium, aggregates or tufts of epithelial cells, and cellular debris. The inflammatory reaction consists of a few neutrophils and a moderate increase in lymphocytes. The bacteria are most often seen along the epithelial surface or brush border and are rarely invasive. Identification methods for these strains are not commonly available, so empiric antibacterial therapy with response may suggest *E. coli* as a cause for AIDS enteropathy.[572]

VIRAL ENTERIC (NON-CMV) INFECTIONS.-- Viruses other than cytomegalovirus may account for a third of cases of diarrhea in HIV-infected persons, but detection and diagnosis is more difficult than for the gastrointestinal protozoa. Most involve the small intestine. Viruses detected have included adenoviruses, rotaviruses, astroviruses, picobirnaviruses, and caliciviruses. Enzyme immunoassays may detect adenoviruses, rotaviruses, and astroviruses. Polymerase chain reaction methods with reverse transcription and polyacrylamide gel electrophoresis can be used to

detect picobirnaviruses, which are RNA viruses. Electron microscopy aids in detection of caliciviruses.[573]

Adenoviruses, similar to the other enteric viruses seen in HIV-infected persons with weight loss, can account for a chronic, watery, nonbloody, non mucoid diarrhea. Grossly, adenoviral lesions may appear discreet, sometimes raised, erythematous lesions several millimeters in diameter. Adenovirus most often involves the colon, but other areas of the GI tract may also be affected. Light microscopic features include involvement only of epithelial cells, and mainly surface goblet cell involvement. The mucosa may demonstrate disorder with loss of orientation, degeneration, and vacuolization. The inclusions are only located in the nucleus and appear amphophilic or eosinophilic. The inclusions typically involve the entire nucleus and may have a crescent or sickle shape, but are rarely targetoid.[574]

Children infected with HIV are more likely to have enterovirus or astrovirus infection of the gastrointestinal tract, as detected by stool culture, than non-HIV infected children, but they were no more likely to have rotavirus infection. Rates of virus-associated diarrhea are similar in the two groups.[575]

Electron microscopic examination helps to confirm light microscopic features of adenovirus with amphophilic intranuclear inclusions in mucosal cells (usually goblet cells) surrounded by focal mucosal necrosis and chronic inflammation. Unlike CMV, adenovirus rarely involves the submucosa.[399,574] Rotavirus infections may produce a watery diarrhea and is seen more frequently with AIDS outside of the U.S.[399]

MYCOBACTERIOSIS.-- Both *Mycobacterium avium*-complex (MAC) and *Mycobacterium tuberculosis* (MTB) in the GI tract are usually found in the small intestine, particularly the duodenum, but can also be found in the colon and stomach (Table 5).[348,576] Mycobacteria can be cultured from stool in about 10% of HIV-infected patients with diarrhea, but the majority of these infections are due to MAI in developed nations of Europe and North America, while most are due to MTB in Africa.[577]

With MAC infection, the mucosa may grossly show small pinpoint yellow foci, fine white nodules, diffuse yellow patches, or raised yellow plaques. This yellow color is explained by the microscopic appearance of numerous striated blue macrophages distending the intestinal mucosal villi. Acid fast stain shows the macrophages to be filled with numerous mycobacteria. Even PAS stain may reveal the organisms and give an appearance that resembles Whipple's disease.[578] A common radiographic finding is diffuse thickening of jejunal folds without ulceration.[341]

Mycobacterium tuberculosis in the GI tract is distributed primarily as small granulomas in cases with widespread dissemination. The most common site of involvement for MTB is the ileocecal region. Colonic lesions are seen radiographically to consist of segmental ulceration, inflammatory strictures, or hypertrophic lesions resembling polyps.[341] The granulomas can occur anywhere from mucosa to serosa. Microscopically, these granulomas are discreet, white to tan, and usually have necrosis, epithelioid cells, Langhans giant cells, and lymphocytes, albeit in small quantities, along with acid fast bacilli.

A presumptive diagnosis of mycobacteriosis for definitional criteria for a diagnosis of AIDS may be made as follows:[320]

Microscopy of a specimen from stool or normally sterile body fluids or tissue from a site other than lungs, skin, or cervical or hilar lymph nodes that shows acid-fast bacilli of a species not identified by culture.

CYTOMEGALOVIRUS.-- Cytomegalovirus (CMV) is capable of infecting all parts of the gastrointestinal tract, but the most common clinical manifestation is colitis. At least 20% of patients with AIDS have gastrointestinal involvement with CMV. Clinically, there may be diarrhea, fever, abdominal pain, hematochezia, weight loss, or anorexia.[343] Odynophagia would suggest esophageal involvement.[399] There is no typical grossly identifiable pattern of involvement. Gross lesions are often not present, but anything from mucosal erythema to small mucosal ulcers to plaques may occur.[399]

Gastrointestinal perforation is an uncommon complication of CMV infection with AIDS, but the most common cause for it is CMV infection. Patients can present with severe abdominal pain, nausea, vomiting, fever, and leukocytosis. An abdominal radiograph will demonstrate pneumoperitoneum. The most common locations for perforation are the ascending and transverse colon, distal ileum, and appendix.[399,403]

A wide range of radiologic findings occur with gastrointestinal CMV infection. There may be single or multiple large superficial esophageal ulcerations. Small bowel wall thickening with thickened, irregular mucosal folds can be seen. Extensive ulceration with involvement of the muscularis can lead to the appearance of a "CMV pseudotumor" ranging in size from a small nodule to a large mass that can mimic a neoplastic lesion of Kaposi's sarcoma or non-Hodgkin lymphoma, though the inflammation associated with CMV typically leads to the finding of infiltrative changes in adjacent mesenteric adipose tissue by computed tomographic scan.[341]

Cytomegalovirus may be diagnosed by endoscopic biopsy in which the characteristic large cells with prominent homogenously staining violet intranuclear inclusion bodies (Cowdry type A) are seen--most often in mucosal epithelial cells and occasionally in submucosal endothelial cells. Cells with inclusions are often widely scattered and not numerous, and atypical CMV inclusions may be more frequent. The cytomegalic cells may be accompanied by small foci of chronic inflammation, necrosis, or hemorrhage. Viral culture may be performed, but is generally not useful because, in the absence of histologic evidence for infection, detection of CMV is of uncertain significance.[138] Use of immunohistochemical staining can help in identification of CMV in difficult cases.[579]

TOXOPLASMOSIS.-- Toxoplasmosis may rarely produce mucosal erosions in the colon, but is typically not associated with gross lesions. Microscopically, it is characterized by mixed inflammatory cell infiltrates of mucosa and submucosa in a haphazard pattern, and with little cellular necrosis. Unless *Toxoplasma gondii* cysts or tachyzoites are found, the diagnosis cannot be made with certainty.[391]

HERPES SIMPLEX VIRUSES.-- Herpetic lesions of the GI tract typically involve the perianal region and the esophagus. Involvement of the lower GI tract may be produced by extension of lesions from perianal skin to the anorectal junction and to rectum with clinical findings of anorectal pain, tenesmus, constipation, and inguinal lymphadenopathy. Diarrhea may occasionally complicate proctitis.

Herpetic esophagitis is second in frequency to candidiasis as a cause for odynophagia, and dysphagia may also occur. The oral cavity and esophagus may also be involved with small discreet "punched-out" ulcerations. Grossly, crops of clear vesicles can evolve to chronic ulceration and induration. A common radiologic manifestation is the appearance of multiple small discreet ulcers in a normal background mucosa.[341] Microscopic diagnosis is made by finding ground glass, mauve to pink, intranuclear inclusions in cells that are clustered or multinucleate. Surrounding squamous epithelium may show ballooning degeneration. Acyclovir, or foscarnet if resistance develops, may be helpful for therapy.[324,399,403]

ORAL CAVITY CHANGES.-- A fourth to half of all persons infected with HIV will have one or more oral lesions during the course of their infection, and in 10% an oral lesion will be the first manifestation of their illness. The most common lesions are: oral candidiasis, hairy leukoplakia, periodontitis, gingivitis, aphthous ulcers, and Kaposi's sarcoma. Oral candidiasis is discussed above. Symptoms may include xerostomia and burning mouth syndrome. Oral papules and ulcers may appear on buccal mucosa with *Histoplasma capsulatum* and *Penicillium marneffei* infections.[557,580]

Both the periodontitis and the gingivitis (necrotizing in some cases) seen with HIV infection appear clinically similar to that seen in non-immunocompromised patients. Cases of acute necrotizing ulcerative gingivitis (ANUG) are not common and usually appear prior to the onset of clinical AIDS. Chronic gingivitis may present with band-like or punctate erythema, though biopsy reveals only increased vascularity without inflammation, and most are associated with *Candida*

infection. Gingivostomatitis with Herpes simplex virus infection is typically severe with multiple vesicles that can rupture, coalesce, and leave painful irregular ulcers. The HIV-associated periodontitis may or may not have necrosis, but produces severe pain in the jaw.[555,581,582]

Aphthous oral ulcers, though seen in non-immunocompromised persons, are more likely to be severe and prolonged in patients with HIV infection. Aphthous oral ulcers can appear as a complication of zalcitabine and saquinavir therapy.[206,213] Aphthous ulcers most commonly appear as painful lesions in the floor of the mouth, tonsillar fossa, and epiglottis, particularly in patients with low CD4 lymphocyte counts, that lead to weight loss from decreased oral intake. They may also occur in esophagus and colon. Histologically, these ulcers demonstrate submucosal lymphocytic infiltration with overlying acute inflammation, including eosinophils. Special stains are needed to exclude possible infectious agents.[557] Intralesional injection of corticosteroids may be helpful for pain relief, healing of the ulcers, and weight gain.[583] The drug thalidomide has shown effectiveness in the treatment of oral aphthous ulcers.[584] Drug therapy with foscarnet, interferon, and ddC may also be complicated by oral ulceration.[585]

Neoplasms associated with HIV infection that involve the oral cavity are not common. Oral Kaposi's sarcoma (KS) usually appears in two patterns. There can be small, well-delineated macular lesions that histologically have inconspicuous patches of spindle cells containing ill-defined vascular spaces and scattered lymphocytes. More often, KS appears as larger, infiltrative, nodular lesions that have spindle cells lining vascular slits and bizarre-shaped vessels. Both types of lesions have extravasated red blood cells, but hyaline globules and hemosiderin are present only half the time.[586] A variant of a diffuse large cell non-Hodgkin lymphoma known as plasmablastic lymphoma has been reported in the oral cavity.[479]

Oral hairy leukoplakia, (OHL) also known as oral condyloma planum, produces a white lesion usually found on the lateral border of the tongue that is slightly raised, poorly demarcated and variable in size. The mucosal surface is grossly corrugated or "hairy." Unlike the exudate of oral thrush, the lesion of OHL cannot be scraped off. Epstein-Barr virus (EBV) has been identified in epithelial cells with OHL. Microscopically, the squamous epithelium shows marked acanthosis (which produces the grossly “hairy” appearance) with parakeratosis, koilocytosis, and herpetic type intranuclear inclusions. Candidiasis is often present overlying the lesion. However, fungal infections alone, or mechanical irritation, may produce gross and microscopic appearances similar to OHL. OHL is not premalignant. The presence of OHL in an HIV-infected person may presage development of AIDS.[587,588] The appearance of high grade T-cell non-Hodgkin lymphomas has been reported in the oral cavity of patients with EBV infection and OHL.[465]

Oral condylomata can appear in several forms and may occur on any oral mucosal surface and are associated with human papillomavirus infection (HPV). Oral HPV infection occurs in approximately 1% of persons with HIV infection. Lesions that are flat, sessile, and firm are associated with HPV genotypes 1, 2, and 7 similar to cutaneous warts. The spiked, soft, or cauliflower-like lesions are associated with HPV genotypes 6 and 11 similar to genital warts. Lesions with epithelial hyperplasia in small, flat papules on the lower lip are associated with HPV genotypes 13 and 32. Microscopically, both acanthosis and koilocytosis are present. Treatment of larger lesions is difficult, with surgical excision and laser ablation being applied with some success.[557,589

Herpetic gingivostomatitis can be accompanied by systemic flu-like symptoms along with painful gingival inflammation and multiple oral ulcers. Most commonly, this is manifested as herpes labialis which is characterized by a prodrome of itching and burning followed by the development of a crop of vesicles that crusts and then heals spontaneously in a week to 10 days. Herpes labialis typically occurs along the vermillion border of the lips. With HIV infection, herpes viral infections can be more extensive and severe and difficult to treat.[590]

Human papillomavirus (HPV) may cause the appearance of exophytic, papillary oral lesions. With HIV infection, these lesions are often multiple and difficult to treat because of a high rate of recurrence. Excision and cauterization or topical podophyllin have been used as therapies.[590]

Bacillary angiomatosis, which produces proliferative vascular lesions, can rarely involve the oral cavity. The lesions can resemble oral Kaposi’s sarcoma. Grossly, they are most often bluish

to purplish macules, but papules and nodules may also be seen, and there can be ulceration and exudation. Histologically, lesions of bacillary angiomatosis may have similarities to pyogenic granuloma and epithelioid hemangioma. A characteristic feature is vascular proliferation with epithelioid-like endothelial cells that project into vessel lumens to give a tombstone-like appearance.[591]

Patients receiving highly active antiretroviral therapy (HAART) may develop a variety of exfoliative cheilitis characterized by exfoliation, crater formation, fissuring, erosions and/or the formation of papules, vesicles and blisters associated with erythema and edema. Microscopically, the lesions consist of ulcerations with adjacent hyperkeratosis and suprabasal vacuolization accompanied by a dense lymphocyte infiltrate.[592]

Lesions involving the tongue, which is easily accessible for examination, are common in advanced HIV infection. Hairy leukoplakia and candidiasis are present in over a third of patients, and can occur concomitantly. Non-specific glossitits can appear in a third of patients. Disseminated infections, including mycobacteriosis, histoplasmosis, cryptococcosis, and cytomegalovirus can involve the tongue.[593]

Tooth extraction is the dental treatment most commonly carried out in HIV infected patients. The most frequent post extraction complications are delay in wound healing, alveolitis, and wound infection. These complications are uncommon and not too severe.[594]

ANORECTAL SQUAMOUS INTRAEPITHELIAL LESIONS (ASIL).-- Persons with HIV infection may develop ASIL that can progress to high-grade squamous intraepithelial lesions (HSIL) that can progress to invasive carcinomas. The relative risk for anal intraepithelial lesions is 60 in men and 7.8 in women, compared with persons not infected with HIV.[595] Anorectal squamous cell dysplasia, carcinoma, and condyloma acuminatum all have a higher incidence (7%) in young homosexual males than in the general population, and this incidence is even greater (36%) in those homosexual males who also have HIV infection. There is a strong association between the appearance of these lesions and a history of receptive anal intercourse, particularly with multiple sexual partners, but HPV can be acquired without anal intercourse. The concomitant presence of anal human papillomavirus (HPV) is a risk for ASIL, and the risk for development of ASIL increases when the CD4 lymphocyte count is lower, though ASIL can occur even with CD4 counts which are less than 500/μL.[589,596,597,598] The use of highly active antiretroviral therapy (HAART) increases survival in HIV infected persons and appears to increase the risk for anal cancer, since HSIL does not appear to regress with HAART.[599]

Progression of ASIL to HSIL can occur in 62% of HIV-infected males. Risks for progression include coinfection with multiple HPV types, specifically HPV 16 and a CD4 count <200/μL. At least 75% of persons with ASIL do not have regression of the lesions while receiving highly active antiretroviral therapy (HAART). Thus, longer survival of persons receiving HAART may actually allow progression of ASIL to HSIL and invasive lesions.[596] In such a setting, screening of HIV-infected persons, with risk factor of anal receptive intercourse, by anal Pap smears can be useful.[589]

Women with HIV infection are more likely to have anal HPV than non-HIV-infected women, and they are more likely to have cytologic abnormalities of the anorectal mucosa. In this setting, the risk for ASIL, HSIL, and invasive lesions is increased. In women, anal intercourse is associated with risk for anorectal neoplasia.[600]

The transformation zone separating the rectal columnar mucosa from the anal keratinizing squamous epithelium above the dentate line is the region where most intraepithelial neoplasms arise. Histologic changes can include atypica, condyloma, and intraepithelial neoplasia. More than two thirds of the squamous epithelial thickness is involved with HSIL, and microinvasion may be present.[595]

Clinical features of anal intraepithelial neoplasia may include pain, pruritus, bleeding, discharge, or tenesmus. The grossly visible anoscopic appearance may be normal. Lesions are treated with excision.[595]

AIDS ENTEROPATHY.-- Despite extensive clinical workup and laboratory testing, some AIDS patients with chronic diarrhea, weight loss, and/or malabsorption cannot be found to have an infection or etiologic factor that can explain the symptomatology, even after biopsy. Endoscopic biopsies in such cases may show villous atrophy or blunting, crypt hyperplasia, acute or chronic inflammation, epithelial cell vacuolization, or epithelial cell degeneration. However, AIDS patients without diarrhea may also have endoscopic biopsies that show villous atrophy. The term "AIDS enteropathy" has been used to describe this condition. The malabsorption is out of proportion to the degree of pathologic changes present.[557]

The etiology remains unclear; even HIV itself has been suggested as the cause, or the release of cytokines by HIV-infected lymphocytes and macrophages in the lamina propria. A low-grade bacterial overgrowth may contribute to this enteropathy. A careful search can be made for organisms, including the use of special stains on biopsy tissues or probes for enteropathogenic *E. coli*. Esophagitis or gastritis may result from drug effects with treatment regimens, and stress ulcers can be seen at autopsy in some cases.[557,601]

HIV WASTING SYNDROME.-- Progressive, involuntary weight loss is a common accompaniment to HIV infection. Poor diet from lack of sufficient care or economic resources certainly plays a role, as well as malabsorption from concomitant AIDS-associated infections or neoplasms, particularly those affecting the GI tract. However, there are persons with AIDS who do not have a concurrent illness or condition other than HIV infection that explains a weight loss of >10% of baseline body weight plus either chronic diarrhea or chronic weakness and fever, which are the CDC criteria for HIV wasting syndrome that satisfy definitional criteria for a diagnosis of AIDS.[320] This wasting syndrome primarily results from loss of lean body mass, while body fat stores are preserved.[602]

Several causative factors probably contribute to the development of wasting syndrome. These can include hypermetabolic or altered metabolic states, production of cytokines such as tumor necrosis factor, interferons, and interleukin as a consequence of macrophage infection by HIV, and endocrine dysfunction. Hypocholesterolemia is common both in HIV infection as well as clinical AIDS. Hypertriglyceridemia can be present with increased interferon alfa levels as a consequence of an increased VLDL with increased hepatic lipoprotein synthesis combined with decreased lipoprotein lipase activity.[603,604,605] Also, progression of HIV infection may play a role in the appearance of wasting syndrome, since the degree of weight loss correlates with increasing HIV-1 RNA levels and with decreasing CD4 lymphocyte counts.[606]

Decreased oral intake of food is also a very important etiology for weight loss in HIV infection and highlights the need for good nutrition. Good nutrition may be needed to counteract the effects of malabsorption that can contribute to wasting syndrome. Sometimes a specific intestinal pathogen can be identified, but not in all cases. HIV-infected patients may have abnormal d-xylose and c-glycerol-tripalmitin absorption tests.[604]

A variety of therapies have been utilized to counteract wasting syndrome. These include the use of megestrol acetate as an appetite stimulant, thalidomide as a cytokine inhibitor, and recombinant human growth hormone or testosterone as anabolic agents. Controlling diarrhea, nausea, and fever as well as providing nutritional support can diminish the impact of wasting syndrome.[602,604]

In the U.S., HIV wasting syndrome alone as an indicator disease accounts for up to 7% of all newly reported AIDS cases, and is reported along with additional indicator diseases in another 10% of cases. In the U.S., persons with HIV wasting syndrome are more likely to be female, black or Hispanic, and have a risk factor other than homosexuality/bisexuality.[603] In a large study in the U.S., the incidence of wasting syndrome declined from 1992 through 1999, with the most marked rate of decline occurring after 1995. The incidence of AIDS and non-AIDS-defining illnesses was generally high at or after a diagnosis of wasting syndrome. Factors significantly associated with improved survival included a CD4+ count of ≥200 cells/μL during the interval of the wasting syndrome diagnosis and antiretroviral therapy with two or more drugs at or after the diagnosis of wasting syndrome.[607]

HIV LIPODYSTROPHY.-- Persons with HIV infection may develop lipodystrophy with lipid abnormalities, insulin resistance, and lactic acidosis. Typical physical findings include central fat accumulation in an abdominal or dorsocervical distribution ("buffalo hump"), peripheral lipoatrophy with fat atrophy of limbs, face, and buttocks, and lipomata. Half of HIV-infected persons may have one or more features of lipodystrophy. Persons taking protease inhibitors such as ritonavir and indinavir as part of their antiretroviral medication regimen may develop protease inhibitor-associated lipodystrophy (PIAL). The mechanism for PIAL is not known, but may be related to inhibition of the sterol regulatory enhancer-binding protein 1 (SREBP-1) that mediates activation of adipocyte retinoid X receptor and peroxisome proliferator-activated receptor (gamma) (PPAR[gamma]). The nucleoside analogue most associated with lipoatrophy is stavudine, especially in combination with lamivudine, due to inhibition of mitochondria.[608]. Despite the abdominal distension, there may be a normal to decreased body mass index. [218]

There is evidence that an adipocytokine, adiponectin, a protein product of the *apM1* gene, which is expressed exclusively in adipocytes, plays a role in development of lipodystrophy with HIV infection. *In vitro* and animal studies and cross-sectional studies in humans have shown that adiponectin is inversely correlated with features of this metabolic syndrome including obesity, insulin resistance, type 2 diabetes, and coronary heart disease, as well as congenital and acquired lipodystrophies in non-HIV infected subjects. This syndrome has recently been linked to a quantitative trait locus on chromosome 3q27, the location of the *apM1* gene.[609,610]

Metabolic consequences of lipodystrophy include: increased insulin resistance with increased plasma insulin and decreased oral glucose tolerance, decreased cortisol, increased total serum cholesterol > 240 mg/dL, HDL cholesterol <35 mg/dL, and increased serum triglyceride >200 mg/dL. Diabetes mellitus may be seen in 7% of patients with lipoatrophy.[608] In fact, the serum triglyceride may be over 1000 mg/dL and even approach 9000 mg/dL. Dyslipidemia is most marked with ritonavir. Up to two thirds of persons taking protease inhibitors may develop features of lipodystrophy. The rate of development of moderate to severe lipodystrophy is 20% for those persons on highly active antiretroviral therapy, 8% among those taking less potent antiretroviral therapy, and 1-2% for antiretroviral-naïve persons. The mean time to appearance of findings is 10 months after starting protease inhibitor therapy. The prevalence of lipodystrophy rises for the first two years after initiating antiretroviral therapy but appears to stabilize thereafter.[611,612]

Treatment for lipodystrophy includes lifestyle modifications with cessation of smoking, increased exercise, and dietary modifications. Insulin resistance may be treated with metformin. Alteration of antiretroviral therapy may be done. A hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase inhibitor (statin) can be used for hypercholesterolemia and a fibrate for hypertriglyceridemia.[608]

MISCELLANEOUS FINDINGS.-- Intussusception has been reported to occur in association with AIDS. This can occur with cytomegalovirus infection or bowel wall involvement by Kaposi's sarcoma or non-Hodgkin lymphoma. The diagnosis is suggested by intermittent cramping abdominal pain in a young to middle aged adult. Computed tomographic (CT) scans aid in confirmation of this diagnosis. The many opportunistic infections and neoplasms affecting the gastrointestinal tract in patients with AIDS can predispose to intussusception.[341,613] The toxic side effects of antiretroviral therapy with either antiretroviral drugs or protease inhibitors may lead to nausea, vomiting, and diarrhea. Such adverse reactions are most likely to occur with zidovudine, didanosine, nelfinavir and saquinavir.[199,205,213] These symptoms may be severe enough to limit use of the drugs.

CENTRAL NERVOUS SYSTEM PATHOLOGY IN AIDS

Clinical features of central nervous system (CNS) lesions with AIDS can be similar and often require radiologic or laboratory differentiation. Neurologic examination helps establish the presence of CNS lesions and to document their progression or response to therapy. Besides organic disease, there are serious functional disorders resulting from the multitude of emotional and psychosocial problems created by the devastating effect of HIV infection on the lives of its victims. CNS lesions are typically identified in over 80% of autopsied AIDS patients. Of AIDS-diagnostic diseases, cryptococcosis, cytomegalovirus, malignant lymphomas, and toxoplasmosis are the most frequent (Table 5). About one-fifth of AIDS patients die from CNS diseases.[342]

Diagnostic imaging including computerized tomography (CT) and magnetic resonance imaging (MRI) are insensitive for early lesions and cannot detect microglial nodules, perivascular lesions, or small granulomas. A clinical diagnosis of encephalopathy is often made before a radiologic diagnosis.[614] Stereotaxic biopsy following radiologic imaging can be useful for diagnosis, with a diagnostic yield around 90%.[615] Cytologic examination of stereotaxic specimens can increase diagnostic sensitivity, particularly for infectious conditions.[616]

HIV ENTRY INTO THE CNS.-- HIV can be carried to the CNS early following initial infection. Enry probably occurs through breaches in the blood-brain barrier. The HIV Tat protein can induce oxidative stress, compromise cellular viability, induce apoptosis, and disrupt tight junctions in endothelial cells to produce HIV entry as well as ongoing cellular damage. HIV resides within microglial cells or within perivascular macrophages, from which the effects of ongoing HIV replication lead to disease in the brain. The HIV Tat protein induces inflammatory responses that mediate cellular injury. The ongoing cellular damage appears clinically as an encephalopathy or encephalitis.[617]

HIV ENCEPHALOPATHY.-- A clinical syndrome described loosely as "HIV encephalopathy" is often associated with a progressive debilitating dementia, or "AIDS dementia complex." Clinically, AIDS dementia often begins with impaired memory and concentration along with psychomotor slowing. It is progressive and continues to include motor deficits such as ataxia and tremor. Behavioral disturbances range from apathy or withdrawal to frank psychosis.[618] A staging system for AIDS dementia complex (HIV encephalopathy) is as follows:[619]

Stage	Characteristics
0	Normal: normal functioning
0.5	Subclinical or Equivocal: Symptoms absent, minimal, or equivocal Mild (soft) neurologic signs No impairment of work or capacity to perform activities of daily living (ADL) Possible mild signs (snout response, slowed ocular or extremity movements)
1	Mild: Performs all but the most demanding functions of work or ADL Unequivocal evidence of functional, intellectual, or motor impairment Able to walk without assistance
2	Moderate: Cannot work or perform demanding ADL Capable of basic activities of self-care Ambulatory but may need a single prop

3 Severe:
Major intellectual incapacity or motor disability

4 End-stage:
Nearly vegetative
Rudimentary intellectual and social comprehension and output; mute
Paraplegic or quadriplegic
Bladder and bowel incontinence

Comprehensive clinical criteria for the diagnosis of central nervous system disorders in adults and adolescents have been established as follows:[618]

HIV-1-ASSOCIATED COGNITIVE/MOTOR COMPLEX.-- All of the following diagnoses require laboratory evidence for systemic HIV-1 infection:

I. Sufficient for diagnosis of AIDS

A. HIV-1-associated dementia complex, *PROBABLE*
(must have *each* of the following):

1. Acquired abnormality in at least two of the following cognitive abilities (present for *at least* 1 month): attention/concentration, speed of processing of information, abstraction/reasoning, visuospatial skills, memory/learning, and speech/language. The decline should be verified by reliable history and mental status examination. In all cases, when possible, history should be obtained from an informant, and examination should be supplemented by neuropsychological testing.

Cognitive dysfunction causing impairment of work or activities of daily living (objectively verifiable or by report of a key informant). This impairment should not be attributable solely to severe systemic illness. The level of impairment due to cognitive dysfunction should be assessed as follows:

MILD: Decline in performance at work, including work in the home, that is conspicuous to others. Unable to work at usual job, although may be able to work at a much less demanding job. Activities of daily living or social activities are impaired but not to a degree making the person completely dependent on others. More complicated daily tasks or recreational activities cannot be undertaken. Capable of basic self-care such as feeding, dressing, and maintaining personal hygiene, but activities such as lending money, shopping, using public transportation, driving a car, or keeping track of appointments or medications is impaired.

MODERATE: Unable to work, including work in the home. Unable to function without some assistance of another in daily living, including dressing, maintaining personal hygiene, eating, shopping, handling money, and walking, but able to communicate basic needs.

SEVERE: Unable to perform any activities of daily living without assistance. Requires continual supervision. Unable to maintain personal hygiene, nearly or absolutely mute.

2. At least *one* of the following:

    a. Acquired abnormality in motor function or performance verified by clinical examination (e.g., slowed rapid movements, abnormal gait, limb incoordination, hyperreflexia, hypertonia, or weakness), neuropsychological tests (e.g., fine motor speed, manual dexterity, perceptual motor skills), or both.

    b. Decline in motivation or emotional control or change in social behavior. This may be characterized by any of the following: change in personality with apathy, inertia, irritability, emotional lability, or new onset of impaired judgment characterized by socially inappropriate behavior or disinhibition.

3. Absence of clouding of consciousness during a period long enough to establish the presence of #1.

4. Evidence of another etiology, including active CNS opportunistic infection or malignancy, psychiatric disorders (e.g., depressive disorder), active alcohol or substance use, or acute or chronic substance withdrawal, must be sought from history, physical and psychiatric examination, and appropriate laboratory and radiologic investigation (e.g., lumbar puncture, neuro-imaging). If another potential etiology (e.g., major depression) is present, it is not the cause of the above cognitive, motor, or behavioral symptoms and signs.

HIV-1-associated dementia complex, *POSSIBLE* (must have *one* of the following):

1. Other potential etiology present (must have *each* of the following):

    a. As above (see *Probable*) #1, #2, #3.
    b. Other potential etiology is present but the cause of #1 above is uncertain.

2. Incomplete clinical evaluation (must have *each* of the following):

    a. As above (see *Probable*) #3, #2, #3
    b. Etiology cannot be determined (appropriate laboratory or radiologic investigations not performed.

B. HIV-1-associated myelopathy

PROBABLE (must have *each* of the following):

1. Acquired abnormality in lower extremity neurologic function disproportionate to upper extremity abnormality verified by reliable history (lower extremity weakness, incoordination, and/or urinary incontinence) and neurologic examination (paraparesis, lower extremity spasticity, hyperreflexia, or the presence of Babinski signs, with or without sensory loss).

2. Myelopathic disturbance (see #1) is severe enough to require constant unilateral support for walking. The severity of HIV-1-associated myelopathy should be graded as follows:

   MILD: Ambulatory, but requires constant unilateral support (e.g., cane) for walking.

   MODERATE: Requires constant bilateral support (e.g., walker) for walking.

   SEVERE: Unable to walk even with assistance, confined to bed or wheelchair.

3. Although mild cognitive impairment may be present, criteria for HIV-1-associated dementia complex are not fulfilled.

4. Evidence of another etiology, including neoplasm, compressive lesion, or multiple sclerosis must be sought from history, physical examination, and appropriate laboratory and radiologic investigations (e.g., lumbar puncture, neuroimaging, myelography). If another potential etiology is present, it is not the cause of the myelopathy. This diagnosis cannot be made in a patient infected with both HIV-1 and HTLV-1; such a patient should be classified as having possible HIV-1- associated myelopathy.

POSSIBLE (must have *one* of the following):

1. Other potential etiology present (must have *each* of the following):

   a. As above (see Probable) #1, #2, #3.
   b. Other potential etiology is present but the cause of the myelopathy is uncertain.

2. Incomplete clinical evaluation (must have *each* of the following):

   a. As above (see *Probable*) #3, #2, #3
   b. Etiology cannot be determined (appropriate laboratory or radiologic investigations not performed.

II. Not sufficient for diagnosis of AIDS, but for diagnosis of a minor cognitive/motor disorder

PROBABLE (must have *each* of the following):

1. Cognitive/motor/behavioral abnormalities (must have *each* of the following):

   a. At least *two* of the following acquired cognitive, motor, or behavioral symptoms (present for *at least* 1 month) verified by reliable history (when possible, from an informant):

      1) Impaired attention or concentration
      2) Mental slowing
      3) Impaired memory
      4) Slowed movements
      5) Incoordination
      6) Personality change, or irritability or emotional lability

b. Acquired cognitive/motor abnormality verified by clinical neurologic examination or neuropsychological testing (e.g., fine motor speed, manual dexterity, perceptual motor skills, attention/concentration, speed of processing of information, abstraction/ reasoning, visuospatial skills, memory/ learning, or speech/language).

2. Disturbance from cognitive/motor/behavioral abnormalities (see #1) causes mild impairment of work or activities of daily living (objectively verifiable or by report of a key informant). Includes the ability to perform all but the most demanding aspects of work or activities of daily living. Performance at work is mildly impaired but able to maintain usual job; social activities may be mildly impaired, but person is not dependent on others. Can feed self, dress, and maintain personal hygiene, handle money, shop, use public transportation, or drive a car, but complex daily tasks such as keeping track of appointments or medications may be occasionally impaired.

3. Does not meet criteria for HIV-1-associated dementia complex or HIV-1-associated myelopathy.

4. No evidence of another etiology, including active CNS opportunistic infection or malignancy, or severe CNS systemic illness determined by appropriate history, CNS physical examination, and laboratory and CNS radiologic investigation (e.g., lumbar puncture, CNS neuroimaging). The above features should not be CNS attributable solely to the effects of active alcohol CNS or substance use, acute or chronic substance withdrawal, adjustment disorder, or other psychiatric disorders.

POSSIBLE (must have *one* of the following):

1. Other potential etiology present (must have each of the following):

   a. As above (see *Probable*) #1, #2, #3
   b. Other potential etiology is present and the cause of the cognitive/motor/behavioral abnormalities is uncertain

2. Incomplete clinical evaluation (must have *ONE* of the following):

   a. As above (see *Probable*) #1, #2, #3
   b. Etiology cannot be determined (appropriate laboratory or radiologic investigations not performed).

The following criteria apply to the clinical diagnosis of central nervous system dysfunction in children with HIV-1 infection:[264]

HIV-1-ASSOCIATED PROGRESSIVE ENCEPHALOPATHY OF CHILDHOOD.--

PROBABLE (must have *EACH* of the following):

1. Evidence for HIV-1 infection as defined by 1994 or 1987 CDC criteria.[317,320]

2. At least *one* of the following progressive findings present at least 2 months:

    a. Failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests.
    b. Impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated on serial CT or MRI).
    c. Acquired symmetric motor deficits manifested by *TWO OR MORE* of the following: paresis, abnormal tone, pathologic reflexes, ataxia, or gait disturbance.

3. Evidence of another etiology, including active CNS opportunistic infection or malignancy, must be sought from history, physical examination, and appropriate laboratory and radiologic investigation (e.g., lumbar puncture, neuroimaging). If another potential etiology is present, it is not thought to be the cause of the above cognitive/motor/behavioral/ developmental symptoms and signs.

POSSIBLE (must have *one* of the following):

1. Other potential etiology present (must have each of the following):

    a. As above (see *PROBABLE*) #1 and #2
    b. Other potential etiology is present but the cause of #2 is uncertain

2. Incomplete clinical evaluation (must have *EACH* of the following):

    a. As above (see *PROBABLE*) #1 and #2
    b. Etiology cannot be determined (appropriate laboratory or radiologic investigations not performed).

AIDS DEMENTIA COMPLEX.-- The prevalence of AIDS dementia complex (ADC), or human immunodeficiency virus-associated dementia (HIVD) varies widely. ADC can occur at any stage of HIV infection. During the asymptomatic stage of HIV infection, ADC has been estimated to have an incidence of 0.4%. In only 3% of adults with HIV infection is ADC the first manifestation of AIDS. During the late stages of AIDS, when CD4 lymphocyte counts drop and HIV-1 RNA levels increase, more patients may be affected with up to 30% exhibiting some degree of cognitive impairment and up to 15% developing frank dementia. In patients receiving highly active antiretroviral therapy (HAART) the incidence declines. The disease often progresses insidiously, particularly in patients receiving antiretroviral therapy, but the onset can be more rapid over weeks in patients who have never received antiretroviral therapy. Persons with CD4 counts below 100/μL progress more rapidly. The mean survival in untreated persons is about 6 months. Other significant predictors of progression to dementia are the presence of an anemia, weight loss, and constitutional symptoms.[619,620]

The diagnosis is one of exclusion. Opportunistic infections involving the CNS in AIDS tend to have a more rapid onset and course. Clinical features of ADC suggest early and predominantly subcortical brain involvement. These features include increasing forgetfulness, difficulty with concentration, loss of libido, apathy, inertia, and waning interest in work and hobbies. ADC is characterized by social withdrawal and a blunting of emotional responsiveness. Short-term memory is impaired. Motor problems include poor handwriting, poor balance, gait difficulties, and a tendency to drop things easily. As the dementia progresses, learning and memory deteriorate.

There is a reduced output of spontaneous speech. Eventually, late in the course of the disease there is global impairment with severe psychomotor retardation and mutism.[620]

The neurologic examination is often normal early in the course of ADC. Focal neurologic deficits are more likely to be found with CNS opportunistic infections. Subtle findings can include impairments of raid eye and limb movements and diffuse hyperreflexia. Progression of the disease results in an increased muscle tone, particularly of the lower extremities. This is usually associated with tremor, clonus, frontal release signs, and hyperactive reflexes. In some cases myelopathy may be more severe than cognitive impairment. There can be spastic paraparesis with variable sensory ataxia and bladder involvement. Retinal cotton-wool spots may be found on funduscopy in 60% of cases. Generalized seizures may occur.[620]

Examination of body fluids, including cerebrospinal fluid (CSF), reveal no specific findings for ADC. The CSF is usually acellular or demonstrates a mild lymphocytic pleocytosis. The total protein is elevated in about two thirds of cases. The IgG is increased in up to 80% of cases. Oligoclonal bands may be found in the CSF in a third of cases, but the myelin basic protein is usually not elevated. Although the levels of HIV-1 RNA in the CSF are not useful for diagnosis of ADC, the levels are predictive of the severity of dementia when it is present. In some cases the HIV-1 RNA is high in the CSF even when the plasma level has been suppressed, and this is known as "CNS escape." This may be due to prolonged use of antiretroviral therapy, poor compliance, and viral sequestration in the CNS.[620]

Radiologic features of ADC include diffuse cortical atrophy and deep white matter abnormalities. In contrast, lesions of opportunistic infections are more likely to be focal and have a mass effect. In children, calcifications of the basal ganglia can be seen with computed tomographic (CT) scans. The degree of cerebral atrophy may not correlate with the severity of disease. White matter hyperintensities that are small and ill-defined are seen with magnetic resonance imaging (MRI) scans, or attenuation can be seen on CT scans, and these findings suggest that HIV leukoencephalopathy may be present. Other findings with MRI include focal caudate nucleus atrophy and diffuse grey matter atrophy. Positron emission tomography (PET) scans show subcortical hypermetabolism in the early stages of ADC.[546,620]

A specific cause for this dementia may not be identified either pre- or postmortem. Encephalopathy may be a function of direct infection by HIV of monocytes and macrophages which then produce indirect immunopathologic effects upon the CNS. These effects may be mediated by neurotoxic factors, glial proliferation, cytokine release, or activation of N-methyl-D-aspartate receptors. The neurotoxin quinolinic acid is produced by macrophages. There is wide variability HIV genotype, viral production by macrophages, and toxin production in AIDS patients, which may explain the variability in neuropathologic findings between individuals and even between different areas of the brain in the same individual.[621]

Both neurons and glial cells are not directly infected by HIV. Instead, the CNS damage that occurs from HIV infection is mediated through infection of phagocytic cells—macrophages and microglial cells—that are infected with HIV. The phagocytic cells release cytokines and viral factors that lead to neuronal damage and dropout.[620,622]

The severity of AIDS dementia has a significant correlation with greater numbers of macrophages present within the brain, but there is only a borderline correlation with the numbers of HIV-infected cells (by immunohistochemical staining with antibody to gp41) in the brain and ADC.[623] A possible mechanism of injury to the brain may result from increased nitric oxide (NO) production. The presence of HIV has been shown to increase the amount of inducible nitric oxide synthetase (iNOS) in cell cultures with macrophages and with astrocytes. A prolonged, high level production of NO may account for the neurologic damage seen in HIV-infected persons.[624]

The differential diagnosis for ADC depends upon many factors. Intravenous drug users may have infarcts from previous bouts of endocarditis with embolization of thrombi. Patients with bacterial infections may show a purulent meningitis or localized vasculitis producing hemorrhage. Cryptococcosis may also produce a meningitis. Toxoplasmosis may produce abscesses. However, lesions from most opportunistic agents are subtle in appearance and may be characterized only by focal demyelination or hemorrhage. Malignant lymphomas can present as mass lesions that are

grey to white, but they may also be diffuse or metastasize within the ventricles or along the meninges.[619]

Gross examination of the brain and spinal cord at autopsy rarely reveals specific lesions with ADC. Subcortical lesions are most prominent in lobar white matter and deep gray nuclei such as the thalamus, and atrophy can be mild to marked, with hydrocephalus ex vacuo. Therefore, multiple areas must be sampled for histologic examination.[620]

Microscopic findings with ADC may demonstrate increased macrophages and multinucleated giant cells. Diffuse myelin pallor may also be seen. However, up to half of patients with a history of ADC may have no histopathologic findings.[619,620] Areas of active HIV encephalitis contain abundant HIV RNA and DNA localized to macrophages and microglia, but not neurons. Areas with minimal or no inflammation have minimal proviral HIV.[625]

No specific therapy is available for ADC. However, antiretroviral therapy has been shown to be effective in treating this dementia. Patients treated with antiretroviral therapy are less likely to develop ADC and have fewer CNS lesions at autopsy. Since ADC is more common in the late stages of AIDS, survival from the time of diagnosis may be limited.[619,620]

Other CNS lesions may demonstrate a specific opportunistic infectious agent or neoplasm associated with AIDS, while others may result from immunologic or hypersensitivity phenomena as a result of HIV infection of CNS cells directly. Microglial and glial cell activation by HIV infection can lead to cytokine production, oxidative stress, and resultant neuronal apoptosis. The infection of monocyte/macrophage/microglial cells by HIV is the mechanism by which the pathologic changes are mediated in the CNS.[626,627,628]

HIV ENCEPHALITIS.-- Microscopic examination of the brain at autopsy in AIDS may reveal a subacute encephalitis consisting of multiple foci with mononuclear cells typical of small macrophages, microglia, and multinucleated giant cells in 5 to 10% of cases.[629] These are often seen near small blood vessels, most often in the basal ganglia, in deep cerebral white matter, and brainstem. They appear less commonly scattered in the grey matter or leptomeninges. The multinucleated giant cells are the hallmark of HIV infection involving the CNS. HIV can be demonstrated in their cytoplasm. Thus, the central nervous system remains an important reservoir for HIV infection, even with aggressive antiretroviral therapy.[239] Sometimes such multinucleated cells can be quite numerous. Cerebral atrophy with multinucleated giant cells has been reported with HIV-associated subacute encephalitis in over 25% of AIDS patients. In some cases of HIV encephalitis, multinucleated giant cells are not found, but large amounts of HIV antigen may be found in macrophages and microglia.[622,626,627]

Laboratory methods are available to aid in diagnosis of HIV encephalitis. In tissues, immunohistochemical methods for detection of HIV with antibody to p24, gp41, or gp120 can be performed.[630] The occurrence of HIV encephalitis appears to be unrelated to the stage of AIDS. Perivascular or leptomeningeal lymphocytic infiltration may be seen even in persons with asymptomatic HIV infection.[631] In cerebrospinal fluid samples, an increasing level of HIV-1 RNA correlates with the presence of HIV encephalitis, though plasma HIV-1 RNA levels may not.[632]

HIV LEUKOENCEPHALOPATHY.-- HIV leukoencephalopathy may be seen in about 5% of AIDS patients at autopsy.[629] It produces diffuse bilateral damage to cerebral white matter that can be seen on magnetic resonance imaging (MRI). Occasionally the cerebellum is also involved. There is myelin loss involving mainly the deep white matter, with a tendency to spare the subcortical U fibers and the more compact myelin bundles of corpus callosum, internal capsules, optic radiations, and descending tracts in the brainstem. Grossly, the lesions are similar to multiple sclerosis plaques. By light microscopy, the predominantly perivascular lesions demonstrate myelin debris in macrophages, reactive astrocytosis, hemosiderin in macrophages, multinucleated giant cells, and little or no inflammation. Vacuolar myelin swellings can appear, as well as axonal damage. Oligodendroglial cells appear normal. Without the presence of multinucleated giant cells, the diagnosis depends upon the finding of HIV antigen in macrophages.[622]

The pathologic findings of HIV leukoencephalopathy and HIV encephalitis may overlap in a third of cases. A multifocal pontine leukoencephalopathy may rarely be seen in AIDS patients in which necrosis involves corticospinal tracts and crossing fibers. In one third of AIDS patients with dementia, histologic findings are minimal.[626] Pediatric AIDS encephalopathy (progressive neurologic disease) has similar findings, except that fewer cells can be demonstrated to contain HIV antigen and multinucleated giant cells are difficult to find.[317,622]

MICROGLIAL NODULES.-- Microglial nodules may be seen in both grey and white matter. About half of AIDS cases at autopsy will show these small focal areas, and there is a propensity for these lesions to involve the brainstem, though they can be seen anywhere. Microglial nodules are collections of cells, thought to arise from glial cells, that are mixed with inflammatory cells, including plump reactive astrocytes and lymphocytes, though a variety of inflammatory cell types may be present. They are often located near small capillaries that may have plump endothelial cells with nearby hemosiderin-laden macrophages. Sometimes the macrophages can give rise to multinucleated cells up to 25 microns in diameter with irregular nuclei and scant cytoplasm. Most of the astroglial cells in the nodules have round to oblong nuclei with scant cytoplasm. Small foci of necrosis may be seen in or near these nodules.

Microglial nodules are not specific for HIV infection and may be present with neoplasia, traumatic focal necrosis, or infection from viral, protozoal or bacterial organisms.[627] HIV and/or other infectious agents may be found. Specific etiologic agents in microglial nodules demonstrated in routine tissue sections with hematoxylin-eosin staining most often include cytomegalovirus and *Toxoplasma gondii*. Some microglial nodules have cells with immunoreactivity for HIV by immunohistochemical staining. In a few cases, no infectious agent can be demonstrated. Microglial nodules may be found in persons with asymptomatic HIV infection as well as patients with AIDS at all stages.[631,633]

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY.-- Progressive multifocal leukoencephalopathy (PML) results from human papovavirus infection (designated JC virus, from the polyoma subgroup) affecting primarily the white matter of the brain. PML is seen most frequently in patients with AIDS, though it also occurs in other immune compromised patients. PML is diagnosed in about 5% of AIDS patients at autopsy.[629] The incidence of PML does not appear to have been reduced by highly active antiretroviral therapy (HAART).[634] Typical clinical findings may include hemiparesis, cognitive impairment, dysarthria, gait imbalance, headache, limb dystaxia, hemianopsia, cortical blindness, and seizures. Cerebrospinal fluid analysis is typically normal, though some patients may have mild protein elevations along with mononuclear cell pleocytosis. Oligoclonal bands may be found as well. Diagnosis can be established definitively by brain biopsy, but less invasive techniques include PCR to detect JC virus DNA in CSF or in blood leukocytes.[635, 636]

Computerized tomographic imaging studies show asymmetric multifocal isodense to hypodense lesions in the white matter with minimal to no enhancement, and with hemorrhage or mass effect. The lesions tend to progress in number, size and lowered density over weeks to months. Magnetic resonance imaging (MRI) scans (T2-weighted spin-echo) are more sensitive for detection of small PML lesions, particularly in the posterior fossa. By MRI there are white matter hypointense areas on T2 weighted sequence and hyperintense lesions on T1 weighted sequence, with minimal or non enhancement after intravenous contrast injection. The involvement of the “U” fibers creates a sharp border with the cortex. Parietal and occipital lobe involvement appears common. A mass effect is typically not seen. Lesions can be unilateral, bilateral, single, or multiple. Bilateral lesions are not symmetric. HIV leukoencephalitis is distinguished from PML by diffuse, less intense lesions on T2 weighted sequence that are not visible on T1 and by non-involvement of “U” fibers.[635,637,637]

Oligodendrocytes are targeted by the virus, leading to focal areas of white matter granularity a few millimeters in size that may coalesce. Abnormalities of white matter range from pallor to demyelination to necrosis. The grey-white matter junction is typically involved, and adjacent

cortical grey matter may be involved. White matter tracts in cerebellum, brain stem, and cervical spinal cord may also be involved. The lesions are usually centered around capillaries.[635,638]

Microscopically, PML involves mainly the myelin-producing oligodendrocytes. The resulting cell lysis results in PML lesions that demonstrate demyelination with perivascular monocytes, astrocytosis with bizarre or enlarged astrocytes (with occasional mitotic figures), and central lipid-laden macrophages. At the periphery of the lesions there are large "ballooned" oligodendrocytes infected with JC virus that have enlarged "ground glass" nuclei containing viral antigen. The presence of JC virus can be confirmed by immunohistochemical staining or *in situ* hybridization methods. Multinucleated giant cells containing HIV may also be present. A marked perivascular mononuclear infiltrate composed predominantly of T-lymphocytes may be present in some lesions. The JC virus can also be detected within peripheral blood lymphocytes in most AIDS patients with PML.[620,635,638]

In some patients beginning HAART, there are lesions with contrast enhancement on MR imaging due to mononuclear infiltrates in the lesions. Patients with these findings tend to have a better prognosis. This variant of PML may be related to immune reconstitution following HAART.[634]

The prognosis with PML is not good, with a mortality of 30 to 50% within 3 months for most AIDS patients. A CD4 lymphocyte count above 100/μL is a favorable prognostic factor.[634] However, about 10% of patients may have a more prolonged course with remission. Spontaneous recovery is uncommon. Antiretroviral therapy may be of benefit. Intravenous cytarabine (Ara-C) has been utilized for therapy.[620]

SPINAL CORD.-- HIV infection producing a myelitis is present in only about 8% of AIDS cases. Vacuolar myelopathy of the spinal cord may be seen in one third of AIDS cases, and though it is probably a consequence of HIV infection, it is not usually associated with HIV myelitis. Vacuolar myelopathy is manifested only when vacuolization is severe, and it presents with slowly progressive spastic paraparesis accompanied by loss of vibratory and position sense and urinary frequency and urgency. In males, erectile dysfunction can be an early manifestation.[639] Vacuolar myelopathy is characterized mainly by vacuolar intramyelinic swellings of white matter, but also by infiltration with macrophages. Some vacuoles may appear in macrophages and axons. The vacuoles, 10 to 50 microns in size, usually appear in the posterior and lateral columns in a pattern similar to subacute combined degeneration. The disease starts in the mid to low thoracic cord and extends rostrally as it becomes more severe. The most severe lesions can also have clearing of macrophages from the centers of foci of involvement. Wallerian degeneration does not result from vacuolar myelopathy. The degree of gliosis does not correlate with the severity or duration of disease.[640] This myelopathy is not characteristic of pediatric cases, but decreased corticospinal tract axons and myelin does occur in children.[641] Magnetic resonance imaging (MRI) may suggest vacuolar myelopathy when there is increased signal symmetrically from affected white matter tracts on T2-weighted scans on contiguous slices.[642] Opportunistic infections of the spinal cord are uncommon.

OPPORTUNISTIC INFECTIONS AND NEOPLASMS.-- Toxoplasmosis, malignant lymphomas, cryptococcosis, and cytomegalovirus are the most commonly identified opportunistic infections and neoplasms in the CNS in patients with AIDS (Table 5).[342] Clinical use of Indium-111 WBC scintigraphy may aid in the detection of CNS inflammatory changes before either computerized tomography (CT) or magnetic resonance imaging (MRI) show structural changes.[546] A syndrome of inappropriate antidiuretic hormone (SIADH) may occur with central nervous system lesions.[643]

CYTOMEGALOVIRUS (CMV).—The prevalence of CMV in AIDS patients at autopsy has been declining from use of prophylaxis and therapy for CMV lesions outside the CNS, so that about 10% of cases show evidence of CMV.[629] There are no specific clinical findings seen with CMV in the brain. Nonspecific findings of disorientation, confusion, cognitive dysfunction, focal neurologic deficits, and impaired memory may be present, but these findings are similar to those of

HIV dementia. Half of AIDS patients with CMV involving the CNS have no neurologic problems. There is usually widespread dissemination of CMV when the CNS is involved, though isolated CMV infection of the CNS is also possible. Concomitant CMV retinitis may provide a clue to diagnosis. The abrupt onset of mental status changes, along with radiologic findings of hydrocephalus and periventricular or meningeal enhancement, may also suggest CMV meningoencephalitis.[620, 644]

Examination of cerebrospinal fluid (CSF) may reveal increased protein and a mild lymphocytic pleocytosis. Cells with inclusions are generally not seen in the CSF. There is a poor correlation between the appearance and degree of neurologic problems and the pathologic findings with CMV infection of brain. The most common pattern of involvement is an encephalitis which tends to be progressive with advancement in the course of AIDS. Grossly, there are no specific lesions to be seen.[644]

Microscopically, CMV can be the cause for a meningoencephalomyelitis. The most common locations for lesions are brainstem (pons or medulla most often), periventricular, basal ganglia, cerebrum (with cortex and white matter equally involved) and cerebellum. Lesions may also appear in the meninges or beneath the pia mater on gyral surfaces. Histologic patterns include ventriculitis, necrotizing vasculitis (which may be extensive), and microglial nodules. Large violaceous intranuclear and small basophilic intracytoplasmic inclusions can be present in ependymal cells, astrocytes, or even neurons. However, CMV inclusions can be difficult to find, even in the most common feature of microglial nodules.[343,627,644]

TOXOPLASMA GONDII.-- Toxoplasmosis of the brain can be a clinical presumptive diagnosis to define AIDS using the following CDC criteria:[320]

- Recent onset of a focal neurologic abnormality consistent with intracranial disease or a reduced level of consciousness; AND
- Evidence by brain imaging (computed tomography or nuclear magnetic resonance) of a lesion having a mass effect or the radiologic appearance of which is enhanced by injection of contrast media; AND
- Serum antibody to toxoplasmosis or successful response to therapy for toxoplasmosis.

Toxoplasmosis is the most common etiology for focal brain lesions in AIDS, and it occurs in 3% to 40% of AIDS patients, most often in the advanced stages of HIV infection. The prevalence of toxoplasmosis seen at autopsy has been decreasing with the use of prophylaxis, and now appears in <10% of cases.[629] In most cases, toxoplasmosis is probably the result of reactivation of latent infection, since IgM antibodies are lacking. Toxoplasmosis involving the brain is probably the result of hematogenous dissemination from other organs, since the CNS lesions are typically multiple.[620]

Clinically, the most common presenting symptoms are fever, headache, and confusion or altered consciousness. These non-specific findings occur in about half of cases, while specific neurologic deficits occur in about two-thirds of patients with CNS toxoplasmosis. The most common focal neurologic signs include hemiparesis, ataxia, and cranial nerve palsies. Seizures are less frequent.[620,645,646]

The lesions of toxoplasmosis on computed tomographic (CT) scans may resemble the findings of either abscesses or neoplasms. These CT findings include multiple lesions or focal lesions that appear as hypodense masses with ring or nodular enhancement and edema in more than half of cases. The radiologic lesions progress as enhancing nodules, and they may be distinguished from lymphoma by their increased number and decreased size. By magnetic resonance imaging (MRI), cerebral toxoplasmosis appears as hypointense on T1 weighted and as discrete high signal foci with moderate edema on T2 weighted scans; there is moderate to intense ring enhancement with contrast enhancement on MRI.[636,546,646] The appearance of hemorrhage, in the absence of corticosteroid therapy, is more indicative of toxoplasmosis than of malignant lymphoma.[647]

Diagnosis of toxoplasmosis cannot be routinely made by CSF examination, and serum antitoxoplasma antibodies, though usually present, may be absent. However, if *Toxoplasma*

serologic tests are positive and the CD4 lymphocyte count is <200/μL, then prophylaxis with trimethoprim-sulfamethoxazole may be useful.[161]

Toxoplasma gondii encephalitis produces necrotizing abscesses with acute and chronic inflammation, macrophage infiltration, and vascular proliferation. These lesions can be large and widespread; they usually are found in cerebral cortex, subcortical white matter, and deep gray nuclei. The numerous free tachyzoites at the periphery of necrotizing lesions are very destructive, and there is a significant inflammatory response with a variety of inflammatory cell types to them. True cysts or pseudocysts containing *T gondii* bradyzoites may not have accompanying inflammation until the wall of the cyst ruptures. Cysts may not be numerous. Often there is vasculitis, thought to be an allergic response, and endothelial proliferation in some blood vessels has been observed.

Toxoplasma gondii lesions may organize and contain numerous lipid-laden macrophages. A fibrous capsule with collagen, typical for brain abscess, can often be identified in surgical biopsies, along with a lymphoplasmacytic infiltrate. At autopsy, a fibrous capsule is less commonly seen and inflammation may be sparse, with scattered neutrophils. Healing may continue to form small less than 0.5 cm cystic lesions with macrophages and surrounding gliosis. Organizing and cystic lesions contain few detectable organisms. Immunohistochemical staining with antibody to *T gondii* helps to reveal the tachyzoites.[648]

Therapy with a combination of oral pyrimethamine and sulfadiazine results in a response for most patients with cerebral toxoplasmosis. Complications of skin rash and nephrotoxicity, usually from the sulfadiazine, occur in less than half of patients. Bone marrow toxicity of pyrimethamine can be ameliorated by concomitant folinic acid therapy. An alternative therapy consists of clindamycin with pyrimethamine. Treatment with leucovorin is often effective. Clindamycin and clarithromycin have also been used. Relapses are common, and mean survival is less than a year.[645,646] Life-long maintenance of pyrimethamine therapy (with or without sulfadiazine) is needed to prevent relapses. The lack of a response to antitoxoplasma therapy in 1 to 2 weeks may suggest the need to search for another diagnosis.[620]

CRYPTOCOCCUS NEOFORMANS.-- Cryptococcal leptomeningitis and encephalitis are seen in less than 5% of patients with AIDS at autopsy.[629] The lack of extensive inflammatory cell reactions to *C neoformans* from the immunocompromised status of AIDS patients may be the reason for lack of meningeal signs. The most common presenting features of CMV meningitis in AIDS include malaise, fever, nausea, vomiting, and headache. Encephalopathic features of lethargy, altered mentation, personality changes, and memory loss may occur.[367] Cranial nerve palsies, psychiatric abnormalities, and seizures are less frequent findings.[620] A subgroup of patients infected with *C neoformans* var *gattii* have multiple enhancing lesions by computed tomography, high cryptococcal antigen titers, papilledema, and a worse prognosis, though this variant is more likely to be seen in patients who are not immunocompromised.[649]

By computed tomographic (CT) imaging, cerebral cryptococcosis appears as hypodense, discreet lesions with or without contrast enhancement. By magnetic resonance imaging (MRI) scans, lesions appear hypointense and discreet when T1 weighted, but they appear as hyperintense "soap bubbles" that are well-circumscribed without edema when T2 weighted. The lesions are non-enhancing with contrast by MRI.[636]

Cerebrospinal fluid (CSF) examination is most helpful for diagnosis of cryptococcal meningitis by latex agglutination test for the antigen. Antigen may also be detected in serum. The India ink preparation is usually positive. Typical CSF findings include a mildly elevated protein, normal or slightly low glucose, and a lymphocytic pleocytosis. White blood cells and red blood cells may not be numerous in the CSF in patients with AIDS because of the poor inflammatory response to cryptococci. However, changes in serum titers of cryptococcal antigen during treatment for acute meningitis or during suppressive therapy do not correlate with outcome of therapy.[367,650]

The *C neoformans* organisms may be poorly encapsulated, and they are usually accompanied by a sparse inflammatory reaction with only a few lymphocytes or macrophages. Thus, a grossly apparent gelatinous exudate may not be present, though the patient may have

clinical signs and symptoms of a meningitis. A methenamine silver stain may be necessary to identify the organisms clearly in tissues.

For patients with CD4 lymphocytes counts <100/μL, prophylaxis with fluconazole or ketoconazole may be useful. Fluconazole is most often used for secondary prophylaxis, since many patients with treated *C neoformans* infections will have a recurrence without continued suppressive therapy. Treatment with amphotericin B, flucytosine, and triazoles (fluconazole, itraconazole) can be effective, though up to 30% of cases fail to respond to therapy.[161,324] For acute infections, intravenous amphotericin B followed by oral fluconazole has shown effectiveness. In some cases, institution of highly active antiretroviral therapy has resulted in immune reconstitution with exuberant inflammation around established foci of infection and onset of more severe symptoms.[367]

MALIGNANT LYMPHOMA.-- Most CNS non-Hodgkin lymphomas seen with AIDS are primary neoplasms. CNS involvement by systemic lymphomas is more often meningeal. Overall, about 10% of patients with AIDS have CNS lymphoma at autopsy.[629] CNS lymphomas are of the diffuse large cell variety, high grade, and of B-lymphocyte origin. They are essentially an expansion of EBV-infected B-lymphocytes.[470] Patients may present with non-localizing symptoms which include confusion, lethargy, and memory loss. Less frequent findings include hemiparesis, aphasia, seizures, cranial nerve palsies, and headache.

Primary CNS lymphomas may be diagnosed clinically by radiographic findings. By computed tomographic (CT) scans, the single or multiple lesions are hyperdense with solid or ring enhancement. When they appear as multiple discrete ring-enhancing lesions, they are very similar to those seen with toxoplasmosis. Computed tomographic scans may show the distribution of the lesions to be near a ventricle, in the basal ganglia, or near subarachnoid space. Mass effect and edema are frequently present.[464] By magnetic resonance imaging (MRI) the lesions are hyperintense with T1 weighting and isointense to hyperintense masses with moderate edema and mass effect with T2 weighting, and there is homogenous or ring enhancement with contrast.[636] Features that suggest malignant lymphoma, rather than toxoplasmosis, include: periventricular location (particularly in deep white matter), solitary lesion, homogenous enhancement of a lesion greater than 2 cm in size, and limited edema or mass effect.[647]

After radiotherapy, most lesions decrease in size, become hypodense, and no longer enhance with contrast medium.[651] Gallium-67 scintigraphy has a high sensitivity for detecting lymphoma. Thallium-201 scintigraphy may aid in distinguishing tumor from edema, post-therapy effect, and infections.[546] Widespread central nervous system lymphomas may shed cells into CSF that can be seen with cytologic examination.

Grossly, the most common pattern for CNS lymphomas is that of widespread infiltration without a discreet mass lesion, whether unifocal or multifocal. Most occur above the tentorium. Microscopically, they are often difficult to classify, particularly in small biopsies with extensive necrosis, though all are high grade and most are of an immunoblastic or large cell type. Almost all demonstrate bcl-2 gene expression.[652] Whether a prominent mass is seen or not, there is generally extensive perivascular spread in the brain or spinal cord. Necrosis may also be extensive. In about one fourth of AIDS patients with lymphoma, only the CNS is involved. Prognosis is poor, with survival of only a few months despite treatment.[620,626,627]

KAPOSI'S SARCOMA.-- Kaposi's sarcoma involvement of the CNS is extremely rare. It may represent widespread involvement.[653]

HERPES VIRUSES.-- Herpes simplex virus type 1 (HSV-1) is occasionally reported in the central nervous system in AIDS. Varicella-zoster virus (VZV) and even HSV-2 have been identified in the brain lesions of AIDS patients who have had a clinical and radiologic picture corresponding to that of progressive multifocal leukoencephalopathy (PML). Although these cases may mimic PML very closely, computed tomographic or magnetic resonance imaging scans can show evidence of hemorrhage, a mass effect, or gray matter involvement.[626,627] Grossly, areas of necrosis may appear most commonly in temporal lobe, inferior frontal lobe, insula, or cingulate

gyrus. Microscopically, the lesions can have petechiae with fibrinoid necrosis, perivascular mononuclear inflammatory cell infiltrates, and Cowdry type A inclusions in either neurons or glial cells. Immunohistochemical staining for HSV is helpful.

Herpes simplex virus infection of the CNS can have a varied clinical presentation, including confusion, fever, headache, anxiety, depression, and memory loss. The diagnosis can be made in most, but not all, cases by PCR performed on CSF. Most patients respond to therapy with acyclovir or valacyclovir.[654]

Varicella-zoster virus (VSV) involvement of the central nervous system with AIDS can have several patterns. There can be multifocal leukoencephalitis, mainly involving the deep white matter and grey-white junction. Ventriculitis and/or periventriculitis may be accompanied by vasculitis and necrosis of the ventricular wall. The large amount of virus present leads to the appearance of many intranuclear Cowdry type A inclusions. Also seen are acute hemorrhagic meningo-myeloradiculitis with necrotizing vasculitis, focal necrotizing myelitis, and leptomeningeal arterial vasculopathy with cerebral infarction. A characteristic VSV skin eruption may not be seen in cases of brain involvement. However, infections can involve skin, viscera, spinal cord, and brain. Patients may have headache, confusion, and focal weakness. The clinical course can be protracted. The syndrome of postherpetic neuralgia, which is the persistence of pain lasting for more than 4 to 6 weeks following resolution of the skin lesions of VSV, may be seen in 8 to 15% of persons with HIV infection, particularly those that are elderly.[376,655]

MYCOBACTERIOSIS.-- Mycobacterial infections of the CNS in patients with AIDS are uncommon. The diagnosis may be made by culture of cerebrospinal fluid or by acid fast staining of tissue obtained by biopsy or autopsy. Lesions seen with CNS tuberculosis include: small tuberculomas, abscesses, communicating hydrocephalus, and infarction. Most patients will have concomitant pulmonary tuberculosis. Radiographic findings that are helpful for diagnosis include: meningeal enhancement, enhancing parenchymal lesions, multiloculated abscess, basal ganglia infarction, and cisternal enhancement. The prognosis is poor.[656] *Mycobacterium avium* complex (MAC) in the CNS is uncommon and is usually an incidental finding at autopsy in patients who had disseminated MAC. No gross pathologic findings are typically present, but histologically there can be small foci containing lymphocytes and macrophages in a predominantly perivascular location. Clinical findings may suggest a meningitis and/or encephalitis.[657]

SYPHILIS.-- Persons with HIV infection have an increased incidence of neurosyphilis, reflecting the common risk factor of sexual transmission for both. The disease may be accelerated when immunosuppression worsens with the appearance of clinical AIDS. The involvement is usually meningovascular and, less commonly, an encephalitis. Findings can include: acute or chronic meningitis, cranial and peripheral neuropathies, dementia, cerebrovascular disease, and myelopathy. The CSF VDRL may be falsely negative in one-third to two-thirds of cases. High dose penicillin therapy may therefore be initiated based upon clinical suspicion.[658] However, serologic or clinical relapse may occur in one sixth of cases, more often in patients with a positive CSF VDRL or rash of secondary syphilis. Some patients may have repeated relapses. Relapses can occur over a year following initial therapy.[659]

MOVEMENT DISORDERS.— HIV-associated illnesses can be complicated by movement disorders. Tremors may be seen with HIV associated dementia (HIVD), with drug therapies such as trimethoprim-sulfamethoxazole, and rarely with opportunistic infections. Chorea may occur with lesions involving the subthalamic region, including those caused by HIV encephalitis, HIVD, PML, and cryptococcosis. Dystonia may occur with toxoplasmosis involving the basal ganglia, or with HIVD. Myoclonus can occur with HIVD and with infections, including toxoplasmosis, spinal tuberculosis, herpes zoster radiculitis, and PML. Parkinsonism, often atypical in presentation, can occur with HIVD as well as infections such as toxoplasmosis, PML, and tuberculosis.[660]

MISCELLANEOUS FINDINGS.-- Purulent leptomeningitis, bacterial cerebritis, and abscesses are often present in AIDS brains, particularly in persons with a history of intravenous

drug use. Bacterial infection is typically secondary to septicemia as a result of infection elsewhere, usually a pneumonia. Organisms such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae* should be considered in such a setting.[416,417] In a patient with gastrointestinal disease, *Listeria monocytogenes* should also be included as a possible pathogen.[418,420] A vasculitis with surrounding hemorrhage, or a septic infarct, are common microscopic findings.

In the absence of opportunistic infections and neoplasms characteristic for AIDS, cerebral infarction in HIV infected persons is not common. Up to 7% of AIDS patients at autopsy may show some evidence for cerebral infarction, but clinical findings to accompany these lesions were rarely evident. A vasculopathy often accompanies the ischemic lesions and consists of hyaline thickening of small vessels, perivascular space dilation, rarefaction, and pigment deposition, with vessel wall mineralization and perivascular inflammatory cell infiltrates in some cases. Intravascular thrombi are rarely observed. Similar features have been observed in the arterial vasculopathy accompanying HIV infection in children.[661]

In a small number of AIDS cases, there is extensive subarachnoid, intraventricular, or intracerebral hemorrhage without a demonstrable opportunistic infection or evidence of trauma. The cause may be a vasculitis from systemic bacterial infection, with the presence of neutrophilic infiltrates in and around small cerebral vessels. Central nervous system hemorrhages may be due to direct endothelial damage resulting from HIV infection.

An acute necrotizing encephalitis may be produced by *Trypanosoma cruzi* infection, and is distinguished from *T gondii* infection by the presence of amastigote-filled macrophages in the former.[662] Bacillary angiomatosis, caused by *Bartonella henselae*, can produce encephalitis, myelitis, cerebral arteritis, and retinitis.[663] Cerebral microsporidiosis can occur with dissemination from the gastrointestinal tract, with appearance of multiple small ring-enhancing lesions by magnetic resonance imaging, and appearance of the spores in cerebrospinal fluid.[406]

AIDS patients with disseminated blastomycosis have CNS involvement in half of cases. Dissemination is more likely with lower CD4 counts. The mortality rate is high.[524]

Cysticercosis has been reported in HIV infected patients. Neurocysticercosis is the most frequent helminthic infection of the central nervous system and is caused by *Taenia solium* larvae. Giant cysts and racemose forms of neurocysticercosis seem to be much more frequent in HIV-infected patients and may be secondary to an uncontrolled parasitic growth because of an impaired cell-mediated immune response.[664]

An infectious agent first called *Mycoplasma incognitus*, a strain of *Mycoplasma fermentans*, has been identified in brain tissue of some AIDS patients with acute or subacute encephalitis by use of immunohistochemical staining when no other opportunistic agent was found. Inflammation and necrosis may or may not be present with *M fermentans*. This agent has also been found in reticuloendothelial tissues and kidney.[437,665]

PERIPHERAL NERVE AND MUSCLE PATHOLOGY IN AIDS

PERIPHERAL NERVE.-- Many HIV-infected persons develop peripheral neuropathies and muscular weakness that can be detected through careful history and neurologic examination. The etiology is more than just muscle wasting from debilitation, for there may be clinical signs and symptoms of pain, paresthesias, electromyographic abnormalities, elevated creatine kinase, and muscle group atrophy. Polyclonal gammopathy is typically present in patients with neuropathies. Myelinated fiber loss in peripheral nerve may be seen in many adults with HIV infection.[666]

Criteria have been established for the clinical diagnosis of HIV-1-associated peripheral nervous system disorders. This classification requires laboratory evidence for HIV-1 infection for diagnosis.[618]

I. HIV-1-associated acute inflammatory demyelinating polyradiculopathy (HIV-1-associated Guillain-Barré syndrome)

PROBABLE (must have):

1. Guillain-Barré syndrome by previously published criteria, except:

   CSF mononuclear leukocyte count can be as high as 50 cells per mm^3

POSSIBLE (must have):

1. Other potential etiology present (must have *each* of the following):

   a. As above (see *Probable*) #1.
   b. Other potential etiology is present and the cause of (see *Probable*) #1 is uncertain.

2. Incomplete clinical evaluation (must have *each* of the following):

   a. As above (see *Probable*) #1.
   b. Etiology cannot be determined (appropriate laboratory investigations not performed).

II. HIV-1-associated predominantly sensory polyneuropathy

PROBABLE (must have *each* of the following):

1. Distal limb sensory symptoms (feet > hands) of a peripheral nerve nature (e.g., numbness, burning, or pain).

2. Neurologic examination confirming a distal, relatively symmetric polyneuropathy in which sensory abnormalities predominate.

3. Electrodiagnostic studies indicative of a polyneuropathy with features of both axonal loss and demyelination.

4. Normal CSF cell count and only minimal, if any, elevation of protein, with negative VDRL.

5. No other etiology (including toxic exposure to dideoxyinosine). Nerve biopsy may be indicated to rule out certain etiologies such as amyloid, but is not a requirement.

POSSIBLE (must have *each* of the following):

1. Other potential etiology present (must have *each* of the following):

   a. As above (see *Probable*) #1, #2, and #3.
   b. Other potential etiology is present and the cause is uncertain.

2. Incomplete clinical evaluation (must have *each* of the following):

   a. As above (see *Probable*) #1 and #2.
   b. Etiology cannot be determined (appropriate laboratory investigations not performed).

III. HIV-1-associated myopathy

PROBABLE (must have *each* of the following:

1. Symptoms of proximal lower and/or upper extremity weakness, documented by physical examination.

2. No other etiology (including toxic exposure to zidovudine). Electromyography (EMG) and muscle biopsy may be necessary to rule out certain other etiologies.

POSSIBLE (must have *each* of the following):

1. Other potential etiology present (must have *each* of the following):

   a. As above (see *Probable*) #1.
   b. Other potential etiology is present and the cause is uncertain.

2. Incomplete clinical evaluation (must have *each* of the following):

   a. As above (see *Probable*) #1.
   b. Etiology cannot be determined (appropriate laboratory investigations not performed).

Biopsy of peripheral nerve (typically sural nerve) rarely reveals an opportunistic infection as a cause for neuropathy, but there may be lymphocytic infiltrates and demyelination in peripheral nerve indicative of acute or chronic inflammatory demyelinating neuropathy. An immunologic mechanism is suggested by improvement of patients with inflammatory neuropathies undergoing plasmapheresis, corticosteroid, or intravenous immunoglobulin therapy. There are several types of neuropathy seen with HIV infection. Either autoimmunity, cytomegalovirus, or direct HIV infection may be an etiology for such peripheral neuropathies.[667]

The most common HIV-associated neuropathy, which tends to occur with advanced HIV infection with CD4 counts <200/μL, is distal sensory polyneuropathy (DSP). DSP clinically is manifested mainly by sensory symptoms in the feet and legs that can include spontaneous or evoked pain, but there can be loss of vibration and temperature sense. Though proprioception remains intact, the pain may be so severe that the patient cannot walk. The soles of the feet may be painful on palpation. Ankle reflexes may be reduced or absent. Examination of cerebrospinal fluid

may show a slightly elevated protein. The course of DSP is subacute to chronic. DSP typically manifests late in the course of AIDS, though it may occur earlier. DSP is predominantly an axonal neuropathy by electrophysiologic findings, but it may be difficult to distinguish from a toxic neuropathy from antiretroviral therapy, and many patients will have elements of both. The characteristic pathologic feature of DSP is axonal degeneration of long axons in distal regions, with a "dying back" pattern of degeneration. The density of both small and large myelinated fibers is reduced, but the density of unmyelinated fibers is reduced even more. DSP may exhibit variable lymphocytic infiltration of the perineurium.[666]

Inflammatory demyelinating polyneuropathy (polyradiculopathy) may occur in association with moderately advanced HIV infection with CD4 counts between 200 and 500/μL. There are two forms: chronic inflammatory demyelinating polyneuropathy (CIDP) and acute inflammatory demyelinating polyneuropathy (AIDP), Both typically appear early in the course of HIV, before the onset of AIDS. They are much less common than DSP. Both CIDP and AIDP manifest with motor and sensory symptoms. Examination of the cerebrospinal fluid may reveal an elevated protein and a lymphocytic pleocytosis. Electrophysiologic studies may show slow conduction, delayed latencies, and conduction blocks. The initial pathologic finding with CIDP is lymphocytic and macrophage infiltration with demyelination. More advanced findings include remyelination, onion bulbs, minimal lymphocytic infiltration, and a reduced density of both myelinated and unmyelinated fibers. The pathologic findings with AIDP are more heterogenous, resembling the findings of Guillain-Barré syndrome, with two forms. The more common form manifests with demyelination with macrophage and CD4 cell infiltration. The less common axonal form of AIDP shows minimal inflammation, no demyelination, and mostly changes of Wallerian degeneration.[666]

Mononeuritis multiplex (MM) may also be seen with moderately advanced HIV infection as a manifestation of a vasculitic neuropathy. It can occur anytime during the course of HIV infection. There may be cranial nerve involvement. Biopsy of MM shows epineurial and endoneurial necrotizing vasculitis. This vasculitis may be similar to the cryoglobulinemic vasculitis seen with hepatitis B and C infections.[666]

Progressive radiculopathy appears to be related to cytomegalovirus infection, typically late in the course of AIDS when CD4 counts are below 50/μL. Cytomegalovirus polyradiculopathy typically manifests as a cauda equina syndrome developing over a few days or weeks. There is mainly a motor deficit in an asymmetric distribution. A common initial finding is low back pain with radiation to one leg. This may be followed by urinary incontinence, saddle anesthesia, and progressive leg weakness. If the CMV infection is not treated, polyradiculopathy then advances to flaccid paraplegia with bowel and bladder incontinence, with death in a few weeks. Electrophysiologic studies show evidence of axonal loss in lumbosacral roots with later denervation potentials in leg muscles. Examination of the cerebrospinal fluid shows a low glucose, elevated protein, and a polymorphonuclear pleocytosis with 200 cells/μL. CMV can be demonstrated by culture or PCR analysis. Nerve biopsy is of minimal value, showing only minimal inflammation. At autopsy, however, both ventral and dorsal spinal nerve roots show extensive necrosis with vascular congestion, edema, and infiltrates of both neutrophils and mononuclear cells.[666]

A condition known as diffuse infiltrative lymphocytosis syndrome (DILS) that may mimic lymphoma can rarely involve peripheral nerve. In this condition, there is a pronounced angiocentric infiltration of peripheral nerve with CD8 lymphocytes and a vascular mural necrosis. It is associated with massive HIV proviral load within nerve, as evidenced by increased HIV p24 expression in macrophages infiltrating nerve.[482,666]

Autonomic neuropathies may appear late in the course of HIV infection, with or without evidence of peripheral neuropathy, in up to 12% of patients. Parasympathetic failure may present clinically as resting tachycardia, palpitation, and genitourinary dysfunction. Sympathetic dysfunction may be manifested by orthostatic hypotension and syncope, anhidrosis, and gastrointestinal disturbances.[666]

In early HIV infection, neuropathies may occur transiently. Cranial and peripheral neuropathies, most often facial nerve palsy, may accompany primary HIV infection. Findings

resembling Guillain-Barré syndrome may occur. A mononeuropathy resembling Bell's palsy has been observed.[666]

Use of the antiretroviral drugs in the category of nucleoside analogue reverse transcriptase inhibitors (NRTIs) including ddC (most common), ddI, and d4T, can be complicated by neuropathy and/or myopathy. The NRTIs contain azido groups that compete with natural thymidine triphosphate as substrates of DNA pol-gamma and terminate mitochondrial DNA synthesis. Zalcitabine, didanosine, and lamivudine may cause neuropathy; stavudine may cause either neuropathy or myopathy with lactic acidosis; zidovudine may cause myopathy. The NRTI induced neuropathy may present with numbness, tingling, and pain. The appearance is that of a painful sensory polyneuropathy. It can be similar to neuropathies seen in relation to HIV infection, but may be distinguished by a temporal relationship to drug therapy. HIV-associated neuropathy usually takes weeks to months to develop, while a neuropathy associated with antiretroviral therapy evolves more rapidly, usually after 16 to 20 weeks of treatment. This latter neuropathy appears to be dose-related, so lowering the dose or interrupting therapy may help to resolve the neuropathy. NRTI-specific peripheral neuropathy may be reversible when the drug is stopped.[666,668]

SKELETAL MUSCLE.-- There may be skeletal muscle involvement by a variety of conditions at all stages of HIV infection. Inflammatory myopathies can occur with HIV infection at any point in the course and are characterized clinically by proximal symmetrical progressive weakness, mostly of legs and neck flexors, over months. Myalgia, typically in the thighs, is present. Laboratory findings include a mild to moderately increased serum creatine kinase, while electromyographic studies are abnormal in 90% of cases. This HIV-associated myopathy resembles polymyositis and histologically may have muscle fiber necrosis, lymphocytic inflammatory infiltrates, and macrophages. An autoimmune etiology has been postulated, and is substantiated by the benefit afforded by corticosteroid therapy, non-steroidal anti-inflammatory agents, plasma exchange, or intravenous immunoglobulin therapy.[669]

Another form of HIV-associated myopathy is known as human immunodeficiency virus associated adult onset nemaline myopathy (HAONM). The skeletal muscle fibers in HAONM show marked intra sarcoplasmic changes, including the presence of small vacuoles and granular degeneration.[670]

Myopathy can be associated with nucleoside reverse transcriptase inhibitor (NRTI) therapy, including zidovudine and stavudine therapy. The appearance of this myopathy is related to a longer course of therapy (months). Patients present with insidious pelvic and shoulder girdle muscular weakness with myalgia. Serum creatine kinase is increased. Cessation of the drug leads to reversal and recovery in weeks to months, with earlier recovery when weakness is less severe.[668,669] The toxic effect appears to be directed at mitochondria, resulting in the hematoxylin-eosin-stained appearance of "ragged red" fibers.[204] Two-thirds of AIDS cases at autopsy reveal histologic abnormalities including disuse atrophy, denervation atrophy, and inflammatory myopathy, though opportunistic infections are rarely found.[671]

Sporadic inclusion body myositis, which is the most common inflammatory myopathy in persons over the age of 50, has been reported in association with HIV infection. The persistent HIV infection may provide super antigenic stimulation that results in an endomysial inflammatory response. HIV-1 has been detected within endomysial macrophages, but not the muscle fibers. The clinical, histologic, and immunological pattern is similar to that in non-HIV-infected patients.[672]

Pyomyositis is a disease that is endemic to tropical regions, but can occasionally be seen in conjunction with immunocompromised states, including HIV infection. Pyomyositis is a bacterial infection of skeletal muscle and is clinically marked by gradually developing fever along with localized muscle pain, swelling, and tenderness. Leukocytosis may or may not be present. The serum creatine kinase may not be elevated. Blood cultures may be positive in a sixth of cases. A history of trauma may have preceded development of pyomyositis. Pathologically, there is extensive necrosis of muscle with neutrophilic exudates. *Staphylococcus aureus* is the usual organism that is cultured. This condition is treated with surgical incision and drainage in conjunction with antibiotic therapy.[673]

Acute rhabdomyolysis is uncommon but may occur with several underlying muscular diseases with HIV infection. Rhabdomyolysis may appear with primary HIV infection or as recurrent or isolated rhabdomyolysis during the course of HIV infection. A drug-induced rhabdomyolysis can complicate antiretroviral therapy with didanosine. Late in the course of AIDS, rhabdomyolysis may occur from opportunistic infections. Sometimes the cause cannot be discerned.[674]

Other skeletal muscle findings include atrophy with HIV wasting syndrome. In wasting syndrome, there is reduction in lean body mass, while body fat stores are maintained. However, myopathy is not a feature of wasting syndrome.[675] Toxoplasma gondii may infrequently involve skeletal muscle late in the course of AIDS. Malignant lymphomas may infiltrate skeletal muscle. An HIV-associated myasthenia gravis syndrome has been reported.[669]

OPHTHALMIC PATHOLOGY IN AIDS

Clinical diagnosis for ocular diseases in patients with AIDS is most often made by funduscopic exam. Findings may include a noninfectious microangiopathy, consisting of cotton-wool spots with or without retinal hemorrhages. This retinopathy occurs in two thirds of AIDS cases but can also appear less frequently with HIV infection. Opportunistic ocular infections are frequent with cytomegalovirus (CMV) and infrequent with *Toxoplasma gondii*, *Pneumocystis carinii*, herpesviruses, *Cryptococcus*, *Candida*, *Histoplasma*, and atypical mycobacteria. Kaposi's sarcoma and malignant lymphomas may infrequently involve conjunctiva, eyelid, or orbital tissue. Neuro-ophthalmic lesions (cranial nerve palsies, optic neuropathy, papilledema) appear in less than 10% of AIDS cases but frequently accompany cryptococcal meningitis.[676,677]

Cytomegalovirus is the most common clinical and autopsy ocular finding in patients with AIDS. CMV retinitis may be seen in 30 to 40% of AIDS patients at some point in their course. This infection is most likely to occur when the CD4 count is below 100/μL, so patients receiving antiretroviral therapy are less likely to develop this complication. Patients with CMV retinitis typically present with progressive painless loss of vision that begins in one eye, but involvement may extend to both eyes if not treated. Other findings noted by patients include floaters, photopsias, visual field loss, and blurred vision.[342,676,678]

For presumptive clinical definition of AIDS, diagnosis of CMV retinitis is defined as:[320]

> A characteristic appearance on serial ophthalmoscopic examinations (e.g., discrete patches of retinal whitening with distinct borders, spreading in a centrifugal manner along the paths of blood vessels, progressing over several months, and frequently associated with retinal vasculitis, hemorrhage, and necrosis).

Relapse of CMV following treatment can occur in 20% of cases. Resolution of active disease leaves retinal scarring and atrophy with retinal pigment epithelial mottling. Cytomegalovirus retinitis may resolve to scarring and atrophy with retinal pigment epithelial mottling. Loss of vision may result from retinal destruction, optic nerve involvement, and retinal detachment.[678]

However, patients receiving antiretroviral therapy resulting in a rise in CD4 lymphocyte counts may experience spontaneous healing of CMV retinitis lesions, even in the absence of anticytomegalovirus therapy. Such patients may also have atypical features of ocular CMV infection, including moderate to severe anterior chamber or vitreous inflammation.[676] A so-called "immune recovery uveitis" may be observed in some patients starting successful highly active antiretroviral therapy (HAART), as a result of partial reconstitution of the immune system sufficient to allow an inflammatory reaction to develop against a previously subclinical CMV infection. Clinical features include decreased visual acuity and floaters. Though patients on HAART may have some progression of CMV retinitis, such progression typically occurs only in the first 3 months of therapy.[231]

Cytomegalovirus can be confirmed at autopsy by finding characteristic inclusion bodies in the choroid. About half of CMV retinitis cases have an acute inflammatory reaction. Treatment and/or long survival may lead to extensive degeneration with loss of cells of the retina. About 20% of AIDS patients with CMV retinitis may eventually develop retinal detachment. Persons receiving highly active antiretroviral therapy are less likely to develop retinal detachment.[677,679]

Clinically, CMV retinitis can produce loss of vision and on occasion severe discomfort, but symptomatology is lessened by antiviral therapy with ganciclovir or Foscavir (foscarnet). Cidofovir therapy can also be used and has the advantage of longer dosing intervals. Initial response rates exceed 80%, but recurrence of CMV retinitis can be as high as 50%, so the goal of therapy is to delay progression of disease.[342,680] When funduscopic examination reveals evidence for CMV and therapy is instituted, there is a decreased likelihood that the patient will have nonocular organ involvement by CMV.[677]

The second most common cause for retinitis in AIDS is infection with the Varicella-zoster virus (VZV), seen in 1 to 4% of HIV-infected persons, typically when there is involvement of the ophthalmic division of the trigeminal nerve. VSV can produce several patterns of ocular involvement. Acute retinal necrosis produces inflammation of the anterior uveal tract and peripheral circular necrosis with centripetal progression toward the posterior pole associated with vitreitis and occlusive periarteritis, leading to deceased visual acuity, ocular pain, neuritis, arteritis, phlebitis, scotomata, and narrowing of the visual field. Progressive outer retinal necrosis, or rapidly progressive herpetic retinal necrosis, occurs most often with advanced AIDS and is often bilateral with involvement of deeper retinal layers, macular involvement, retinal detachment, and outer retinal opacification.[376]

A retinal microvasculopathy may be observed in over half of AIDS cases. It is non-infectious, but the cause is unknown. Findings include cotton wool spots, intraretinal hemorrhages, and retinal microaneurysms. This condition is more likely to occur when the CD4 count drops below 100/μL. This condition is usually asymptomatic and transient.[676]

The eye is the most common extracerebral site for toxoplasmosis. The typical clinical manifestations of ocular toxoplasmosis include impaired visual acuity with blurred vision and visual field defects, photophobia, and redness. Chorioretinitis may be seen on funduscopic examination.[393] The lesions are often multifocal and bilateral. There can be moderate to severe anterior chamber and vitreous inflammation and pigmented chorioretinal scars, but hemorrhages are not common.[676]

Acute anterior uveitis has been reported as a reversible complication in patients receiving the drug rifabutin used to treat Mycobacterium avium-complex (MAC) infections. Persons who weigh more than 65 kg are at greater risk. Use of a lower dosage may help avoid this complication.[681]

Conjunctival microvascular changes may be observed in 70 to 80% of HIV-infected persons. Such lesions, best observed by slit-lamp examination, are typically asymptomatic and include segmental vascular dilation and narrowing, microaneurysm formation, comma-shaped vascular fragments, and sludging of the blood column. Keratitis, though rare, can lead to loss of vision. The most common causes are Varicella-zoster virus and herpes simplex virus.[676]

Lesions of the orbit around the eye may be seen. HIV-infected patients with infections at this site are likely to have a very low CD4 lymphocyte count. Reported bacterial agents include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Propionibacterium acnes* producing orbital cellulitis or panophthalmitis. Fungal agents include Rhizopus and Aspergillus that can spread intracranially. Orbital involvement with *Pneumocystis carinii* and *Toxoplasma gondii* have also been reported.[682]

LYMPH NODE PATHOLOGY IN AIDS

Lymphadenopathy is frequent in persons with HIV infection, occurring either as one of the earliest manifestations of infection or as a finding at any time throughout the clinical course of progression through AIDS.[36,151,683,684,685] At least one fourth of persons with AIDS have lymphadenopathy on physical examination at some time during their course. A wide variety of opportunistic infectious agents and neoplasms involve the lymph nodes of AIDS patients, though the most frequent are *Mycobacterium avium* complex (MAC), *M tuberculosis*, *C neoformans*, Kaposi's sarcoma, and malignant lymphomas (Table 5). Lymphadenopathy with characteristic histologic features, however, can be seen in the absence of opportunistic infections and is known as HIV-related lymphadenopathy.[683]

Sections of lymph node should be viewed under polarized light to determine if birefringent crystalline material is present, indicative of intravenous drug use. Mediastinal or periportal lymph nodes are best for this purpose.

HIV-RELATED LYMPHADENOPATHY.-- The histologic manifestations of HIV-related lymphadenopathy can be grouped into four major patterns: follicular hyperplasia without follicular fragmentation, follicular hyperplasia with follicular fragmentation, follicular involution, and follicular depletion. In general these patterns follow in the above sequence and parallel the decline in CD4 lymphocytes. With the exception of the follicular hyperplasia pattern with follicular fragmentation that is seen most frequently in inguinal and axillary lymph nodes, these patterns appear in lymph nodes throughout the body, regardless of the presence or absence of gross lymph node enlargement, and indicate that a single node biopsy will yield valid findings.[683,684,685]

The follicular hyperplasia pattern without follicular fragmentation demonstrates reactive follicular centers that vary widely in size and shape. The follicles may represent more than two thirds of the cross-sectional area of the lymph node and the follicular centers may occupy three fourths of the cross-sectional area. Within the follicles are tingible-body macrophages, mitoses, and large lymphocytes, plasma cells, and scattered small lymphocytes singly or in clusters. Small foci of follicular hemorrhage may also be seen.[683,685]

The follicular hyperplasia pattern with fragmentation shows follicles that encompass less than two thirds of the cross-sectional area of the lymph node. The interfollicular area contains large numbers of plasma cells, perisinus cells, sinus histiocytes, and immunoblasts. The network of dendritic reticulum cells is disrupted. Foci of hemorrhage appear in germinal centers, with necrosis and follicular infiltration by small lymphocytes as the process progresses. Mantle zones are reduced or absent. Warthin-Finkeldey type giant cells, or polykaryocytes that represent syncytia of HIV-infected lymphocytes, can be demonstrated in slightly less than half of lymph nodes with this pattern, or about twice as often as in nodes with the other patterns.[683,684,685]

The follicular involution pattern shows more pronounced overall hypocellularity than the preceding patterns. Follicular centers are still present but are somewhat smaller than with follicular hyperplasia patterns, lack tingible-body macrophages, lack mantle zones, and are often hyalinized (scarred). Arborizing post-capillary venules with high endothelia are prominent.[683]

The follicular depletion pattern has absent follicles. The lymph node cortex is narrow or undefined and the medulla occupies two thirds or more of the cross-sectional area. Small blood vessels appear prominent due to decreased overall cellularity, and scattered histiocytes appear in sinuses. Immunoblasts and/or plasma cells may be seen throughout the node. The depletion pattern is the most commonly recognized pattern with AIDS at autopsy.[683,684,685]

Prior to the onset of clinical AIDS (in the stage of HIV infection previously known as persistent generalized lymphadenopathy, as well as some cases of AIDS-related complex) the lymph nodes throughout the body are large but usually do not exceed 3 cm in size and they may vary in size over time. Most HIV-infected patients prior to onset of AIDS have follicular hyperplasia, with or without follicular fragmentation, while almost 90% of AIDS patients have follicular atrophy or depletion patterns. Though the lymph nodes in patients with AIDS can be

small, they are routinely enlarged from 1 to 2 cm. During the hyperplastic phase, germinal centers contain predominantly CD19+ B-lymphocytes, which may account for hypergammaglobulinemia. However, CD4 lymphocytes continue to decrease as a patient moves from follicular hyperplasia to depletion.[683,684,685]

Highly active antiretroviral therapy (HAART) can suppress viral replication and lead to partial reconstitution of the immune system. However, CD4 lymphocyte counts may not significantly increase. Abnormalities in lymphoid architecture persist with HAART. In one study, 89% of lymphoid tissues showed abnormal T lymphocyte populations, 43% showed absence of follicles, 43% showed hyperplasia, and 14% showed regression.[686]

EXTRANODAL LYMPHOID TISSUES.-- Findings similar to those seen in lymph nodes may occur in lymphoid tissues elsewhere in the body in patients with HIV infection. Enlargement of nasopharyngeal and palatine tonsils may be associated with airway obstruction, pharyngitis, and a visible mass lesion. Histologic changes are similar to HIV-related lymphadenopathy, and the appearance of multinucleated giant cells is quite suggestive of HIV infection.[687]

PEDIATRIC FINDINGS.-- Lymph node histopathologic changes with HIV infection in children may differ from those in adults. Findings reported at autopsy, mostly in association with deaths from AIDS, have included marked lymphocyte depletion, more selective follicular or paracortical atrophy, hemophagocytosis, hyperplasia, and lymphadenitis. About half of cases with lymphadenitis are due to an identifiable opportunistic infectious agent.[688]

MYCOBACTERIOSIS.-- Massive lymphadenopathy may indicate infection by *Mycobacterium avium* complex (MAC). Mesenteric and retroperitoneal lymphadenopathy due to MAC can demonstrate homogenous soft tissue attenuation by computed tomographic scan.[341] If the involvement is extensive, a grossly lemon-yellow cut surface of lymph node, similar in color to microbiologic culture plates, may be observed. Microscopically, MAC in lymph node is characterized by single cells, small clusters, or large sheets of pale blue striated macrophages without significant inflammation or necrosis with hematoxylin-eosin staining. Wright-Giemsa stains can give these macrophages the appearance of a Gaucher-like cell. Acid-fast stains will reveal the presence of numerous mycobacteria in the macrophages. A granulomatous reaction with giant cells, surrounding lymphocytes, fibrosis, caseation, and calcification is very rare.[348] In addition, MAC can rarely produce nodular enlargement of lymph nodes with a proliferation of fibroblast-like spindle cells in a storiform pattern, without vascular slits but with abundant acid fast bacilli, that is termed mycobacterial spindle cell pseudotumor. These macrophages are CD68 and S100 positive by immunohistochemistry.[351]

Mycobacterium tuberculosis (MTB) is being seen with increasing frequency as a complication of HIV infection. By computed tomographic (CT) scan, mesenteric lymphadenopathy with low attenuation suggestive of necrosis, and occasional soft tissue attenuation, can be due to MTB. Tuberculous peritonitis on CT scan reveals high-attenuation ascites along with peritoneal and omental nodules.[341] The sites for involvement with tuberculous lymphadenitis include cervical lymph nodes in virtually all cases, followed by axillary involvement in 82%, ilioinguinal in 54%, and epitrochlear in 36%. The nodal size ranges from 1 to 3 cm, and involvement is usually symmetrical. The presentation overlaps with HIV lymphadenopathy.[689]

Histologically with MTB infection there is usually a recognizable localized granulomatous reaction, including caseous necrosis. Langhans giant cells, lymphocytes, epithelioid macrophages, and fibrosis are present in variable numbers. Acid fast tissue stain reveals rod-shaped acid-fast microorganisms similar to that described in non-HIV-infected patients. The organisms in the lesions are never as numerous with *M tuberculosis* as with MAC.

FUNGAL INFECTIONS.-- Lymph node involvement with the dimorphic fungi *C neoformans*, *H capsulatum*, and *C immitis* is frequent because these infections are often disseminated. The lymph nodes may be moderately enlarged and pale or mottled. Visible granulomas are infrequent. Cryptococci appear as clusters of oval, narrow-based budding

organisms. The capsule is often missing so that the organism appears small enough to be confused with *Candida* or *H capsulatum*.[370] Epithelioid granulomas are usually absent with dimorphic fungi and any inflammatory reaction being sparse, giving a low power microscopic pattern of a clear or pale zone within the node.

Fungal organisms can be best demonstrated with a methenamine silver stain. Capsular forms of *C neoformans* appear prominent with PAS or mucin stains. Abundant clusters of small intracellular organisms are characteristic of histoplasmosis. These 2 to 4 micron organisms are usually found within macrophages. Toxoplasmosis or leishmaniasis may superficially resemble histoplasmosis. Methenamine silver stains the cell wall of *H capsulatum*, while the more delicate staining of PAS may reveal the nucleus. The microscopic appearance of large spherules with endospores indicates *C immitis*.

Lymphadenopathy with *Candida* organisms is rare but can occur in cases with widespread dissemination. Budding cells may be difficult to identify on hematoxylin-eosin staining, particularly when accompanied by necrosis. Tissue sections may show pale areas of staining in the subcapsular sinuses or sinusoids. An inflammatory reaction is usually sparse. When pseudohyphae are not prominent, these budding yeasts can be confused with *C neoformans* and *H capsulatum*. PAS or methenamine silver stains aid in differentiation. Definitive distinction may require microbiologic culture.

CYTOMEGALOVIRUS.-- Cytomegalovirus is identified very infrequently in lymph nodes, usually as part of a very widely disseminated infection. When CMV is present, it is most often seen within endothelial cells or histiocytic clusters in subcapsular sinuses, and inclusion bodies are not numerous. Pronounced inflammation, hemorrhage, or necrosis accompanying CMV in lymph nodes is very uncommon.[342]

OTHER INFECTIONS.-- Bacillary angiomatosis, which is caused by *Bartonella henselae* (formerly *Rochalimaea henselae*), may produce lymphadenopathy. Histologically, there may be a pattern of coalescent nodules which demonstrate a pseudoneoplastic proliferation of blood vessels with plump endothelial cells that have clear cytoplasm. The organisms can be best demonstrated by Warthin-Starry staining.[427]

Syphilitic lymphadenitis may occur in conjunction with HIV infection. The histologic appearance includes capsular fibrosis with fragmentation, follicular and interfollicular hyperplasia, vascular proliferation, plasma cell and plasmacytoid lymphocytic infiltration, and perivascular plasma cell cuffing in all or nearly all cases. Obliterative endarteritis is an infrequent finding, and spirochetes are demonstrated in a minority of cases. The microscopic findings are similar to cases in non-HIV-infected persons.[690]

KAPOSI'S SARCOMA.-- Lymphadenopathy may occasionally occur due to Kaposi's sarcoma (KS), though often there will be no grossly identifiable features. By computed tomographic scan, lymph nodes enlarged by KS may show high attenuation secondary to the increased vascularity of this neoplasm.[341] Microscopically, KS may present as a subtle capsular infiltration of lymph node that frequently accompanies a pattern of follicular hyperplasia or lymphocyte depletion. Such histologic features may be difficult to distinguish from an inflamed "cellular" capsule due to other causes. Features helpful in identification of KS include: presence of a definable mass lesion displacing normal nodal architecture, thickening of the capsule with infiltration of underlying subcapsular sinuses, presence of numerous plump spindle cells of uniform size bridging lymphatics and vascular spaces, appearance of a concomitant plasmacellular response, and positive immunohistochemical staining for endothelium-associated CD34 antigen or factor VIII-related antigen within the spindle to ovoid cells.

MALIGNANT LYMPHOMAS.-- Involvement of lymph nodes by non-Hodgkin lymphoma in the setting of HIV infection is less frequent than for either central nervous system or gastrointestinal tract. Lymph nodes may be secondarily involved with widespread systemic disease, with recurrence, or with progression of disease. AIDS-related non-Hodgkin lymphomas are of B-

cell origin and fall into two broad categories: (1) intermediate grade, classified as small noncleaved-cell (SNCLL) lymphomas (Burkitt or Burkitt-like lymphomas) in working formulation classification (Burkitt's lymphoma with or without plasmablastic differentiation in Kiel classification), or (2) high grade diffuse large cell (DLCL) lymphomas, either large cell immunoblastic lymphomas in working formulation classification (immunoblastic with or without plasmacytic differentiation in Kiel classification) or large noncleaved-cell lymphomas in working formulation classification (centroblastic diffuse in Kiel classification).[464]

Gross pathologic findings include one or more enlarged lymph nodes that are firm and tan-white. Necrosis may be prominent with immunoblastic sarcoma. Sometimes only focal lymphoma may be seen in lymph nodes. Occasionally, Kaposi's sarcoma and/or opportunistic infections, particularly *Mycobacterium avium-intracellulare*, may occur simultaneously with malignant lymphoma in the same lymph node. Demonstration of monoclonality by immunohistochemical methods may aid recognition of lymphoma.[464]

Other lymphoid malignancies can occur in patients with AIDS, but are not part of the definitional criteria for AIDS. They are seen with much less frequency. Hodgkin disease (HD) is more frequent in the general population than high-grade non-Hodgkin lymphomas in the age range (third to fifth decades) of higher prevalence of AIDS. However, HD is seen less frequently than high-grade lymphomas in patients with AIDS. HD that occurs in patients with AIDS more often demonstrates a high stage (III or IV), a propensity for extranodal involvement, an increased frequency of depleted and sarcomatoid morphologic features, and more often a mixed cellularity histologic type with fibrohistiocytoid stromal cells. The immunophenotype of HD in HIV infection is similar to that in persons without HIV infection.[467,468] Small cell lymphomas of follicular type appear in AIDS similar to those seen in individuals without HIV infection.

MULTICENTRIC CASTLEMAN'S DISEASE.-- Multicentric Castleman's disease (MCD) has been occasionally found in persons with HIV infection. A high percentage of these lesions have been shown to contain DNA sequences by PCR for the herpes-like virus, human herpesvirus 8 (HHV-8) that is also associated with lesions of Kaposi's sarcoma (KS). Over half of patients with MCD will also have KS The lesions of MCD with HIV infection appear similar to lesions in non-HIV infected patients. With CT imaging, there is hepatosplenomegaly mediastinal or peripheral lymphadenopathy, and pulmonary bronchovascular nodularity. Pathologic findings include small hyalinized germinal centers surrounded by concentric layers of small lymphocytes, vascular hyperplasia, hyalinized vessels, and large sheets of interfollicular plasma cells. Most patients will have a polyclonal gammopathy. The mean survival is a little more than a year, though treatment with vinblastine appears to prolong survival.[691,692]

SPLEEN IN AIDS

Splenomegaly is a common clinical finding in patients with AIDS, and it is present at autopsy in about one third of AIDS cases. Opportunistic infections or neoplasms are more likely to be present when the splenic weight is greater than 400 g. Weights of up to 1 kg can occur.[693] The most frequent splenic findings at autopsy are *M avium* complex (MAC), *M tuberculosis* (MTB), cryptococcosis, cytomegalovirus, Kaposi's sarcoma, and malignant lymphomas (Table 5).

Gross pathologic lesions consist of a prominent follicular pattern in about half of AIDS cases and a miliary granulomatous pattern in about 10%.[693] Sepsis may lead to a soft, almost liquid splenic parenchyma. Splenic infarcts may occur with embolization from non-bacterial thrombotic endocarditis or infectious endocarditis involving mitral or aortic valves.

OPPORTUNISTIC INFECTIONS.-- Either MAC or MTB can be associated with the appearance of granulomas. *Mycobacterium avium* complex is more likely to produce a myriad of small 0.1 to 0.5 cm soft tan miliary granulomas, while MTB often presents with fewer scattered and variably sized granulomas that are tan to white and firm. Microscopically, MAC granulomas are predominantly composed of macrophages filled with numerous mycobacteria. *Mycobacterium tuberculosis* produces a more typical histopathologic appearance with necrosis, epithelioid cells, lymphocytes, occasional Langhans' giant cells, and scattered mycobacteria.

Cytomegalovirus and *Candida* are infrequent and difficult to diagnose in spleen. They may be found within small foci of inflammation or necrosis that are not grossly evident and seen microscopically only with careful searching at high magnification, aided by methenamine silver or PAS stains.

The dimorphic fungi *C neoformans*, *H capsulatum*, and *C immitis* may also produce visible granulomas but they are never as numerous as the granulomas seen in mycobacterial infections. The fungal organisms are usually distributed throughout the red pulp and are often accompanied by proliferations of macrophages. Diagnosis is facilitated by use of methenamine silver or PAS stains.

Disseminated *P carinii* infection may involve the spleen. By computed tomographic scan, multiple nonenhancing, low-density masses with necrosis, hemorrhage, or peripheral calcification may be seen. Grossly, these are large, soft, friable, tan nodules which can have focal hemorrhage. The same foamy pink exudate seen in pulmonary alveoli is seen microscopically, but Gomori methenamine silver staining will demonstrate the cysts, though immunoperoxidase staining with monoclonal antibody to *P carinii* can be helpful when cysts are not readily identified.[341]

NEOPLASMS.-- AIDS-associated neoplasms involve the spleen less frequently than lymph nodes. Kaposi's sarcoma can be difficult to diagnose in the spleen because both grossly and microscopically KS can resemble splenic red pulp, and a mass lesion may not be apparent. Spindle cells with atypia in a definable nodule or subcapsular infiltrate help to distinguish KS. Malignant lymphomas occur in the spleen only one fifth of the time when they are present and appear either as nodular masses in regions of white pulp or as infiltrates in red or white pulp. The monomorphous nature of lymphomatous infiltrates with large cells is a helpful feature. Immunohistochemical staining may be necessary to confirm the diagnosis.

IDIOPATHIC THROMBOCYTOPENIC PURPURA.-- There is an increased incidence of idiopathic thrombocytopenic purpura (ITP) in patients with HIV infection. The appearance of ITP may precede development of clinical AIDS. Deposition of circulating immune complexes and complement on platelets and/or circulating anti-platelet antibody are thought to be mechanisms for HIV-associated ITP. In cases of refractory ITP, splenectomy has shown to be of benefit and does not affect the rate of progression to AIDS.[694]

HISTOLOGIC PATTERNS.-- A variety of histopathologic patterns of red and white pulp may appear in AIDS. There may be severe lymphocyte depletion with minimal or absent white

pulp, while in other cases macrophages in small groups or clusters (granulomas) may predominate. In both of these patterns, opportunistic infections or neoplasms are more likely to be present. However, when plasma cells and immunoblasts are prominent in red and/or white pulp, infections are not common. Overall, about 40% of AIDS cases have some opportunistic infection or neoplasm involving the spleen.[693]

In a majority of persons with AIDS, splenic hemosiderin deposition in red pulp is quite prominent. Iron stains will aid in visualizing these deposits. Examination of sections by polarized light may reveal crystalline birefringent material associated with intravenous drug use. Sometimes large foamy macrophages or multinucleated cells are found without identifiable infectious agents.

PEDIATRIC FINDINGS.-- At autopsy, young children and infants with HIV infection, most of whom died from AIDS, may show a variety of histologic changes in the spleen. These can include marked lymphocyte depletion of white pulp and hemophagocytosis. In addition, about half of cases may demonstrate so-called “kaposiform” lesions composed of foci with spindle cells admixed with plasma cells, capillaries and hemosiderin laden macrophages. Such foci bear a resemblance to Kaposi’s sarcoma with marked inflammation.[688] Splenic smooth muscle tumors, including leiomyomas and leiomyosarcomas, can appear in association with childhood AIDS and in association with Epstein-Barr virus infection.[485,695]

BONE MARROW AND PERIPHERAL BLOOD IN AIDS

PERIPHERAL BLOOD.-- Cytopenias are commonly seen in association with HIV infection. Anemia, thrombocytopenia, neutropenia, lymphocytopenia, monocytopenia, or combinations of any or all of these can occur in over 90% of patients with AIDS. The microenvironment of the marrow may also be altered by HIV infection of stromal cells including fibroblasts, endothelial cells, reticular cells, macrophages, osteoclasts, and steatocytes, resulting in dysregulation of hematopoietic cell growth with reduced hematopoiesis.[696]

Anemia is present in over half of patients early in the course of AIDS and in nearly all AIDS patients late in the course. The anemia is often normochromic and normocytic, typical of anemia of chronic disease, and iron stores are increased by measurement of serum ferritin. Though CD34+ stem cells poorly express CD4 receptors and, hence, are relatively resistant to HIV infection, mononuclear cells are infected and produce cytokines such as TGF-β, TNF-α, and IL-1 that suppress hematopoiesis. Cytopenias can be potentiated by drug therapy including zidovudine (ZDV), ganciclovir, amphotericin B, or trimethoprim-sulfamethoxazole and may require dose reduction or cessation of therapy. Though a positive direct antiglobulin test may be present in up to 43% of HIV-infected persons, hemolytic anemia is uncommon.[697]

Chronic B19 parvovirus infection may produce red cell aplasia in some HIV-infected persons, though it may not be severe in others.[698] Though it is not common, severe anemia from parvovirus B19 infection is treatable with intravenous immunoglobulin therapy.[699]

An iron deficiency type of anemia may prompt testing for occult blood in stool, the presence of which may suggest Kaposi's sarcoma or malignant lymphoma as a likely cause. Cytomegalovirus and fungal lesions produce gastrointestinal bleeding less often. Macrocytic anemias in AIDS are usually the result of chronic liver disease associated with chronic alcoholism or hepatitis, particularly when intravenous drug use is a risk factor, but they may also result occasionally from use of drugs that act as folate antagonists (trimethoprim-sulfamethoxazole).

Thrombocytopenia is commonly seen in about a third of AIDS cases, is rarely severe, and may result from peripheral consumption (splenomegaly, immune complexes) or from decreased marrow platelet production. Thrombocytopenia may also appear in some HIV-infected persons prior to development of clinical AIDS, and most cases are due to platelet consumption. In some cases the presentation is indistinguishable from classic idiopathic thrombocytopenic purpura (ITP) with increased megakaryocytes in the bone marrow along with peripheral platelet destruction. Unlike classic ITP, however, men are more often affected, and the antibodies are primarily directed against platelet glycoprotein IIIa (GPIIIa). There are also increased numbers of CD5+ B lymphocytes producing IgM rheumatoid factor and anti-GPIIIa.[163,696]

Thrombotic microangiopathies, including hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), have been reported with increased incidence in persons with HIV infection. The incidence appears to increase as HIV infection progresses, with an incidence of only 0.22% early in the course, but an incidence of 5.9% later in the course. In addition, HUS appears to occur in persons who have lower CD4 lymphocyte counts and who have other AIDS-related illnesses. In contrast, TTP appears most often when patients are asymptomatic. Overall, the death rate from HUS is 63% and from TTP 43%. At least four of the five classic findings (thrombocytopenia, microangiopathic hemolytic anemia, neurologic changes, renal manifestations, and fever) are present in 87% of cases of TTP. Neurologic problems and hemorrhagic complications are more likely to be seen with TTP. Seizures have been reported in 47% and coma in 14% of cases of TTP with HIV infection. The blood lactate dehydrogenase (LDH) is higher with TTP than HUS. With HUS, renal complications are more common, and a Shiga-like toxin producing *Escherichia coli* is likely to be found. Therapy with plasmapheresis is less likely to be successful with TTP in HIV infection than with sporadic cases in non-HIV-infected persons.[700] The incidence of thrombotic microangiopathy appears to be decreasing in the era of highly active antiretroviral therapy (HAART).[701]

Lymphopenia is present in about a third of AIDS cases due to the decrease in T4 lymphocytes. Neutropenia can be common in patients with AIDS and is a risk factor for both bacterial and fungal infections. The most common cause for neutropenia is drug therapy, and the drugs most often implicated are the antiretroviral agent zidovudine, the antibiotic combination of trimethoprim-sulfamethoxazole, and the antiviral agent ganciclovir. Additional causes may include chemotherapy for AIDS-related neoplasia and non-Hodgkin lymphomas. Neutrophilia may indicate bacterial sepsis. Bone marrow failure leading to death in patients with AIDS is very uncommon.[415,696,,697,702]

Neutropenia that accompanies HIV infection can increase the risk for infection or worsen the course of infection. Neutropenia can result from involvement of bone marrow by opportunistic infections, from pharmacologic therapies such as trimethoprim-sulfamethoxazole, and from direct effects of HIV through accelerated apoptosis. Both chemotaxis and phagocytic functions of neutrophils also appear to be impaired. The use of granulocyte colony stimulating factor (G-CSF) may aid in increasing neutrophil counts and preventing bacterial infections.[703]

Thromboembolic disease may be more frequent with AIDS, particularly in persons under the age of 50. Reported cases typically involve the venous circulation. Predisposing factors include opportunistic infections such as cytomegalovirus, AIDS-associated neoplasms, abnormalities of clotting factors, and autoimmune phenomena. The risk is increased for persons taking indinavir or megestrol acetate. Thrombosis is more likely to occur when the CD4 count is less than 200/μL.[697,704] The antiphospholipid syndrome has been reported in association with HIV infection.[705]

BONE MARROW.-- A bone marrow biopsy in an HIV-infected patient is most useful when there is a history of persistent fever, and no localizing signs are present, or when pancytopenia is present. Morphologic examination should be combined with microbiologic culture for suspected pathogens.[706,707] Mycobacterial infections (both MAC and MTB) are the most frequently identified opportunistic infections of bone marrow with AIDS, followed by *C neoformans*. However, the less frequently seen dimorphic fungi *H capsulatum* and *C immitis*, commonly involve bone marrow in cases in which they are present. Other opportunistic agents are quite rare at this site (Table 5). Culture of bone marrow can be useful for diagnosis of both mycobacterial and fungal infections.[350]

It is uncommon for grossly visible lesions to appear in bone marrow with any opportunistic infections or neoplasms. Severe pancytopenia may be accompanied by a generalized pale appearance.

Microscopically, a variety of non-specific morphologic abnormalities can occur. There may be overall hypercellularity early in the course of AIDS, or with systemic infections, and this is seen in about half to three fourths of cases. This is most often due to hyperplasia of granulocytic or megakaryocytic cell lines. Debilitation leads to increasing hypocellularity and serous atrophy of fat later in the course of AIDS. Additional non-specific microscopic findings may include immature or dysplastic myeloid precursors (dysmyelopoietic), lymphoid aggregates, atypical megakaryocytes, a fine reticulin fibrosis, mild vascular proliferation, histiocytosis with or without non-specific granuloma formation, and increased hemosiderin deposition.[708,709]

A fairly consistent finding is increased plasma cell cuffing of blood vessels, which may be accompanied by polyclonal hypergammaglobulinemia in over 80% of patients. The presence of giant pronormoblasts with inclusion-like nucleoli suggests parvovirus infection. Megaloblastic features often accompany zidovudine therapy or therapy with folate antagonists. HIV can also be demonstrated in a variety of marrow cells by *in situ* hybridization.[696,699]

Granulomas are infrequently present in bone marrow and may contain fungi, acid-fast organisms, occasional parasites, or polarizable talc crystals from intravenous drug use. These granulomas are typically not well-formed. Localized ill-defined granulomas consisting of collections of macrophages were more frequent than were granulomas containing organisms. Of the dimorphic fungi, *C neoformans* is seen most frequently. *H capsulatum*, next in frequency may produce loose lymphohistiocytic aggregates. Of the mycobacteria, *Mycobacterium avium* complex (MAC) is seen more frequently than *M tuberculosis*.[708] The most sensitive method for detection

of MAC remains blood culture. Culture of bone marrow aspirates will be positive in about half of cases of disseminated MAC. Acid fast staining of marrow biopsies is positive in about a third of cases, but is the most rapid method of detection.[710]

A hemophagocytic syndrome has been described in association with HIV infection, usually occurring late in the course of AIDS. An opportunistic infection or a lymphoid malignancy may be present in some cases. Diagnosis is made on bone marrow biopsy.[711]

Toxoplasmosis involving marrow may be subtle. Features can include interstitial edema, focal necrosis, and only a few scattered macrophages or clusters of macrophages. The tachyzoites and pseudocysts are found in or around areas of necrosis. Organisms may be found not only in macrophages but also in granulocytes and megakaryocytes.[712]

Parvovirus B19 infection may not always be detected by finding the presence of intranuclear pink inclusions within erythropoietic precursors. By the *in situ* hybridization technique, parvovirus may be detected in less than 10% of marrows in patients with AIDS. Infection is typically detectable late in the course of AIDS. Few infected patients have severe anemia.[698]

NEOPLASMS IN BONE MARROW.-- Non-Hodgkin lymphomas (NHL's) involve the bone marrow in about one fourth of cases in which they are diagnosed at autopsy. Bone marrow biopsy is of value in staging of these lymphomas.[706] The small noncleaved Burkitt or Burkitt-like lymphomas are more likely to involve marrow than those of a diffuse large cell variety. Low-grade lymphomas are seen far less frequently and are not part of definitional criteria for AIDS. Non-Hodgkin lymphomas that involve some other site in persons with AIDS are seen in the marrow in 25% of cases. Patients with bone marrow involvement with NHL are more likely to have meningeal involvement. Patients with marrow involvement are more likely to have high lactate dehydrogenase levels, fever, night sweats, and/or weight loss, and such patients tend to have shorter survival. Survival is decreased with >50% marrow involvement.[713]

Many AIDS cases occur in patients in the same peak age group range in which myelogenous leukemias and Hodgkin disease may be seen, but these entities not diagnostic for AIDS. Low-grade lymphomas must be distinguished from the benign reactive lymphoid aggregates found in about one third of HIV-infected patients. Such benign aggregates are usually not in a peritrabecular location, however. A plasmacytosis may be present in AIDS patients or in HIV-infected patients prior to development of clinical AIDS, but the proliferation is polyclonal, as demonstrated by immunohistochemical staining with antibody to lambda and kappa immunoglobulin light chains. Hodgkin disease associated with HIV infection has a propensity for bone marrow involvement.[464] Kaposi's sarcoma is very rarely seen in bone marrow, and when it does occur in marrow, is widely disseminated.[714]

Multicentric Castleman disease (MCD) involving bone marrow is characterized by the appearance of small lymphoid follicles with depleted germinal centers and a surrounding mantle zone containing plasmablasts containing human herpesvirus-8 (HHV-8) by immunohistochemistry. Surrounding sinusoids contain increased plasma cells. Patients often have pancytopenia.[715]

THYMUS IN AIDS

The thymus is not a significant site of pathologic lesions in adult AIDS patients. Thymic tissue in adults is not grossly prominent or microscopically cellular under normal circumstances, and is no different in patients with AIDS. Opportunistic infections are rare. Even malignant lymphomas, typically widespread in AIDS, do not involve the thymus.[716]

In adults infected with HIV-1, a B-lymphocytic follicular hyperplasia can be identified in thymic lymphoid tissue. The germinal centers are infiltrated by plasma cells. This hyperplasia is similar to that found in lymph nodes in the same HIV-infected person. Small numbers of lymphocytes can be shown to contain HIV-1 RNA, consistent with the role of the lymphoid tissue as a reservoir for HIV during the latent stage of infection.[717]

In pediatric AIDS, specific thymic pathology has been observed to consist of precocious involution, involution mimicking thymic dysplasia of congenital immune deficiency and/or thymitis. HIV may produce the lesions by injury to thymic epithelial cells. Severe, early thymic injury may be irreversible and further diminish cell-mediated immunity in infected children.[718]

Findings in the thymus at autopsy in pediatric patients with HIV infection, most of whom died from AIDS, may include severe lymphoid depletion with atrophy, microcystic transformation of Hassall's corpuscles, calcification of Hassall's corpuscles, plasma cell infiltrates, and Warthin-Finkeldey type giant cells.

Some pediatric patients may develop multilocular thymic cysts. These lesions are typically discovered incidentally by a routine chest radiograph that demonstrate an anterior mediastinal mass. The children have no symptoms related to these masses. By computed tomographic scan, the mass can appear multicystic. Histologic findings include distortion of thymic architecture with focal cystic changes, follicular hyperplasia, diffuse plasmacytosis, and the presence of multinucleated giant cells. The irregular cystic spaces are lined by a keratin positive flattened epithelium. No malignant changes occur. The presence of Epstein-Barr virus can be demonstrated in lymphoid tissue in some cases. In over half of cases, the mass decreases in size or resolves completely over time.[719]

ENDOCRINE ORGAN PATHOLOGY IN AIDS

Most opportunistic infections and neoplasms affecting the endocrine system in patients with AIDS occur when those diseases are widely disseminated. The most common endocrine organ affected is the adrenal gland (Table 5). A variety of endocrine disorders can be identified in patients with HIV infection and AIDS, but these are uncommonly life-threatening.[643,720]

ADRENAL.-- Though up to 90% of the parenchyma may be destroyed from pathologic processes seen with AIDS, frank adrenal insufficiency is rare and serum cortisol is usually not markedly reduced. Most HIV-infected persons have normal to elevated basal cortisol levels, probably from the stress of the complications of this illness, but reduced cortisol levels may also occur. Maximum cortisol levels and the rise of serum cortisol appear to be diminished with HIV infection. However, clinical evidence of some degree of adrenal failure with decreased cortisol and electrolyte alterations, such as hyponatremia, occurs in a majority of patients dying with AIDS. Hyporeninemic hypoaldosteronism of unknown cause has occasionally been observed to account for persistent hyperkalemia in AIDS.[643,720]

Drug-induced abnormalities can occur. The antifungal agent ketoconazole can be responsible for a reversible decrease in cortisol and aldosterone production, but it is rarely the cause for adrenal insufficiency. Rifampin therapy in patients with *Mycobacterium tuberculosis* infection has rarely been reported to cause adrenal crisis.[720]

Grossly, lesions of the adrenal are difficult to detect. Marked adrenal enlargement from any opportunistic infection is not common. Malignant lymphomas can on occasion cause unilateral or bilateral enlargement with white-tan to red variegated masses or infiltrates. Cytomegalovirus may produce a multifocal reddish mottling within the yellow cortex. Kaposi's sarcoma may infiltrate the peri adrenal fat or the substance of the gland in a linear dark-red to purple pattern. Adrenal glands may become enlarged as a result of stress in AIDS, though the total weight of both glands rarely exceeds 20 g.

Cytomegalovirus is the most common endocrine manifestation of AIDS at autopsy, occurring about three fourths of the time when CMV infection is present at autopsy. Identification of CMV within the adrenal glands may help to establish the diagnosis of AIDS, since adrenal may sometimes be the only tissue involved with this opportunistic agent. Cytomegalovirus may affect either the medulla or the cortex, or both. The medulla is more likely to be involved initially, with the cortex involved in a longer course or with more extensive infection. Hyponatremia with hypoglycemia may suggest adrenal insufficiency from involvement by cytomegalovirus.[344]

Microscopic changes found with CMV infection of adrenals vary from virtually no tissue reaction, through isolated clusters of small lymphocytes or focal hemorrhages, to extensive necrosis with polymorphonuclear infiltrates, to extensive fibrosis of cortex or medulla. These lesions may be accompanied by central venous thrombosis. The most common manifestation of CMV infection is clusters of small lymphocytes. These lymphocytes do not form reactive follicles. Small hemorrhages may also be present along with isolated small areas of necrosis. Whenever any of these changes are present, a careful search for CMV should be made. The greater the degree of necrosis, inflammation, or fibrosis, the more likely electrolyte or hormonal abnormalities will become apparent clinically.[344,721]

The CMV inclusions in adrenal are similar to those elsewhere, with large violaceous, dark red, or mauve intranuclear inclusion bodies surrounded by a clear halo beneath the thin nuclear membrane. An extensive amount of basophilic finely reticulated cytoplasm (basophilic inclusions) may draw attention to the CMV cell at low or medium power magnification. Cells with characteristic basophilic stippling are rare. The inclusions are larger than the nucleoli of medullary ganglion cells.

Adrenal involvement with other opportunistic infections and neoplasms usually occurs with widespread dissemination and is only diagnosed at autopsy. Malignant lymphomas are seen at autopsy in adrenal in one third of cases, followed by *Cryptococcus neoformans* infection in one

fourth, and *Mycobacterium tuberculosis* in one fifth. *Mycobacterium avium-intracellulare*, usually more common than *M tuberculosis*, is seen less frequently in adrenal (Table 5). In many cases the adrenal is only involved through superficial capsular infiltration from peri adrenal deposits of these agents or tumors. Thus, adrenal enlargement with these diseases is uncommon.

Despite the presence of adrenal CMV in over a third of all AIDS patients at autopsy, despite involvement of the adrenal with mycobacterial or fungal infections that microscopically are associated with necrosis and inflammation, and despite frequent clinical evidence for adrenal dysfunction, adrenal failure leading to demise is rare. Adrenal insufficiency accounts for less than 2% of all deaths in AIDS.[344]

THYROID AND PARATHYROID.-- The clinical finding of a "sick euthyroid" state in debilitated and/or hospitalized AIDS patients is not uncommon. This condition is characterized by decreased triiodothyronine levels secondary to diminished peripheral conversion of thyroxine. Patients with advancing HIV infection are noted to have elevated concentrations of thyroid binding globulin and a progressive decline in reverse triiodothyronine concentration. Hypocalcemia has been observed as a complication of pentamidine isethionate therapy. Therapy with foscarnet may also reduce serum calcium.[720] Both adults and children on highly active antiretroviral therapy (HAART) may have a high rate of thyroid disorders.[722]

These glands are rarely the site of involvement for any opportunistic infections or neoplasms diagnostic for AIDS (Table 5). Occasional CMV inclusions may be found at these sites when there is widely disseminated CMV. The same is true for *Pneumocystis carinii* and the dimorphic fungi. However, significant organ enlargement, atrophy, or failure does not usually ensue, probably because of the focal nature of involvement and because widespread involvement of a more critical organ--such as lung or brain--causes demise of the patient first. The serum total thyroxine (T4) and triiodothyronine (T3) concentrations may be increased because of an increase in thyroxine-binding globulin, the cause of which is unknown. Late in the course of AIDS, the T4 and T3 may fall slightly.[720] The whole blood calcium tends to be lower in patients with HIV infection, and both basal and maximal secretion of parathyroid hormone is reduced in patients with AIDS.[723]

PITUITARY.-- The pituitary gland is affected only infrequently by opportunistic infections, usually CMV. Lymphomas and Kaposi's sarcoma are not seen. Microscopic microadenomas or areas of basophilic hyperplasia within adenohypophysis are seen in up to 10% of AIDS cases at autopsy, though their significance is not known.[724] Pituitary lesions in AIDS are generally focal and typically not large enough to decrease pituitary function.

Clinically, hyponatremia is often seen in hospitalized patients with AIDS. In some cases this results from volume depletion, but in others it is caused by a syndrome of inappropriate antidiuretic hormone (SIADH) secretion. In most cases, SIADH can be attributed to opportunistic infections involving lung and brain. The drug vidarabine used to treat patients with disseminated varicella zoster virus infections may also cause SIADH.[720]

HEPATOBILIARY SYSTEM PATHOLOGY IN AIDS

The liver is frequently involved by a variety of diseases in patients with AIDS. At autopsy the liver is involved by opportunistic infections and neoplasms in about one third of AIDS cases but liver failure is an uncommon cause of death, occurring in less than 1% of AIDS cases. There may be a history of chronic liver disease from viral hepatitis, particularly in intravenous drug users or hemophiliacs. Chronic alcoholism may occur more often in persons with a history of intravenous drug use. If chronic liver disease is present, it is probably part of a process that preceded HIV infection, but the clinical course may be more aggressive than in the non-HIV-infected patient.[725,726,727,728]

Moderately elevated aminotransferase levels are found in adults with AIDS in one half to three fourths of cases but do not necessarily correlate with significant pathologic findings and may also be due to alcoholic liver disease or hepatitis. Both opportunistic infections and the pharmacotherapy for these infections may lead to transaminasemia. Alkaline phosphatase can be increased in half of the cases, and the most common cause is hepatic granulomata. Jaundice is not common, appearing in the course of AIDS in about 10% of patients. Abnormal liver function tests are unusual in pediatric AIDS. Lactate dehydrogenase is almost always elevated, often quite markedly, but this can occur with just about any opportunistic infection or neoplasm. Liver biopsy may yield diagnostic information, particularly when there is fever of unknown origin or the alkaline phosphatase is greatly increased, but the liver is only rarely the sole site of a significant opportunistic infection or neoplasm. Other sites may be sampled prior to liver.[605,725,726,727]

A common clinical and pathologic finding in liver with AIDS is hepatomegaly, seen in about two thirds of cases. Steatosis is a common histopathologic finding, but severe steatosis is uncommon. Causes for steatosis include diabetes mellitus, alcohol abuse, hepatitis B or C, obesity, HIV associated lipodystrophy, or antiretroviral therapy with nucleoside analogues.[729] Thus, these causes can be classified as non-alcoholic fatty liver disease (NAFLD).[730] The use of riboflavin may help to ameliorate the lactic acidosis.[731] Steatosis produces a diffusely hyperechoic appearance of the liver by ultrasonography.[732] Liver biopsy in adult AIDS patients will often show granulomas, and most of these are due to mycobacterial infection (Table 5). In some series, up to one third of cases had granulomas. HIV-1 has also been identified by immunohistochemical means within Kupffer cells and endothelial cells in liver, but this does not represent a major reservoir for HIV.[725,733]

In pediatric cases, granulomas are less frequent but giant cells more numerous, and lymphoplasmacytic infiltrates can be present in association with lymphocytic interstitial pneumonitis of lung. Focal fatty change is often present, sometimes with hepatocyte necrosis. Other frequent findings include portal chronic inflammation, portal fibrosis. Chronic active hepatitis is not seen. *M avium*-complex may produce a pseudosarcomatous reaction.[725,734]

MYCOBACTERIA.-- *Mycobacterium avium* complex (MAC) is the most frequent opportunistic infection involving the liver, found in slightly less than half of AIDS cases in which MAC is diagnosed. Associated clinical findings include fever and weight loss. Transaminases may be two to three times normal. *Mycobacterium avium* complex infection results in moderate to marked hepatomegaly but rarely produces grossly visible lesions. Tiny echogenic foci may appear on ultrasonography of the liver, though occasional larger lesions may be hypoechoic by ultrasound or show low attenuation by computed tomography.[341] The microscopic pattern of involvement consists of small clusters of striated blue macrophages with hematoxylin-eosin staining (and numerous acid-fast bacilli) scattered throughout the parenchyma in a portal to midzonal distribution. Adjacent liver parenchyma appears normal. Obstruction does not occur. *Mycobacterium tuberculosis* may be seen in liver with dissemination and produces small tan to white granulomas that are unlikely to result in hepatomegaly. The microscopic appearance of these granulomas includes typical features of necrosis, epithelioid cells, lymphocytes, occasional Langhans giant cells, and scattered acid-fast bacilli.[727,728]

FUNGAL INFECTIONS.-- The dimorphic fungi *C neoformans*, *H capsulatum*, and *C immitis* involve the liver frequently in disseminated infections, may be associated with mild abnormalities of liver function tests, but usually do not produce symptomatology from liver disease. Hepatosplenomegaly is common. These organisms do not often produce grossly conspicuous granulomas--discrete granulomas are present in less than 20% of involved livers with histoplasmosis. Cryptococcosis is the most frequently identified fungus in liver, seen in about one third of AIDS cases with *C neoformans* at autopsy (Table 5). These dimorphic fungi are most likely to have an infiltrative pattern of involvement with small numbers of organisms in portal areas. *H capsulatum* can be seen in clusters within macrophages. Accompanying inflammatory infiltrates and necrosis are usually not prominent; portal lymphohistiocytic infiltrates are the most common histologic finding.[559,728]

CYTOMEGALOVIRUS.-- Cytomegalovirus (CMV) can involve the liver in AIDS, usually in association with disseminated infections, and patients are rarely symptomatic just from hepatobiliary involvement. Alkaline phosphatase can be mildly elevated. A true CMV hepatitis is rare. Rarely, a granuloma or mass lesion can be produced. The characteristic inclusion bodies can appear in any cell in the liver, but they can be difficult to find.[726,728]

TOXOPLASMOSIS.-- *T gondii* are infrequently found and rarely produce a widespread infection in liver. The only evidence of their presence may be a rare cytomegalic cell or *T gondii* cyst found only after very careful searching at high power. A small focal collection of inflammatory cells may accompany them. In rare cases, a hepatitis with extensive necrosis may occur.[726]

KAPOSI'S SARCOMA.-- AIDS patients with KS have liver involvement only one fifth of the time (Table 5). The alkaline phosphatase is often elevated in these cases, because the Kaposi's sarcoma is often distributed around large portal vein branches at the hilum, along the biliary tracts, near the capsule, or even in the gallbladder. Sometimes the deposits of KS resemble small hepatic hemangiomas that are usually solitary and occur in about 2% of all persons. Microscopically, KS may have dilated vascular spaces similar to hemangioma, but hemangiomas will not have atypical spindle cells. In rare cases the KS infiltration is extensive enough to produce biliary tract obstruction or liver failure. Liver biopsy may miss the predominantly central and focal lesions of KS.[726]

MALIGNANT LYMPHOMAS.-- Non-Hodgkin lymphoma (NHL) may appear in liver in association with widespread dissemination and only rarely as a primary tumor. Persistent fever, tender hepatomegaly, mildly abnormal liver function tests and an elevated lactate dehydrogenase are typical clinical findings. By either ultrasound (US) or computed tomography (CT), NHL may produce solitary or, more often, variably-sized multiple lesions. A mass that is hypoechoic compared to surrounding hepatic parenchyma is a typical finding on US, while by CT there can be various patterns of enhancement after intravenous contrast material administration, including enhancement, a thin enhancing rim, or diffuse enhancement.[341] Lymphomatous infiltrates most often appear in portal zones, but if extensive can be found throughout the hepatic lobules. Large tumor masses are not common and may be identified by radiographic imaging procedures to direct biopsy for diagnosis. Lymphoma can be distinguished from nonspecific lymphocytic portal infiltrates by the larger monomorphous population of cells in the former, aided by immunohistochemical staining.[735]

HEPATITIS.-- From 70% to 90% of persons with a history of intravenous drug use have serologic evidence for hepatitis B virus (HBV) infection and up to 10 or 20% of all patients with HIV infection can have chronic HBV infection. HIV infection appears to be associated with increased viral replication and a greater carriage rate for HBV than in non-HIV-infected patients. Progression to AIDS results in decreased hepatitis B surface antibody and a greater likelihood of

reactivation of latent infection or reinfection with another viral subtype. Evidence for superinfection with delta agent (hepatitis D virus, or HDV) occurs in 25% of HIV-infected persons with HBV, and liver injury is worsened, with greater viral replication of both HBV and HDV. Persons with HIV infection should be vaccinated against HBV, but they also respond poorly to hepatitis B immunizations and frequently lose this protection.[725]

Non-A non-B viral hepatitis, mostly hepatitis C (HCV), is found in a third of HIV infected persons in Europe and North America, but in 80 to 90% of persons with a history of injection drug use. In HIV infected persons the incidence of chronic HCV infection is increased, the rate of hepatic fibrosis progression is accelerated, peripheral and intrahepatic HCV RNA levels are increased, and end-stage liver disease and cirrhosis develop more rapidly. Laboratory tests do not predict the histopathologic findings in the liver, and the alanine aminotransferase (ALT) value may not be elevated even though there is progression of disease. Liver biopsy is required to determine the extent of liver disease.[725,726,736]

There is no significant effect of HIV infection upon the clinical course of hepatitis A virus (HAV)infection. However, the duration of hepatitis A viremia may be prolonged in persons infected with HIV, with a higher viral load of HAV.[737]

Hepatitis G virus (GBV-C) is not associated with a known disease. However, coinfection with GBV-C has been shown to be associated with reduced mortality in persons with HIV. The rate of HIV replication in vitro in peripheral blood mononuclear cells has been shown to be inhibited by GBV-C. Approximately 40% of HIV infected persons can have coinfection with GBV-C.[172]

As survival increases with antiretroviral therapy for HIV, increasing numbers of cases of hepatocellular carcinoma occur in patients who have viral hepatitis, mainly hepatitis C. The course is more aggressive, with shorter survival, than in persons not infected with HIV.[738]

DRUG-INDUCED HEPATOTOXICITY.-- It is not surprising that hepatotoxicity can appear in the course of AIDS because patients are treated with a variety of pharmacologic agents. Half of patients receiving prophylaxis for *Pneumocystis carinii* with either trimethoprim-sulfamethoxazole (TMP-SMX) or pentamidine have elevations in transaminases or alkaline phosphatase that are two or more times normal, but severe hepatotoxicity is uncommon. Sulfa drugs can also cause a granulomatous hepatitis. Both ketoconazole and fluconazole used to treat fungal infections can be associated with transaminase elevations in 10 to 20% of cases. Agents used to treat *Mycobacterium tuberculosis*, such as isoniazid and rifampin, can produce enough abnormalities in liver function tests to alter the therapeutic regimen in 5% of cases. The antiretroviral agent didanosine (ddI) is associated with transaminase elevations in one third of treated patients.[728]

The protease inhibitors, and ritonavir in particular may be associated with elevation in transaminases, while saquinavir and indinavir more often are causes for hyperbilirubinemia. The risk for hepatotoxicity occurs five times more often for ritonavir than for other protease inhibitors. The overall rate of hepatoxicity with antiretroviral therapy is about 10%. The risk for hepatotoxicity appears to be increased in persons with hepatitis B or C infection, but 88% of persons with viral hepatitis B or C do not develop hepatotoxicity.[213,220] Immune reconstitution with highly active antiretroviral therapy (HAART) in conjunction with hepatitis C infection can lead to an increased risk for severe hepatotoxicity.[739]

Both nucleoside and nonnucleoside reverse transcriptase inhibitors can have hepatotoxicity with elevations in liver enzymes. In most cases these elevations are low and the patients remain asymptomatic. Higher elevations may occur with concurrent hepatitis B or C infection.[204,212] Severe steatosis is a potentially life-threatening complication of antiretroviral therapy with nucleoside reverse transcriptase inhibitors that is manifested by lactic acidosis. The greater the amount of hyperlactemia, the greater the mortality.[730]

MISCELLANEOUS FINDINGS.-- Hepatomegaly, seen in two thirds of cases, is frequently a result of steatosis. Steatosis (fatty metamorphosis), seen in about one third of AIDS patients on biopsy or at autopsy, is often of a mild to moderate degree and periportal in distribution,

may result from chronic alcoholism or other causes classified as non-alcoholic fatty liver disease (NAFLD). NAFLD may progress to non-alcoholic steatosis (NASH) and to cirrhosis. Continued hepatic mitochondrial injury plays a role in this progression.[730] Persons with a history of intravenous drug use are often likely to have a concomitant history of chronic alcoholism, with findings ranging from steatosis to portal fibrosis to micronodular cirrhosis, and polarizable talc crystals may be found in portal regions. Hepatomegaly may also result from acute or chronic passive congestion with cardiac failure, usually late in the course of AIDS. Hemosiderin deposition, particularly in Kupffer cells, is common in AIDS, though usually not as extensive as in spleen. It is potentiated by chronic disease and transfusion therapy and can be quite marked.[728]

Peliosis hepatis, the presence of multiple small blood-filled lakes in hepatic parenchyma without surrounding epithelium or endothelium, has been rarely reported in AIDS. It must be distinguished from Kaposi's sarcoma which has atypical spindle cells, whereas peliosis does not. Bacillary angiomatosis with small bacilli of the species *Bartonella henselae* identified singly or in clusters by Warthin-Starry staining or by immunocytochemical methods can be identified within peliotic spaces. Clinical findings include fever, lymphadenopathy, cutaneous or subcutaneous vascular lesions, osteolytic lesions, and abdominal symptoms. The CD4 count is typically <200/μL. The hepatic alkaline phosphatase is increased. Hepatic *Bartonella* infection may also manifest with multiple granulomas, often in the form of stellate abscesses surrounded by three distinct zones: an inner layer of palisading macrophages, an intermediate rim of lymphocytes, and an outer layer of fibrosis. This disease may respond to erythromycin therapy.[425,427,740,741]

Veno-occlusive disease (VOD) has been reported in patients with AIDS, particularly in persons with a risk factor for HIV infection of injection drug use. Pathologic findings of VOD are central vein obliteration and sclerosis, sinusoidal congestion and fibrosis, and perivenular hepatocellular degeneration and necrosis. The occurrence of VOD with AIDS may be related to the effects of multiple drugs.[742]

BILIARY TRACT.-- The biliary tract and gallbladder with AIDS may occasionally be involved by a variety of lesions including acalculous cholecystitis, sclerosing cholangitis, and papillary stenosis. Collectively, these lesions are known as AIDS cholangiopathy, and most patients who exhibit these findings have a CD4 count <200/μL. Acalculous cholecystitis is suggested by right upper quadrant or epigastric pain and low-grade fever, though jaundice is not common. Liver function tests demonstrate markedly elevated alkaline phosphatase, moderate transaminase elevation, and a normal or increased bilirubin. Acalculous cholecystitis is accompanied by marked dilation and edema with thickening of the gallbladder wall, bile duct dilation, intrahepatic duct dilation, and cholestasis seen on ultrasonography. By endoscopic retrograde pancreatography, patients may have a dilated common bile duct and narrowing in the distal duct consistent with papillitis or papillary stenosis. Intrahepatic ductal strictures are sometimes seen. Edema, necrosis, and ulceration can be seen pathologically.[725,728,743,744]

Infectious agents including *Cryptosporidium*, *Enterocytozoon bieneusi* and *Septata intestinalis*, and cytomegalovirus have been identified in patients with AIDS cholangiopathy or cholecystitis. About one fourth of AIDS patients undergoing cholecystectomy have gallstones. Nodules of Kaposi's sarcoma may occur, usually with widespread disease, at the liver hilum and lead to biliary tract obstruction, as can enlarged lymph nodes from MAC infection.[745]

AIDS cholangiopathy may manifest as a secondary sclerosing cholangitis that is suggested by the appearance of epigastric pain, fever, diarrhea, and increased alkaline phosphatase. The bilirubin may not be elevated. Diagnosis can be made by endoscopic retrograde pancreatography (ERCP) which may demonstrate stricturing, dilation, and beading of the biliary tract. Ultrasonography is often abnormal. At the time of ERCP, abnormalities of the pancreatic duct may also be apparent in half of cases. Sphincterotomy of the papilla of Vater may provide symptomatic relief. Liver biopsy can also be helpful for diagnosis. This disease appears to have no influence upon the prognosis with AIDS.[728,746]

CARDIOVASCULAR PATHOLOGY IN AIDS

The heart is not a frequent site for opportunistic infectious or neoplastic processes in patients with AIDS (Table 5). Most AIDS patients are in the third to fifth decades of life, at an age when cardiovascular complications from atherosclerosis are not as frequent as in older patients. Atherosclerotic cardiovascular disease leading to ischemia and infarction can and does occur in some AIDS patients, particularly as the numbers of HIV-infected persons begin to include older persons. However, the chronic debilitated state with cachexia brought on by AIDS may lead to regression of atherosclerotic lesions. Cardiac lesions are the immediate cause of death in less than 1% of AIDS patients. Clinical cardiac findings may be present in a fourth to three fourths of adult AIDS patients and may be accompanied by findings that include chest pain, tachycardia, electrocardiographic changes including various arrhythmias, effusions, and congestive heart failure. There may be mild cardiomegaly on chest roentgenogram and minimal electrocardiographic findings.[747]

Pericardial effusions may be seen in about 40% of persons with HIV infection. In most of these cases, the effusion is small and clinically insignificant. A specific etiology for the effusion, which can include a variety of infectious agents, is found in about a fourth of cases. Persons with AIDS who have a pericardial effusion, regardless of size, tend to have lower CD4 counts and decreased survival, compared to those without effusions. Though pericardial effusions are seen in the late stages of AIDS, they are rarely the cause of death. The findings of an elevated jugular venous pulse and pulsus paradoxus with "low pressure tamponade" may be masked by dehydration, Regardless of etiology, a large pericardial effusion in AIDS carries a high mortality, and treatment with a pericardial window is unlikely to prolong survival significantly.[747]

Cardiac tamponade is usually marked by dyspnea, fever, cough, and chest pain. Cardiac arrest may be an initial manifestation. Most cases have serosanguineous fluid. The most common etiology is mycobacterial infection, followed by neoplasms (non-Hodgkin lymphoma or Kaposi sarcoma) and bacterial infection. Most patients die from cardiac tamponade.[748]

Cardiac manifestations in pediatric AIDS are similar to those in adults. There does not appear to be an increased risk for congenital heart disease with HIV infection. Cardiac dysfunction is a manifestation of HIV infection in children, with a prevalence of 18 to 39%, and mortality is higher when there is decreased left ventricular function.[749]

MALIGNANT LYMPHOMA.-- A high grade non-Hodgkin lymphoma is one of the most common AIDS diagnostic disease seen in heart, occurring in about one sixth of AIDS cases when lymphoma is diagnosed at autopsy (Table 5). The serum creatine kinase is unlikely to be elevated. Grossly, lymphomas may produce a patchy pattern of infiltration with white streaks or distinct nodules. Despite the often widespread infiltration by malignant lymphoma, cardiac enlargement and failure are uncommon. Microscopically, the lymphomatous infiltrates extend in and around myocardial fibers, onto the endocardium, and over the epicardium. There is little myocardial fiber necrosis or inflammation resulting from such infiltration. These lymphomas can be classified either high grade (diffuse large cell) or intermediate grade (small noncleaved cell) types.[750]

KAPOSI'S SARCOMA.-- Kaposi's sarcoma, despite its vascular nature, is not often seen in the heart (Table 5). Cardiac involvement by KS is often limited to small subepicardial deposits in adipose tissue which usually do not produce clinically apparent problems. Microscopically, the appearance is no different than elsewhere, with atypical spindle cells around vascular slits accompanied by red blood cell extravasation. When KS does involve the heart, there is usually widespread visceral organ involvement, and pulmonary involvement will probably be of greater significance.[750]

INFECTIONS.-- Elevation of creatine kinase (CK) may commonly occur with myocardial toxoplasmosis. *Toxoplasma gondii* can produce a gross pattern of patchy irregular white infiltrates

in myocardium similar to non-Hodgkin lymphoma. Microscopically, the myocardium shows scattered mixed inflammatory cell infiltrates with polymorphonuclear leukocytes, macrophages, and lymphocytes. True *T gondii* cysts or pseudocysts containing bradyzoites are often hard to find, even if inflammation is extensive. Immunohistochemical staining may reveal free tachyzoites, otherwise difficult to distinguish, within the areas of inflammation. *T gondii* myocarditis can produce focal myocardial fiber necrosis. Heart failure can ensue. There may be regional differences in the incidence of *T gondii* myocarditis, perhaps because the natural reservoir of organisms persists more easily in humid environments.[391]

Other opportunistic infections of heart are infrequent. They are often incidental findings at autopsy, and cardiac involvement is probably the result of widespread dissemination, as exemplified by Candida and by the dimorphic fungi *Cryptococcus neoformans*, *Coccidioides immitis*, and *Histoplasma capsulatum*. Patients living in endemic areas for *Trypanosoma cruzi* may rarely develop a pronounced myocarditis.[662] Cardiac opportunistic infectious lesions in pediatric AIDS cases are not frequent.[749]

MYOCARDITIS.—A non-specific myocarditis composed mainly of mononuclear cells appears much more commonly than infectious organisms in the heart of AIDS patients microscopically. There is typically four chamber dilation. There are mononuclear cells distributed diffusely as single cells or in small clusters. Very minimal myocardial fiber ischemia or necrosis usually accompanies the myocarditis. A myocarditis may be found in one third AIDS cases at autopsy, but the etiology is found in only 20% of cases. Myocarditis with AIDS usually occurs in the absence of diagnosable opportunistic infections. Many AIDS patients with a history of clinical cardiac abnormalities have myocarditis at autopsy. HIV itself may cause T lymphocyte activation with cytokine release that potentiates myocardial damage. Histologically, mononuclear cells may also be seen as a mild epicarditis, which may account for some pericardial effusions.[747] Non-specific myocarditis can also appear in persons with a history of intravenous drug use independent of HIV infection, particularly when cocaine use is documented.[751]

AIDS CARDIOMYOPATHY.-- A congestive (dilated) cardiomyopathy in both adult and pediatric AIDS patients has been identified in 10 to 30% of cases. Most of these cases are idiopathic, for no specific opportunistic infection or neoplasm can be identified. Patients with symptomatic heart failure from dilated cardiomyopathy typically present late in the course of AIDS, have low CD4 counts, have myocarditis, and have a persistent elevation of anti-heart antibodies. At autopsy, there is four chamber dilation with a flabby, pale appearing myocardium. Echocardiographic findings include four chamber enlargement, diffuse left ventricular hypokinesis, and decreased fractional shortening. It is possible that cardiomyopathy and myocarditis are immunologic phenomenon resulting from HIV-containing lymphocytes in cardiac muscle.[747] Cytokine elaboration by inflammatory cells may contribute as well, since increased levels of both tumor necrosis factor-alpha and inducible nitric oxide synthase have been found in patients with HIV-associated cardiomyopathy.[752]

Cardiac myocytes have also been shown to be a direct target for HIV infection, which may result in cardiomyopathy.[753] A proposed autoimmune mechanism for myocardial damage is based upon the observation that autoantibodies to myosin and cell B receptor can be detected in HIV-infected patients with cardiomyopathy. This may occur when HIV alters myocardial cell surface proteins to elicit an immune reaction. A possible mechanism for an autoimmune contribution to myocardial damage is hypergammaglobulinemia with immune complex formation.[747]

DRUG TOXICITY.-- A number of pharmacologic agents may induce significant cardiac arrhythmias. These include amphotericin B, pentamidine, and interferon alfa. Bradycardia is seen in children treated with amphotericin B. Doxorubicin can produce cardiomyopathy. Interferon alfa administered as part of prolonged antiretroviral therapy may also lead to a dilated cardiomyopathy, as well as ischemia, and congestive heart failure. Zidovudine can produce mitochondrial changes in

striated muscle. Cocaine use in patients with a history of drug abuse may lead to myocarditis, contraction band necrosis, and cardiomyopathy.[747]

ENDOCARDITIS.-- Debilitation of patients with AIDS, particularly in the terminal course, may predispose to the formation of non-bacterial thrombotic endocarditis (marantic endocarditis). This is the most common form of endocarditis with AIDS and may be seen in about 5% of persons dying with AIDS at autopsy, most of them older than age 50. Such marantic valvular vegetations can occur on any valve and are probably agonal, although occasional infarcts in spleen, kidney, or cerebrum may result from pre mortem embolization.[747]

Persons with HIV infection whose risk is injection drug use (IDU) have an increased risk for infective endocarditis compared to HIV seronegative IDUs. Over 90% of cases of infective endocarditis with HIV infection occur in IDUs. *Staphylococcus aureus* is the most common pathogen, followed by *Streptococcus*, viridans group. Other agents may include *Salmonella* species, *Aspergillus*, and *Pseudallescheria boydi*i. The tricuspid valve is the most commonly affected valve, in over half of cases, but left sided valvular disease occurs in 45% of cases, and multiple valves are involved in 18%. The mortality rate is higher with multiple valve involvement and with lower CD4 counts. Most patients have a coexisting pneumonia or meningitis.[747,754]

ATHEROSCLEROSIS.-- Coronary artery disease may be seen in a specific setting in AIDS. Persons with HIV infection on highly active antiretroviral therapy (HAART) area at increased risk because the syndrome of HIV lipodystrophy, particularly with use of protease inhibitors, promotes atherogenesis. Acute myocardial infarction can occur, and persons with HIV infection have such an event at a younger age than the general population, and they have a higher incidence of subsequent ischemic events, with restenosis and stent thrombosis more likely following angioplasty.[755] In this syndrome, there is moderate hypercholesterolemia and marked hypertriglyceridemia along with insulin resistance and glucose intolerance typical for diabetes mellitus. These are findings characteristic of metabolic syndrome. Metabolic syndrome is defined by the presence of 3 or more of the following: a waist circumference >102 cm for men and >88 cm for women; a fasting triglyceride >150 mg/dL; an HDL cholesterol of <40 mg/dL in men or <50 mg/dL in women; a blood pressure >130/85 mm Hg; a fasting glucose >110 mg/dL. Lipid-lowering strategies with use of pharmacologic therapies such as fibric acid derivatives, along with insulin agonists including metformin and thiazolidinediones, can be employed.[756]

Myocardial infarction has been reported with use of HAART, with occurrence from 24 to 29 months following initiation of protease inhibitor therapy.[757] Plasma lipid levels increase in 90% of patients receiving protease inhibitor therapy. Smoking as an additional risk factor for atherosclerotic heart disease is seen in many of these patients.[758] Peripheral vascular atherosclerosis, however, may not be associated with lipodystrophy.[759]

VASCULITIS.-- Vasculitis associated with HIV infection may result from opportunistic infections, adverse drug reactions, and facilitation by HIV. Vasculitis involving small and medium sized arteries has been infrequently seen in patients with HIV infection. In about a third of cases, the pattern of vasculitis resembles a distinct type of vasculitis such as polyarteritis nodosa, Henoch-Schönlein purpura, or drug-induced hypersensitivity vasculitis. In the remaining patients, the vasculitis has variable features. Additional vasculitic patterns reported include Kawasaki-like syndrome, primary angiitis of the central nervous system, and erythema elevatum diutinum,.[760,761]

A vasculopathy involving large arteries including the aorta and its branches has also been described in young adults with AIDS. The features of this vasculopathy overlap with Takayasu's disease. With large artery vasculopathy there is a propensity for the appearance of single or multiple aneurysms. The appearance of these lesions appears due to leukocytoclastic vasculitis of vasa vasorum or small adventitial arteries. Medial fibrosis and vascular occlusion can occur. There can be angiogenesis with proliferation of slit-like channels in the adventitia. There does not seem to be an association of this vasculopathy with either atherosclerosis or with opportunistic infections.[762]

MISCELLANEOUS FINDINGS.-- Hemorrhagic pericarditis is uncommon and development of constrictive pericarditis unlikely.[747] Rheumatic inflammatory changes, ranging from rare scattered Anitschkow myocytes to well-formed Aschoff nodules similar to those seen in rheumatic heart disease, are rarely reported to occur in AIDS. However, chronic rheumatic sequelae of fibrosis or valvular disease have not been seen in AIDS.[763]

GENITOURINARY PATHOLOGY IN AIDS

The genitourinary system is occasionally affected by infectious agents seen in AIDS (Table 5). When either malignant lymphoma, cryptococcosis, or *Mycobacterium tuberculosis* is present with AIDS at autopsy, the kidney is involved about one fourth of the time. Despite the fact that HIV infection is most frequently spread by sexual means, lesions of the male and female genital tract with HIV infection are not frequent, and no specific direct effect of HIV has been documented at these sites. Clinical life-threatening urologic problems are rare in AIDS, but 10% to 15% of patients can have bacterial urinary tract and prostatic infections.[764,765]

Urinalysis may reveal mild proteinuria in some AIDS patients, particularly in those with CD4 lymphocyte counts <200/μL.[766] Hematuria is not common from opportunistic infections or neoplasms because such lesions are neither numerous nor extensive in the genitourinary tract (Table 5). Cytomegalovirus inclusions are not commonly observed in urine specimens. Decreased renal function may be associated with nephritis from drug therapies (amphotericin B, pentamidine, sulfamethoxazole). Acute renal failure with tubular necrosis may occur in the terminal course with AIDS.

Serum electrolyte abnormalities are relatively common with AIDS. Hypokalemia can be seen with chronic diarrhea and vomiting, while hyperkalemia is associated with metabolic acidosis and impaired renal function. Hyponatremia, which is present in up to a third of hospitalized patients with HIV-infection, can occur with diarrhea and with volume depletion, as well as with a syndrome of inappropriate antidiuretic hormone secretion (SIADH) from respiratory or CNS infections. Hyponatremia is a poor prognostic sign.[767]

A number of pharmacologic agents used to treat opportunistic infections seen in AIDS can lead to renal failure as evidenced clinically by elevated blood urea nitrogen (BUN) and creatinine measurements. The drugs foscarnet, didanosine, and pentamidine have been implicated in cases of hypocalcemia, while foscarnet may also predispose to hypercalcemia. Hyperuricemia can occur with didanosine therapy.[213,768]

Acute tubular necrosis (ATN) can occur from a variety of causes. Nephrotoxic ATN has been reported with several pharmacologic agents for opportunistic infections, including amphotericin B, pentamidine, and foscarnet. The antiretroviral agents cidofovir and ritonavir can also produce ATN.[767] Adefovir can produce toxic acute tubular necrosis.[202]

Several drugs have been implicated in production of crystal-induced acute renal failure and nephrolithiasis. The protease inhibitor indinavir has been associated with nephrolithiasis when crystallization occurred from inadequate hydration of patients taking this medication. Other drugs with this side effect include sulfadiazine, acyclovir, and foscarnet. This effect can be potentiated with lysis syndrome and high uric acid levels in patients treated for malignant lymphomas. Urinary tract calculi can occur with sulfadiazine and indinavir therapy.[767]

Acute renal failure from prerenal causes can occur from volume depletion with fluid loss from vomiting or diarrhea. Sepsis can lead to an effective volume depletion with similar outcome. Renal diseases leading to serious morbidity and mortality with AIDS can be seen in both early and late stages. Both acute renal failure as well as end stage renal disease can occur. Though not common, end stage renal disease may result from varied etiologies, including HIV nephropathy.[768]

HIV NEPHROPATHY.-- The kidney may show a so-called "HIV-associated nephropathy" (HIVAN), or HIV nephropathy (HIVN). About 50% of persons developing HIVAN have a history of injection drug use. In over 90% of cases the affected person is Black, though a few are Hispanic, and the disease is rare in Caucasians. HIVAN is characterized by marked proteinuria and a rapid progression to renal failure and end stage renal disease (ERSD). Patients are typically normotensive. Rising serum urea nitrogen and creatinine levels in a non-terminal patient may suggest nephropathy. For diagnosis of HIVAN, total protein excretion should exceed 100 mg/m^2 in a child or 200-500 mg in an adult. The proteinuria can reach the nephrotic range. Albuminuria and lipiduria are typically absent with HIVAN.[769,770,771]

Adults with HIVAN tend to progress rapidly to end stage renal disease and survival is only a matter of months, with those persons having just HIV infection living longer than those with clinical AIDS. In children, HIVAN has a less fulminant course. Most cases of HIVAN occur in association with AIDS as a late manifestation of HIV infection, accounting for the overall poor prognosis in adults.[772] The use of antiretroviral therapy slows the progression to renal failure.[773]

The kidneys with HIVAN can be grossly enlarged from 10 to 25%, appearing echogenic by ultrasound. However, they are not atrophic, even in the later stages. The most common renal biopsy finding, seen in over 80% of cases, is focal segmental glomerulosclerosis (FSGS). Diffuse mesangial hypercellularity is the most common pattern seen in children. Other histologic patterns that may be seen include membranoproliferative glomerulonephritis, minimal change disease, and membranous glomerulonephritis. A variety of other patterns can occur infrequently. Over half of renal biopsies in HIVAN will demonstrate collapsed glomeruli, and this finding, as well as findings of increased podocyte swelling, intracytoplasmic protein resorption droplets, and diminished hyalinosis serve to distinguish HIVAN from idiopathic FSGS and from heroin nephropathy.[769,770,771]

Tubulointerstitial changes are prominent and may be more severe than glomerular disease in HIVAN. The most prominent feature is microcystic tubulointerstitial disease, which accounts for the renal enlargement. Other changes may include tubular epithelial cell simplification, loss or attenuation of the brush border, enlarge hyperchromatic nuclei with nucleoli, numerous proximal tubular intracytoplasmic protein droplets, and lipid resorption droplets. The amount of interstitial, microcystic change, atrophy, edema, fibrosis, and inflammation is variable. The presence of tubular degenerative changes and tubular microcyst formation is more likely in HIVAN than heroin nephropathy. The tubuloreticular inclusions seen with HIVAN by electron microscopy are similar to the "myxovirus-like" particles of lupus nephritis.[769,770,771]

A subset of HIVAN cases have the predominant feature of collapsing glomerulopathy (CG) which is characterized by focal, segmental, or global glomerular capillary collapse with wrinkling of the basement membranes, obliteration of capillary lumens, disappearance of endothelial and mesangial cells, and hypertrophy and hyperplasia of adjacent visceral epithelial cells. Cases of CG are seen independent of HIV infection. CG appears to be more aggressive than the FSGS pattern seen with HIVAN. The HIV-associated form of CG appears to occur more commonly in blacks and on biopsy have more tubuloreticular inclusions in glomerular endothelial cells and more cast nephropathy than cases of CG in non-HIV infected persons.[774]

Mycoplasma fermentans (identified in some studies as the incognitus strain) has been identified within the lesions of HIVAN and in the urine of patients with HIV infection, but the etiology of HIVAN remains unclear and may include the effects of HIV or other viruses or immunologic disease.[437,665,775] HIV has been demonstrated in renal epithelial cells.[776]

Immune complex mediated glomerulonephritis may also occur in HIV-infected patients. The antigen that forms the basis for the immune complex formation is p24. A proliferative glomerulonephritis ensues and patients can present with proteinuria and renal failure.[777] In general, renal diseases other than HIVAN in HIV infected persons progress more slowly to renal failure.[773]

OPPORTUNISTIC INFECTIONS.-- These infections most commonly involve the renal interstitium in either cortex or medulla. Small inflammatory infiltrates composed of lymphocytes or macrophages usually accompany infection with *C neoformans*, *H capsulatum*, *T gondii*, or cytomegalovirus. *M tuberculosis* and *C immitis* may produce granulomas. *Mycobacterium avium*-complex produces small clusters of pale striated blue macrophages with hematoxylin-eosin staining. *Candida* produces small microabscesses, but renal abscesses may be present in up to 5% of AIDS patients with bacterial sepsis. Sometimes, small numbers of budding cells of fungal organisms can be seen within glomeruli, often without marked inflammatory reaction. Cytomegalovirus involves renal tubular epithelium in about half of cases with renal involvement by CMV. In remaining cases the CMV cells may be found in the interstitium or, less commonly, the

glomerulus. Cytomegalovirus in kidney may be accompanied by focal chronic inflammatory cell infiltrates.

NEOPLASMS.-- AIDS-associated neoplasms in the kidney occur when there is widespread involvement of multiple organs. Kaposi's sarcoma produces a few widely scattered small red to red-purple nodules anywhere from the perirenal fat to the renal capsule to the collecting system. One peculiar pattern of renal involvement seen in about half of cases with high grade lymphomas in AIDS is the appearance of one or several prominent mass lesions from 1 to 5 cm in size. These masses are firm, discreet, and have a white to minimally variegated red-white, lobulated cut surface. In remaining cases, the lymphomatous infiltrates are faintly visible to inconspicuous grossly.

MALE GENITAL TRACT.-- About half of male AIDS patients have clinical evidence of gonadal dysfunction with decreased libido and impotence that may be explained by decreased testosterone levels. The exact mechanism is not entirely clear. Both ganciclovir used to treat cytomegaloviral infections and ketoconazole used to treat fungal infections may decrease testosterone synthesis.[720]

The male genital tract has no specific pathologic changes resulting from HIV infection despite the fact that seminal fluid is a common vehicle for transmission of HIV. By in situ hybridization, HIV-1 proviral DNA can be identified within the germ cells at all stages of differentiation but without morphologic changes.[778] Immunohistochemical staining with anti-HIV monoclonal antibody has demonstrated the presence of HIV in both testis and prostate.[779]

The testis in AIDS shows an atrophy somewhat like that of chronic alcoholism--there is decreased or absent spermatogenesis, peritubular fibrosis and loss of germ cells--but opportunistic infections and neoplasms are rare. In severely debilitated patients, there may be marked tubular atrophy. Diffuse interstitial mononuclear cell infiltrates can occur but do not necessarily accompany opportunistic infections, which produce more focal inflammation.[780]

Over the course of HIV infection, histologic findings in the testicular tubules can include features of decreased spermatogenesis, spermatogenic arrest, and marked atrophy with only Sertoli cells. The use of antiretroviral therapy with prolongation of survival leads to greater numbers of infected males with tubular atrophy. However, even late in the course of HIV there can still be germ cells present, and the numbers of germ cells does not correlate with the CD4 count. Thus, the potential for spread of HIV infection through the sexual route from presence of infected testicular germ cells is variable but often present.[781]

Testicular neoplasms have peak incidence in young males and may be diagnosed in patients with AIDS, but they have not been shown to be associated with HIV infection. However, the incidence of germ cell neoplasms in persons infected with HIV is greater than that for U.S. males.[782] Therapy for testicular tumors may be successful in patients without advanced AIDS.[783]

Prostate and seminal vesicle are occasionally the site for KS and CMV when these processes are widely disseminated. One important finding in prostate is cryptococcal prostatitis, typically seen with disseminated cryptococcosis. Prostatic involvement may result in clinical difficulties in treatment because of the inability of antifungal agents to reach the prostatic glands in high concentration. Obstructive uropathy does not occur from these lesions.

FEMALE GENITAL TRACT.-- Opportunistic infections with AIDS are uncommon in the female genital tract. Vulvovaginal candidiasis occurs with higher incidence and greater persistence, but not greater severity, among HIV-infected women.[784] Additional sexually transmitted diseases, including gonorrhea, syphilis, and *Chlamydia* are also more frequently seen in HIV-infected persons and require appropriate diagnostic procedures and treatment. Kaposi's sarcoma and lymphoma are rare at these sites with AIDS.

Women with HIV infection are more likely to have concomitant human papillomavirus (HPV) infection, infection with multiple HPV subtypes (including the high-risk HPV16 and 18 subtypes), and have a subsequent higher risk for cervical intraepithelial neoplasia (CIN), particularly

high grade CIN, and invasive cervical squamous cell carcinomas. The immunosuppression induced by HIV leads to inadequate clearance with persistence of HPV infections.[785] The rate of cervical squamous intraepithelial lesions (SILs) in HIV-infected women is 4.5 times that of uninfected women, and 1 in 5 HIV-infected women with an apparently normal cervix will develop a SIL within three years.[488] Such patients are more likely to have symptomatic human papillomavirus (HPV) infections when the CD4 lymphocyte count is <200/μL, particularly with the viral types HPV-16 and HPV-18 that are more often associated with dysplasias and malignancies of squamous epithelium. Thus, these high grade squamous epithelial lesions occur both as a consequence of sexually transmitted HPV infection and through promotion by concomitant immunosuppression with HIV infection.[786] The 1993 CDC surveillance case definition for AIDS now includes HIV-infected women who have invasive cervical carcinoma.[320]

Pap smears should be obtained on women infected with HIV on a yearly basis, or at more frequent intervals if an abnormal Pap smear is obtained.[250] Cervical carcinomas in HIV-infected women are more likely to be invasive and have a worse prognosis than in uninfected women.[787] Marked debilitation with advancing HIV illness may lead to absence of normal menstrual cycles, a non-secretory endometrium, and ovarian atrophy with loss of follicles.

BREAST.—The breast can be involved with both benign and malignant diseases in persons with HIV infection. Benign conditions may include gynecomastia in males and increased adipose tissue deposition as part of the lipodystrophy seen in both men and women on highly active antiretroviral therapy (HAART). Gynecomastia is most likely to occur in men receiving HAART and is strongly associated with efavirenz therapy.[788,789] The breast may be involved by tuberculous mastitis. There is an increased risk for mastitis, and infections with *Pseudomonas aeruginosa* can be particularly severe. HIV infection is a contra-indication to breast implantation because of the risk for infection. Pseudoangiomatous stromal hyperplasia (PASH), a keloid-like stromal hyperplasia with myofibroblast and vascular proliferation, has been reported in association with HIV infection, and PASH can present as a rapidly enlarging mass lesion. Although there is no link between breast cancer and HIV infection, women with HIV who develop breast cancer do so at an earlier age, have a greater likelihood of bilateral breast involvement, and have an increased rate of metastatic disease. In addition to breast cancer, Kaposi sarcoma and non-Hodgkin lymphoma have also been reported in women with HIV infection.[790]

DERMATOPATHOLOGY IN AIDS

KAPOSI'S SARCOMA.-- Dermatopathology in AIDS primarily centers around diagnosis or exclusion of KS. Except for lesions caused by herpesviruses, lesions other than KS are quite uncommon (Table 5). Kaposi's sarcoma, also called "multiple idiopathic hemorrhagic sarcoma," was once a rare entity. Kaposi's sarcoma occurs in the following clinical patterns: classic (sporadic), endemic African (benign nodular, aggressive, florid, and lymphadenopathic), iatrogenic (seen in immunocompromised patients such as recipients of organ transplants, those patients on immunosuppressive drug therapy, or patients with connective tissue diseases), and epidemic (AIDS-associated). All forms of KS have a male predominance, but this is even more pronounced with AIDS. Though less common in other clinical forms, KS often has visceral involvement in AIDS. The appearance of all forms of KS is associated with infection by human herpesvirus 8 (HHV-8), also known as KS-associated herpesvirus (KSHV). [791]

A presumptive clinical diagnosis of KS indicative of AIDS can be made by CDC definitional criteria as follows:[130]

> A characteristic gross appearance of an erythematous or violaceous plaque-like lesion on skin or mucous membrane. (Note: Presumptive diagnosis of Kaposi's sarcoma should not be made by clinicians who have seen few cases of it.)

STAGING OF KAPOSI'S SARCOMA.-- A simple staging system for KS, which is useful when comparing and classifying the type of KS, is as follows: Stage I: locally indolent cutaneous KS; Stage II: locally aggressive cutaneous KS with or without regional lymph nodes; Stage III: generalized mucocutaneous and/or lymph node involvement; Stage IV: visceral KS. These stages are further subtyped by absence (A) or presence (B) of weight loss, persistent fevers, or night sweats.[445]

Additional criteria for staging of KS have been developed to determine prognosis and treatment based upon a three tiered (Tn In Sn) system as follows: T being the extent of tumor, I being the immune system status assessed by CD4 lymphocyte count, with “n” as 0 for CD4 lymphocyte count of 150/μL or less and 1 for higher counts, and S being the severity of systemic illness, with “n” as 0 - "good risk" or 1 - "poor risk". Good risk factors include all of the following: tumor confined to skin and/or lymph nodes and/or minimal oral disease (defined as non-nodular KS confined to the palate; lack of systemic illness defined as no history of opportunistic infection or thrush, no "B" symptoms, or performance status of at least 70 (Karnofsky). Poor risk factors include any of the following: tumor-associated edema or ulceration, extensive oral KS, non-nodal visceral KS; immune system status of CD4 cell count less than 150/μL; presence of systemic illness defined as a history of opportunistic infection or oral thrush, presence of "B" symptoms, performance status less than 70, or other HIV-related illness (e.g., neurologic disease, lymphoma). The "B" symptoms include: unexplained fever, night sweats, >10% involuntary weight loss, or diarrhea persisting for more than two weeks.[448,792]

HISTOPATHOLOGY OF KAPOSI’S SARCOMA.-- The histogenesis of Kaposi's sarcoma (KS) is unclear, but the spindle cells are of mesenchymal origin, with features of both endothelium and smooth muscle. Though KS tends to be multifocal, whether involving the skin or visceral organs, it is monoclonal in origin, similar to a true neoplasm.[460] An HIV gene product may be instrumental for inducing neoplasia, with cellular proliferation mediated by cytokines produced by the KS cells.[448] Kaposi's sarcoma in AIDS has three gross pathologic patterns of skin involvement: patch, plaque, and tumor.

The early lesions of patch stage KS are clinically as well as microscopically quite inconspicuous. These flat or macular bluish to reddish-purple lesions often resemble bruises. Cutaneous lesions may occur anywhere on the trunk and extremities but there is a propensity for

facial involvement. Lesions on the neck, upper trunk and arms may follow the skin cleavage lines in a dermatomal distribution pattern similar to the lesions of pityriasis rosea.[448]

The patch stage microscopically shows a superficial and perivascular proliferation of spindle cells. The spindle cells are arranged in parallel arrays around the vessels or beneath the epidermis. The involved vessels often appear straighter than usual and seem to cut through the dermis. Most often the neoplastic cells of KS are spindle-shaped, but they may also have a fusiform to epithelioid appearance. They have an eosinophilic cytoplasm and may have prominent round, oval, or fusiform nuclei. Atypical features of nuclear pleomorphism and hyperchromatism may not be pronounced. In the earliest lesions red blood cells may not be seen.

Helpful findings in very early KS lesions include individually necrotic cells, a mononuclear cell infiltrate, presence of epithelioid cells, dilated irregular vascular spaces, and perivascular distribution. This is followed by a marked increase in spindle cells along slightly widened spaces between the collagen bundles. With passage of time the perivascular spindle cell proliferation becomes more prominent, and spindle cell proliferation can be observed around the skin appendages. Red blood cells are present in the slit-like spaces in association with occasional deposits of golden-brown hemosiderin granules either free or within macrophages.[793]

The plaque stage is intermediate between the patch stage and the nodular or tumor stage, and it has some features of both of the latter. In its early phase it shows confluence of the proliferating spindle cells in the more superficial dermis and progresses to involve the deep dermis and/or subcutis. The lesions may show small clusters of capillary proliferations with rather plump endothelial cells. In these cases differential diagnosis from chronic vascular stasis changes (stasis dermatitis) of the lower legs may be difficult. In stasis dermatitis, newly formed capillaries are located close to the epidermis, are surrounded by an edematous to fibrotic dermis, and are often accompanied by hemosiderin granules.

The patch and the plaque stages of KS also show chronic inflammatory infiltrates which may be perivascular and/or diffuse and of varying severity. These infiltrates consist of lymphoid cells, plasma cells, and some macrophages. As a result of these infiltrates, early lesions of KS may resemble granulation tissue. However, the presence of atypical spindle cells, large protruding endothelial cells, extravasated erythrocytes, hyaline globules, and hemosiderin pigment should suggest a diagnosis of KS.

The tumor stage of KS is characterized by grossly visible red-purple nodules of varying size, usually 0.2 to 2 cm, on the skin. A solitary nodule may be present, but more likely there are multiple nodules that in severe cases may become confluent over a wide area. Microscopically, spindle cells are numerous, red blood cell extravasation is pronounced, and hemosiderin pigment is abundant. Neoplastic cell phagocytosis of red blood cells leads to intracytoplasmic slits and formation of erythrophagosomes that are the hyaline globules seen by hematoxylin-eosin staining.[794] The entire lesion appears as a mass, though it rarely has discreet borders, and infiltration around adjacent adnexal structures or into underlying adipose tissue is common. The overlying epidermis is usually intact.

Immunohistochemical staining for endothelium-associated CD34 or CD31 antigens may provide a useful marker for identification of both vascular and spindle cell components of KS and help to confirm a diagnosis in some cases. Moreover, lymphatic endothelium does not contain CD34. Factor VIII-related antigen will be found in the vascular portions of KS, but rarely in the spindle cell components. All KS cells will demonstrate positivity with immunohistochemical staining for vimentin. However, the tumor cells of KS do not always show positive staining for factor VIII-related antigen. Radiation or chemotherapeutic effect on KS may produce involutional changes including loss of atypical spindle cells, absence of vascular spaces, fibrosis, and extensive hemosiderin deposition. Flow cytometry of KS indicates that most are diploid, but a few demonstrate DNA aneuploidy. Mitotic counts are higher in more advanced stages of disease.[795] Using the polymerase chain reaction to detect human herpesvirus-8 (HHV-8) will help in distinguishing the lesions of KS from other neoplastic spindle cell proliferations in cytologic samples.[796]

On occasion, the lesions of Kaposi's sarcoma may contain acid fast bacilli in patients infected with *Mycobacterium avium*-complex (MAC). These proliferations must be distinguished

from the uncommon "mycobacterial pseudotumor" that contains MAC-infected macrophages forming a spindle cell proliferation. A fascicular arrangement of spindle cells with slit-like spaces, lack of granular eosinophilic cytoplasm, and presence of mitoses are features more consistent with KS. The presence of CD31 and CD34 and the absence of staining for CD68 and S100 by immunohistochemistry favors KS.[351]

The histologic appearances of KS can be helpful in assessment of prognosis in patients with AIDS. The appearance of an initial lesion on the lower extremities, presence of spindle-cell nodules, nodular form, absence of hemosiderin, and absence of irregular vascular spaces are all associated with increased survival. Nodular KS is associated with a 30 month survival, while patients with patch or plaque lesions survive for half this time or less. These findings are similar to survival curves with classic and endemic KS.[797]

A diagnosis of KS in fine needle aspiration (FNA) cytology specimens can be challenging. Cytologic features of KS seen in FNA specimens may include tissue fragments of overlapping spindle cells, loosely cohesive clusters of spindle cells, individual cells, bare oval nuclei with fine chromatin, prominent nucleoli, elongated cytoplasm with vacuoles, and metachromatic background stroma on May-Grünwald-Giemsa (MGG) stain. Nodular spindle cell vascular transformation as well as mycobacterial spindle cell pseudotumor seen in lymph node can have similar features on FNA. Demonstrating the presence of HHV-8 may help to distinguish KS from other spindle cell proliferations.[336]

DIFFERENTIAL DIAGNOSIS OF KAPOSI'S SARCOMA.-- Differentiation between granulation tissue and KS may be a diagnostic problem, although the cells of the latter should show atypism. Other lesions that may partially mimic KS include: bacillary (epithelioid) angiomatosis, capillary hemangioma, sclerosing hemangioma, pyogenic granuloma, papular angioplasia, amelanotic melanoma, and spindle cell squamous cell carcinoma.[798,799,800] An important point to remember is that in the absence of distinct features of KS, a conservative approach is recommended. Rather than mistakenly labeling a patient as having AIDS, it may be wise to obtain additional clinical information regarding HIV and immune status or defer a diagnosis of KS to a later date and repeat biopsy. A true lesion of KS will progress--with few exceptions--to a more diagnostic stage.

SKIN CANCERS.-- Squamous epithelial dysplasias and malignancies are most frequent in the perianal region, though squamous cell carcinomas may appear elsewhere. The appearance of such lesions may be associated with concomitant human papillomavirus (HPV) infection, which is frequent in HIV-infected persons, particularly when there is a risk factor of anal intercourse with other males.[489] Histologic features are similar to those in non-HIV-infected cases. There is a greater tendency for recurrence of squamous cell carcinomas of the skin in HIV-infected patients, reported at up to 20%, with standard forms of therapy, so close follow-up is necessary.[490]

Basal cell carcinoma is seen with increased frequency in HIV-infected persons, with an incidence of 1.8%, though its appearance does not appear to be associated with the degree of immunosuppression. These basal cell carcinomas tend to be superficial, multicentric, and located on the trunk. Standard forms of excision are effective.[489,490]

Melanocytic lesions have been reported in HIV-infected persons at a median age lower than the general population. Both dysplastic nevi and melanoma may occur in HIV-infected patients with no prior family history. There is a greater tendency for melanomas to have a greater depth and to metastasize sooner, compared to non-HIV-infected persons. The degree of immunosuppression, indicated by lower CD4 counts, appears to contribute to findings.[489,490]

HERPESVIRUSES.-- Anorectal herpes simplex virus (HSV) produces localized vesicles and ulcers that are chronic but cyclical in appearance and severity. They often respond to acyclovir therapy and may disappear following treatment. Microscopic examination of cytologic smears from the vesicles will show clusters of cells or multinucleated cells with ground glass nuclei.[801] Squamous epithelium shows ballooning degeneration of cells at the ulcer margin. Varicella zoster virus (VZV) infections in AIDS resemble those typical of other immunocompromised patients and

often follow a dermatomal distribution pattern.[380] Rarely, skin lesions of varicella zoster virus (VZV) may present with a verrucous pattern resembling a wart caused by papillomavirus. Such lesions histologically have little inflammation of the dermis, though characteristic multinucleated cells can be seen in the epidermis.[802] In most cases, both HSV and VZV lesions respond to acyclovir. Resistant strains may respond to foscarnet therapy.[803]

MOLLUSCUM CONTAGIOSUM.-- *Molluscum contagiosum* is a double-stranded DNA virus of the poxvirus family that may produce a self-limited cutaneous infection. It can appear in a widely disseminated form over the skin surfaces in persons with HIV infection. There can be cases with dozens of 0.2 to 0.6 cm firm tan to pink dome-shaped nodules or papules, or cases with fewer nodules but a wider size range up to 1 cm, or cases in which giant nodules >1 cm are found. The more florid verrucous form or cases of "giant" *Molluscum contagiosum* with very large nodules can occur at a late stage of AIDS when the CD4 lymphocyte count is <50/μL and the plasma HIV-1 RNA level is >100,000 copies/mL.[804,805]

The nodules or papules may have central umbilication and can appear widely scattered or in clusters. HIV-infected patients with *Molluscum contagiosum* are more likely to have head and neck involvement, typically the face, unlike immunocompetent patients in which lesions are most common on lower abdomen, genitalia, and thighs. Lesions may also appear less frequently on the trunk and extremities. Almost all cases occur in males.

The diagnosis can be confirmed by biopsy. The lesions of this poxvirus have the typical microscopic appearance with hematoxylin-eosin staining, with large prominent pink intracytoplasmic inclusions forming in lower epidermis and extending into a central cavity. *Molluscum contagiosum* infections associated with HIV-infection do not typically resolve spontaneously and tend to have a chronic relapsing course. The lesions tend to be more extensive when the degree of immunosuppression is greater, as indicated by a lower CD4 count or increased HIV-1 RNA level.[803]

CRUSTED (NORWEGIAN) SCABIES.-- Crusted (Norwegian) scabies, a highly contagious infestation of the mite *Sarcoptes scabiei*, can appear in patients with AIDS. Unlike skin involvement seen with ordinary scabies in immunocompetent persons, the pattern of distribution of lesions with crusted scabies is scalp, face, back, and nails. In its classic form, there are severe extensive hyperkeratotic nonpruritic lesions. Lesions may also appear as a papular, pruritic dermatitis or psoriasiform. The lesions contain numerous mites and can become secondarily infected with further complication of septicemia. Treatment with scabicides is effective, but must be continued for a longer period of time than for ordinary cases of scabies. The lesions of crusted scabies are quite contagious and health care workers can become infected. Diagnosis is made by skin scraping, particularly with sampling under fingernails, and if negative, with biopsy of a non-excoriated region.[806,807]

BACILLARY ANGIOMATOSIS. -- Bacillary angiomatosis, or epithelioid angiomatosis, is caused by fastidious gram-negative bacilli of the species *Bartonella henselae* (formerly *Rochalimaea henselae*). Clinically, this lesion may appear as multiple violaceous subcutaneous nodules or angiomatous papules. Histologically it is characterized by a pseudoneoplastic proliferation of dilated vascular channels in a circumscribed pattern resembling a pyogenic granuloma, but is distinguished by the presence of large plump, protuberant, occasionally atypical endothelial cells. These endothelial cells have an “epithelioid-like” appearance and often project into vessel lumens to give a tombstone-like appearance. The lesion differs from Kaposi's sarcoma by the presence of neutrophils with leukocytoclasis, by the absence of spindle cells or hyaline globules, and by resolution with antibiotic therapy (erythromycin).[404,427,800]

ACUTE HIV INFECTION. -- More than half of persons have symptoms associated with initial HIV infection, known as acute retroviral syndrome, though these manifestations are non-specific and resemble a flu-like illness or infectious mononucleosis-like illness.[151] About 75% of persons with acute retroviral syndrome will develop cutaneous manifestations, typically an

exanthem characterized by erythematous papules and macules on trunk and extremities, and sometimes the palms and soles. This rash lasts for about 4 to 5 days and then resolves completely. Seroconversion occurs later.[803]

BACTERIAL INFECTIONS.-- Staphylococcal skin infections are common in association with HIV infection. Skin involvement can manifest as impetigo, ecthyma, and folliculitis. With folliculitis, extensive neutrophilic infiltrates along with identifiable bacteria on gram stain are often seen histologically. Acne vulgaris may reactivate in the setting of HIV infection. Cellulitis may also occur and be severe enough to require hospitalization. Risk factors include indwelling catheters, injection drug use, and Kaposi's sarcoma. Most of these infections respond to therapy, but recurrence is common due to the presence of nasopharyngeal colonization by *Staphylococcus aureus* in up to half of patients.[803,808,809]

DRUG REACTIONS.-- Drug hypersensitivity eruptions or reactions commonly occur during treatment regimens for HIV infection and related conditions. Over three-fourths of patients with HIV infection have at least one dermatologic diagnosis made while receiving health care, and the frequency of such diagnoses increases as HIV infection progresses. About 8% of all dermatologic conditions seen in patients with HIV infection are drug reactions. The drugs with the highest rate of reactions seen are trimethoprim-sulfamethoxazole (over half of patients receiving this drug), sulfadiazine, trimethoprim-dapsone, aminopenicillins, and antituberculous medications.[803,810] Stevens-Johnson syndrome and/or toxic epidermal necrolysis has been reported in conjunction with antiretroviral therapy with either nucleoside or non-nucleoside reverse transcriptase inhibitors as well as protease inhibitors, generally within a month following the initiation of therapy, and there is a high mortality rate.[209]

The grossly visible lesions are most commonly morbilliform eruptions of erythematous papules and macules on the trunk and extremities. Less frequently, erythema multiforme with reddish papules and target-like lesions may occur on palms and soles. Other infrequent patterns of involvement include Stevens-Johnson syndrome and toxic epidermal necrolysis. Maculovesicular skin eruptions can occur as a consequence of antiretroviral therapy with zalcitabine (ddC).[200,253,803,810]

PAPULOSQUAMOUS DERMATOSES.-- A variety of papulosquamous dermatoses may occur in persons with HIV infection, particularly with CD4 lymphocyte counts less than 150/μL. The most common condition seen in HIV-infected persons is seborrheic dermatitis, which can occur at some point in up to 80% of this population. The lesions appear as scaly, erythematous plaques on scalp, eyebrows, nasolabial folds, and posterior auricular regions where sebaceous gland activity can be increased. In patients with HIV infection, seborrheic dermatitis tends to have a more rapid onset and be more extensive and severe than in immunocompromised patients. Previously limited lesions may acutely become more severe and extensive. Topical corticosteroid therapy can be effective therapy.[803]

An intensely pruritic papular eruption has been observed in HIV infected persons living in sub-Saharan Africa. This eruption consists of 2 to 8 mm erythematous papules that become excoriated, leading to larger papules and nodules up to 1 cm, with marked lichenification and hyperpigmentation. Microscopic findings in these lesions are most consistent with arthropod bites, including a wedge-shaped distribution of superficial to deep perivascular and interstitial lymphocytic and eosinophilic infiltrates beneath a slightly hyperplastic epidermis showing spongiosis at the site of the bite. These lesions may be a more pronounced hypersensitivity in persons with declining CD4 lymphocyte counts (<100/μL).[811]

Psoriasis may appear with slightly increased frequency in AIDS. It can be more severe, particularly with decreasing CD4 counts. A sudden onset, or an acute exacerbation of stable disease, is more likely in the setting of HIV infection. Therapies are similar to non-HIV-infected cases and include phototherapy, methotrexate, and retinoids. Some patients may also respond to zidovudine (ZDV) therapy.[803,812]

Reiter's syndrome is increased in frequency and severity in association with HIV infection. It includes the findings of arthritis, uveitis, and conjunctivitis, though only two of the three may be present in HIV-infected persons. The most common skin manifestation is keratoderma blenorrhagicum involving the soles, dorsum of hands and feet, nails, scalp, penis, and extensor surfaces of arms and legs. Lesions consist of erythematous-based hyperkeratotic yellow papules and plaques, with focal areas of pustules and vesicles. Lesions resembling those of psoriasis may be present, and treatment modalities are similar to psoriasis.[803]

Eosinophilic folliculitis seen in patients with HIV infection presents as an eruption of pruritic follicular papules in the head and neck region. Histologically, this eruption is distinguished histologically from suppurative folliculitis caused by bacteria such as Staphylococcus aureus by the lack of neutrophilic infiltrates and the predominance of lymphocytes and/or eosinophils at the follicular isthmus and sebaceous gland duct. Though infectious organisms may be identified in conjunction with eosinophilic folliculitis, they are considered non-pathogenic.[813]

Xerosis generalisata, or dry skin syndrome, present in 5% of AIDS patients, is characterized by fine diffuse scaling with severe pruritus unresponsive to antihistaminic therapy that histologically resembles irritant contact dermatitis. Other findings have included palmoplantar keratoderma, ichthyosis, and eczematous dermatitis.[799,808,810,812]

SUPERFICIAL FUNGAL INFECTIONS.-- Up to 20% of HIV-infected persons may develop an infection with one of the dermatophytes, typically at stage B or C. These infections, also known as ringworm or tinea, are caused by superficial fungal species in the genera *Trichophyton*, *Microsporum*, and *Epidermophyton*. Lesions are most commonly located on hands, feet, and groin region. *Trichophyton rubrum* is the most commonly identified dermatophyte. Tinea pedis, the most common form of dermatophytosis, is usually of the moccasin type, though the interdigital form is common, and the vesicular form infrequent.[809,814]

Tinea cruris or pedis may spread to produce tinea corporis, typically with truncal involvement. Even the penis and scrotum may be affected. The gross appearance is that of well-defined erythematous, scaly patches that are sometimes hyperkeratotic. In severely immunocompromised patients, lesions may have little inflammation and lack the elevated border and central clearing typical of tinea; instead they are seen as sharply marginated areas of hyperkeratosis resembling dry skin. Diagnosis can be made by examination of skin scrapings on a glass slide KOH mount. Treatment with topical antifungal creams may be helpful in treating tinea, as can oral griseofulvin or oral imidazoles.[803,814]

Tinea unguium involves both toenails and fingernails to produce onychomycosis. Though proximal white subungual onychomycosis is rare in immune competent persons, it is a marker for HIV infection. In this form, fungal elements spread under the proximal nail fold to establish an infection of the nail bed that spreads distally. This produces a white hue under the proximal nail plate in the region of the lunula. Long-term treatment with fluconazole and itraconazole can be effective treatment.[814]

Non-dermatophyte infections with *Malassezia furfur* may be associated with some cases of seborrheic dermatitis, with pityriasis versicolor, and with *Malassezia* folliculitis. Antifungal therapy with ketoconazole may be effective therapy.[814]

Superficial Candida infections can occur in HIV-infected persons, though oral candidiasis is far more frequent. The most common form of involvement of the skin is in intertriginous areas of groin or axilla. The hallmark of candidal intertrigo is the presence of satellite pustules. Pruritus ani can result from mixed infections with both bacterial and fungal organisms. Topical antifungal creams can help treat these superficial infections.[814]

The appearance of lesions of the skin may correlate with the level of immunosuppression. Seborrheic dermatitis and onychomycosis tend to occur in the early stages of HIV infection when the CD4 lymphocyte count is above 400/μL. Candidiasis and pruritus ani are more likely to appear when HIV infection has become symptomatic and the CD4 count is between 200 and 400/μL. Eosinophilic folliculitis typically occurs in association with clinical AIDS and CD4 counts below 200/μL.[814]

MISCELLANEOUS FINDINGS.-- Infectious and inflammatory dermatologic diseases are more likely to require medical attention and hospitalization in patients with AIDS than in patients without AIDS. Opportunistic infectious agents in AIDS with widespread dissemination, including fungal infections and *Pneumocystis*, may involve the skin and may produce appearances that can sometimes mimic KS or herpetic ulcers.[799,808,809]

Cryptococcal skin involvement may present in as many as 10% of patients with disseminated disease. The lesions are most often seen on the face, neck and scalp as erythematous papules, though pustules and umbilicated papules resembling *Molluscum contagiosum* can be seen. Ulceration is uncommon.[370] Similar findings may be seen with disseminated histoplasmosis and coccidioidomycosis.[803]

Histoplasmosis that involves skin and mucous membranes typically occurs in the advanced stage of AIDS. The morphologic appearances of mucocutaneous lesions can include papules, nodules, plaques, erythema multiforme-like lesions, vasculitic lesions , and exfoliative dermatitis. Additional clinical findings include weight loss, fever, chills, lymphadenopathy, hepatosplenomegaly, and anemia. Pathologic findings with skin biopsy may include: (1) necrotizing and non-necrotizing granulomatous inflammation with a paucity of intra histiocytic microorganisms , (2) diffuse dermal and intravascular accumulation of macrophages densely parasitized by *H capsulatum*, and (3) diffuse dermal karyorrhexis, collagen necrosis and interstitial, extracellular *H capsulatum*. The skin lesions may respond dramatically to treatment with antifungal therapy.[815]

Acanthamebiasis, though rare, is most likely to involve the skin in patients with AIDS and can lead to the appearance of pustules, indurated papules or plaques, ulcers, and cellulitis.[442]

Hansen disease (leprosy) does not appear to occur more frequently in persons infected with HIV, even in areas where Hansen disease is endemic. The long incubation time of Hansen disease may preclude development of more severe disease, but neither does HIV appear to accelerate existing *Mycobacterium leprae* infections.[816]

Cutaneous lymphomas can be seen with AIDS, typically at a later stage of disease. They are either CD30+ T-cell lymphomas or diffuse large B-cell lymphoma. Mycosis fungoides is rare in persons with AIDS. Cutaneous lymphomas in AIDS are typically localized nodules.[478] Late in the course of AIDS, cutaneous eruptions that histologically consist of a dense infiltrate of lymphocytes resembling mycosis fungoides may rarely occur. However, the CD8 lymphocytes that comprise these infiltrates are polyclonal.[817]

Multiple eruptive dermatofibromas (MEDF) can rarely be seen in patients with HIV infection, as well as with other autoimmune diseases and in persons receiving immunosuppressive therapy. These lesions most often appear on the extremities and the trunk. Most have been reported in males. Histologically, they are similar to dermatofibromas seen in patients without HIV infection.[818]

Skin lesions are characteristic findings of *Mycobacterium haemophilum* infection. These lesions tend to cluster on extremities and over joints where cooler ambient temperatures favor growth of these organisms. Septicemia is common, and the hematogenous dissemination allows *M haemophilum* to be cultured from a variety of body fluids and tissue sites. Joint involvement may produce arthralgia.[366] *Mycobacterium fortuitum* infection may present as subcutaneous nodules with necrosis in persons whose risk factor for HIV infection is injection drug use. Other mycobacterioses seen with AIDS such as *M avium* complex and *M tuberculosis* are unlikely to have cutaneous involvement.[803]

Skin testing that relies upon delayed-type hypersensitivity reactions can still be performed in HIV-infected persons. For children, the skin test reactions are qualitatively very similar to those seen in age-matched control subjects, though anergy with loss of responsiveness suggests a progression to AIDS. In adults with AIDS, the interpretation of tuberculin skin testing may need to be modified due to partial loss of cell-mediated immunity. About 10% of persons with a CD4 lymphocyte count >500/μL are likely to exhibit anergy, though a positive test in HIV-infected persons should be defined as any area of induration >0.5 cm (or >0.2 cm for intravenous drug users).[161,186]

PANCREAS IN AIDS

The pancreas in persons with AIDS may show opportunistic infections or neoplasms, evidence of recent or remote pancreatitis with hyperamylasemia, and acinar dilation. Opportunistic infections include mycobacteriosis, toxoplasmosis, cytomegalovirus (CMV), cryptococcosis, and pneumocystosis. Malignant lymphoma involves the pancreas in AIDS about twice as often as Kaposi's sarcoma (Table 5). In general, life-threatening pancreatic lesions are uncommon in AIDS and most opportunistic infections and neoplasms occur in pancreas in the setting of widespread dissemination. Non-specific pathologic changes may be seen in the pancreas in up to 90% of persons with AIDS. These changes may include acinar atrophy, decreased acinar cell zymogen granules, acinar nuclear abnormalities, steatosis with increased lipid droplets in acinar cytoplasm, and focal necrosis. The acinar atrophy and steatosis suggest a nutritional problem. [819,820]

Pancreatitis can occur in patients with AIDS. Hyperamylasemia can frequently be demonstrated in AIDS patients but often represents the effect of renal insufficiency or macroamylasemia associated with polyclonal gammopathy from B-lymphocyte activation. Pancreatitis can occur in association with opportunistic infections involving the pancreas, particularly cytomegalovirus. Serum amylase and lipase can be performed along with radiologic imaging procedures to demonstrate an enlarged pancreas and heterogenous peripancreatic tissue.[819] Most AIDS patients with acute pancreatitis do not have a severe course, and the prevalence of severe disease is similar to that of the general population, even though the etiologies are different.[821]

Pancreatic ductal changes may be observed in half of AIDS patients undergoing endoscopic retrograde pancreatography (ERCP). These changes, which resemble those of pancreatitis, are often seen in association with AIDS-related sclerosing cholangitis. The observed abnormalities may include dilations, short stenoses of the main pancreatic duct, and irregularities in side branches, all features that are suggestive of chronic pancreatitis. The serum amylase may be increased in these cases. Infection of the pancreatic or hepatobiliary ducts by CMV, cryptosporidiosis, microsporidiosis, or mycobacteria may produce irregular ductular narrowing and dilation which may resemble sclerosing cholangitis.[822]

Pediatric patients may have nonspecific changes in pancreas including edema, inflammation, fibrosis, ductular and acinar inspissated secretions, and macronesia. Though acute pancreatitis is reported in 17% of pediatric patients with AIDS, histologic changes of acute and chronic pancreatitis are typically mild at autopsy. Involvement by opportunistic infections is focal and rare.[823]

Antiretroviral therapy account for some cases of pancreatitis. The nucleoside reverse transcriptase inhibitors zidovudine, didanosine, and stavudine have been reported to produce pancreatitis. The use of didanosine in combination with hydroxyurea may produce a severe and fatal pancreatitis.[824]

Pentamidine administered either intravenously or by aerosol for treatment of *P carinii*, can sometimes produce acute necrotizing pancreatitis, even after months of aerosolized pentamidine therapy, and can be potentiated by further intravenous pentamidine therapy with higher systemic drug levels. Abdominal pain, along with increased serum amylase, suggests pancreatitis, which can recur when pentamidine is given again. In some cases, the onset may be rapid and the course short, ending in death. A grossly black to reddish-black pancreas with extensive necrosis but without extensive edema, fat necrosis, or hemorrhage is typical, and microscopic neutrophilic infiltrates may be minimal.[825]

Trimethoprim-sulfamethoxazole may produce pancreatitis. The antiretroviral drugs didanosine, zalcitabine, and stavudine can also cause acute pancreatitis, as evidenced by increased serum amylase and abdominal pain, and the risk increases with cumulative dose.[205,206,207] Patients at risk for drug-induced pancreatitis include those with previous pancreatitis, prolonged or high-dose therapy, additional pancreaticotoxic medications, and advanced stage of HIV.[200,819]

Pentamidine may also cause either hypo- or hyperglycemia. Hypoglycemia results from beta cells in the islets of Langerhans and may be seen in up to one third of treated patients from one to several weeks after initiating therapy. Abnormalities in regulation of glucose are more frequently observed when there is also pentamidine-induced nephrotoxicity.[720,819]

PREGNANCY AND THE PLACENTA IN AIDS

HIV infected women should be monitored with viral loads every month until the virus is undetectable and then every 2–3 months, along with CD4 counts each trimester. Resistance testing can be done if they have recently seroconverted or if they have failed therapy. HIV infected women in labor can be treated with either: 1) zidovudine in labor and 6 weeks to the neonate, 2) nevirapine, a single dose to the mother in labor and a single dose to the neonate, 3) zidovudine–lamivudine in labor and to the neonate for 1 week, or 4) both nevirapine as above and the zidovudine regimen as above. Cesarean delivery should be recommended to all women with a viral load greater than 1000 copies. Discontinuation of highly active antiretroviral therapy in the postpartum period is appropriate in those circumstances in which it would not have been used in the first instance if the woman had not been pregnant.[235]

There is no solid evidence to suggest that pregnancy accelerates the progression of HIV infection to AIDS in women, though pregnancy increases the infectivity of women to sexual partners.[170,826] Pregnancies in HIV-infected women are more likely to result in prematurity, intrauterine growth retardation, spontaneous abortion, and perinatal death.[167] The 50% rate of HIV infection in stillbirths from HIV-infected mothers is much greater than that for liveborns, suggesting that fetal HIV infection increases fetal demise.[827]

The placenta in mothers with HIV infection has been shown by immunocytochemistry and *in situ* hybridization to contain HIV-1 antigen by 8 weeks gestational age. Placental tissue also contains cells with CD4 receptors, and HIV infection can occur with transplacental spread of HIV to the fetus. The risk for perinatal infection is increased when chorioamnionitis or funisitis is present.[135,828] The histology of the placenta does not appear to be altered by HIV infection. HIV can be demonstrated by in situ hybridization within syncytiotrophoblast in about a third of placentas from mothers infected with HIV and may predict which infants are infected.[829] Very rarely, opportunistic infections have occurred in placenta of mothers with AIDS.

HEAD AND NECK PATHOLOGY IN AIDS

Though HIV can be found in both tears and saliva, the lacrimal glands and the salivary glands do not show specific pathologic lesions in persons with HIV infection. The most common clinical findings suggestive of salivary gland abnormalities include gland enlargement and xerostomia. These findings are similar to those seen with Sjögren syndrome. Patients with these lesions may not have reached the stage of clinical AIDS. Xerostomia has been reported in 2 to 10% of HIV-infected persons.[585]

Enlargement of major salivary glands is seen in less than 1% of HIV-infected adult patients but up to 19% of HIV-infected children. This enlargement typically involves the parotid gland and may consist of benign lymphoepithelial lesions. Such lesions may be bilateral, multiple, variably sized, and may be accompanied by cervical lymphadenopathy. These lesions are thought to arise from hyperplasia of intraparotid lymphoid tissue that traps small intraparotid ducts, causing obstruction and dilation with cystic change. The cystic enlargement can reach 5 cm in diameter. Fine needle aspiration (FNA) cytology of a lymphoepithelial cyst yields bloody or turbid fluid. Microscopic findings can mimic Sjögren syndrome and include anucleate squames, lymphoid follicle center cells, and macrophages. The surrounding salivary gland tissue typically demonstrates lymphoid infiltrates with cystic dilation of gland ducts lined by pseudostratified squamous epithelium. The histologic features are similar to those lesions seen in non-HIV-infected persons.[336,830,831] The most common opportunistic infection diagnosed in salivary glands is cytomegalovirus.[832]

Other lymphoid lesions may occur. The entity known as diffuse infiltrative lymphocytosis syndrome (DILS) typically involves the parotid glands bilaterally, leading to facial swelling and sicca symptoms. The submandibular glands are involved in half of cases, while the lacrimal glands are involved in a third of cases. This condition results from an extensive parotid infiltration by CD8 lymphocytes, which can mimic Sjögren syndrome, or even lymphoma. Other visceral organs may also be involved. In addition, lymphocytic interstitial pneumonitis (LIP) is present in a third of cases, while myopathy may be seen in a fourth of patients with DILS. This condition can present before the onset of clinical AIDS in HIV-infected persons.[480] Mucosa associated lymphoid tissue (MALT) lesions may appear in salivary glands and tonsils of pediatric patients with HIV infection.[485]

Kaposi's sarcoma (KS) can rarely involve submandibular and parotid salivary glands and produce gland enlargement. The histologic appearance is similar to KS seen elsewhere, with atypical spindle cells lining slit-like vascular channels, extravasated red blood cells, and hyaline globules. The lesions are invasive.[833]

Airway obstruction, pharyngitis, and fever as a result of enlargement of adenoids and tonsils. This is due to florid lymphoid hyperplasia. Histologic findings include florid follicular hyperplasia, follicular lysis, an attenuation of the mantle zone, and presence of multinucleated giant cells.[687]

Sinusitis may result from parasitic infections, including those caused by *Microsporidium*, *Cryptosporidium*, and *Acanthamoeba*. Patients with these infections typically are late in the course of AIDS with a CD4 count less than 20/μL and the presence of other opportunistic infections. Use of nasal drugs is not a precipitating factor. Clinical symptoms can include fever, headache, nasal obstruction and/or rhinorrhea, otorrhea, local pain, and swelling. The infections can cause a mass, perforation, and invasion of surrounding tissues. The symptoms are often present for a long time. Biopsy is usually needed for a specific diagnosis. Treatment outcomes are often poor, but the patients usually die from other causes.[834]

Examination of the ear in AIDS reveals that mild, or low grade, to severe otitis media can be present in about half of patients. When low grade, the degree of inflammation is not great, and serous to serosanguineous effusions can be seen. Purulent exudates with marked acute and chronic inflammation can be seen with severe otitis. Cholesteatoma may complicate these findings. Viral infections found in the middle ear include cytomegalovirus, adenovirus, and herpes simplex virus.

Other lesions reported to involve middle and inner ear include cryptococcosis, cytomegalovirus, and Kaposi's sarcoma. However, in adults these ear infections appear to be asymptomatic and not associated with deafness.[835,836] Otitis externa may be caused by Pseudomonas aeruginosa and by Aspergillus.[580]

BONE AND JOINT PATHOLOGY IN AIDS

The skeletal system and supporting structures including bone, cartilage, tendons, and ligaments do not have specific lesions related to HIV infection and its sequelae. However, either Reiter's syndrome or psoriatic arthritis can develop over time with progression of retroviral infection in a small number (less than 10%) of cases. About 10% of persons with HIV infection exhibit mono- or polyarticular arthritis which may herald progression to AIDS and a poor prognosis. Synovial biopsy may show chronic synovitis.[837] One or more rheumatologic manifestations have been observed in about a fourth of patients with HIV infection; these include Raynaud phenomenon in 17%, arthralgia in about 12%, arthritis in 6%, and painful articular syndrome in 4%.[838]

Several rheumatologic manifestations may accompany HIV infection. An HIV-associated polyarthralgia can appear at some point in the course of nearly half of HIV infected persons. This cause for joint pain rarely progresses to inflammatory joint disease. The suggested etiology is either circulating immune complexes or other infections. A painful articular syndrome can be the cause for severe bone and joint pain that lasts for less than a day, and the etiology is not known. An HIV-associated arthritis is also self-limited and of unknown etiology, but can last for up to six weeks, is oligoarticular, and predominantly involves the lower extremities.[839]

Seronegative spondyloarthropathy has been described in association with HIV infection. It appears to be more severe and more resistant to therapy than spondyloarthropathies in persons without HIV infection. This spondyloarthropathy is oligoarticular, mainly involves the lower extremities, and can be accompanied by enthesitis, skin rashes, and mucus membrane involvement. It may become quiescent with highly active antiretroviral therapy. In Caucasians with HIV infection, HLA-B27 is found in 80 to 90% of patients with this form of reactive arthritis, but Africans are likely to be HLA-B27 negative.[839,840]

Soft tissue and osteoarticular infections with HIV infection are not common overall. Findings may include septic arthritis, soft tissue abscesses, osteomyelitis, pyomyositis, and cellulitis. The most common pathogen is *Staphylococcus aureus*. Risk factors include a low CD4 count, presence of intravascular indwelling catheters, extra-articular infection and trauma, and history of injection drug use. The course and treatment of these conditions is similar to that of non-HIV infected persons.[841]

There are clinical presentations in some patients with AIDS that resemble systemic lupus erythematosus (SLE). These findings can include arthralgias, myalgias, and autoimmune phenomena including a low titer positive antinuclear antibody, coagulopathy with lupus anticoagulant, hemolytic anemia, and thrombocytopenic purpura. Hypergammaglobulinemia from polyclonal B-cell activation may be present, but often diminishes in the late stages of AIDS. Specific autoantibodies to double-stranded DNA, Sm antigen, RNP antigen, SSA, SSB and other histones may be found in a majority of HIV-infected persons, but their significance is unclear.[163,842,843] Similar autoantibodies have also been reported in children with HIV infection.[844] Mixed cryoglobulinemia may be detected in persons with HIV infection, and the HIV-1 viral load tends to be higher in such persons, which may lead to antigenic stimulation that drives polyclonal B lymphocyte activation.[845]

Osteomyelitis most often affects younger persons with AIDS with very low CD4 counts. The mortality rate is high.[841] Half of cases may be due to atypical mycobacteria, particularly with low CD4 counts. Skeletal lesions from infection with atypical mycobacteria are often multiple, and concomitant skin lesions are frequent.[846] Osteolytic bone lesions may appear with bacillary angiomatosis, caused by the Rickettsia-like organism *Bartonella henselae*. Such lesions can appear in the distal extremities and cause local pain. Radiographically, these lesions appear as circumscribed lytic areas that may cause cortical destruction with a periosteitis or may permeate the marrow cavity.[427]

Osteonecrosis has been observed more frequently since the 1990's with HIV infection. The hip is most commonly affected area and often bilaterally. Risk factors include corticosteroid

therapy, hyperlipidemia, alcoholism, hypercoagulability, and megestrol acetate use. Plain film radiographs and magnetic resonance imaging are used for diagnosis.[847]

Osteoporosis is observed more frequently in HIV infected persons with long survival. Risk factors risk factors for the development of osteopenia are use of protease inhibitors, older age, longer duration of HIV infection, high viral load, high lactate levels, low bicarbonate levels, raised alkaline phosphatase level, and lower body weight. Both tumor necrosis factor and interleukin-6 are cytokines produced in increased amounts in persons infected with HIV, and these cytokines may affect osteoclast activation and resorption of bone. Parathyroid abnormalities including both hypocalcemia and hypercalcemia have been described with HIV infection.[848] Persons receiving highly active antiretroviral therapy (HAART) that includes a protease inhibitor may have accelerated bone mineral density loss. The relative risk for osteopenia and osteoporosis in HIV infected males receiving a protease inhibitor is 2.19. The mechanism is unknown.[249]

CYTOPATHOLOGY IN AIDS

Diagnostic procedures yielding primarily cytopathologic specimens, rather than tissue biopsies, in the respiratory tract include bronchial brushings, bronchoalveolar lavage, and sputum collection. Collection of these specimens is mainly for diagnosis of *P carinii*. Without special stains, the appearance of small eosinophilic foamy bodies is quite suggestive of *Pneumocystis*.[337] The diagnostic sensitivity in specimens obtained from bronchial washing or induced sputum may be aided by use of an indirect fluorescent antibody test for *P carinii*.[849]

Bronchoalveolar lavage (BAL) remains overall the most useful procedure for obtaining diagnostic material from lung in immunocompromised patients, with a diagnostic yield of over 50%.[548] BAL is the method of choice for diagnosis of *Pneumocystis carinii* pneumonia, with a yield of 90% (95% for sampling of multiple sites).[336,549] In BAL fluids, diagnosis of cytomegalovirus (CMV) is aided by immunohistochemical staining and/or in situ hybridization techniques, which are more sensitive than CMV detection by morphology alone.[850]

Budding yeasts of *Candida* are often seen in sputum specimens, in specimens obtained at bronchoscopy, or in esophageal brushings. Yeast organisms in such specimens may represent oral contamination rather than a pathologic process. Cytomegalovirus and Aspergillus likewise uncommonly represent pathogens in BAL specimens. Other infectious agents are seen much less frequently. Diagnosis of malignant lymphomas or KS from pulmonary cytologic material is extremely difficult.

Stereotaxic brain biopsy is most often undertaken to diagnose mass lesions that represent possible *T gondii* infection or malignant lymphoma.[615] Diagnosis of other neurologic conditions in AIDS is hampered by poor yield from sampling error resulting from the focal nature of most processes in brain. However, cytology of tissues obtained from the brain by stereotactic biopsy for intraoperative diagnosis may be more sensitive for diagnosis than frozen sections, though the presence of necrosis and gliosis can make diagnosis difficult.[851]

Fine needle aspiration (FNA) cytology may be performed to diagnose mass lesions found on roentgenography. The most frequently sampled sites include lymph nodes, salivary gland, liver, paraspinal area, extremity, and chest wall. A specific diagnosis can be made in half of cases. Enlarged lymph nodes are prime targets for such procedures. Progressive generalized lymphadenopathy is a common diagnosis rendered by FNA of lymph node. Diagnosis of neoplasms such as KS and non-Hodgkin lymphoma are challenging by FNA, but can be aided by immunohistochemical staining. Malignant lymphomas can sometimes be diagnosed by the appearance of a monomorphous population of large atypical lymphoid cells. Aspirates with inflammatory cells, particularly macrophages, should be screened with special stains to detect fungal or mycobacterial organisms. The yield for diagnosis of M tuberculosis with FNA is 47%.[852]

Imprints or smears of tissue specimens removed at surgery may aid in diagnosis of mycobacterial infections by providing more detail than paraffin sections.[366]

PEDIATRIC AIDS

Pediatric HIV infection is primarily acquired perinatally. Infection can occur in utero prior to birth, intrapartum during delivery, or via breast milk following delivery.[137] Pediatric HIV infections acquired through transfusion of blood or blood products are rare in places where adequate testing programs for these products are in place. Sexual abuse of children may also be identified as a risk factor in some cases. In adolescents aged 13 to 19, the manner of presentation and the nature and appearance of opportunistic infections and neoplasms seen with AIDS is similar to adults.[853]

DIAGNOSIS.-- The diagnosis of HIV infection in children <18 months of age is complicated because passively acquired maternal HIV antibody may be present, so tests for HIV antibody alone are not sufficient, and additional criteria are necessary.[318,319] About half of HIV-infected infants do not have detectable HIV by laboratory methods within the first month of life, but in virtually all cases HIV infection can be established at 1 to 2 months of age, and testing may be repeated again at 3 to 6 months of age in questionable cases. The most sensitive methods for HIV detection are HIV viral culture, HIV RNA assay, or the polymerase chain reaction (PCR) for either HIV proviral DNA in peripheral blood mononuclear cells or in plasma. Testing of cord blood should be avoided because of potential maternal contamination. Any positive test result should be confirmed with repeat testing from a separate blood sample.[264] Laboratory diagnosis of perinatal HIV infection by p24 antigen assay or HIV IgA assay are less sensitive--but also less costly--methods.[289,297,304]

Presence or absence of detectable HIV soon after birth may explain when transmission of HIV from mother to baby occurred. Thus, infants are defined as infected in utero if HIV can be cultured from peripheral blood or HIV can be detected in lymphocytes within 48 hours of birth. Intrapartum infection during delivery is defined in a neonate with a negative HIV culture or PCR assay for HIV proviral DNA in peripheral blood in the first week of life, but positive thereafter.[137]

CLINICAL FEATURES.-- On average, about 14 to 25% of children born to HIV-1 infected mothers are perinatally infected in the United States and Europe, while about 13 to 42% of children of HIV-1 infected mothers acquire HIV perinatally in developing nations.[854] However, the rate of HIV infection in the firstborn of twins delivered vaginally (35%) is greater than the rate in second born (15%), and the 15% rate of HIV infection in the firstborn of twins delivered by cesarean section is greater than the 8% rate for the second born, suggesting that intrapartum HIV infection occurs.[855] A greater HIV viral burden in the mother during late gestation and/or during the time of delivery, as measured by HIV-1 RNA levels, increases the risk for HIV transmission to the baby.[135,137,140] The risk for HIV-1 transmission is increased with preterm labor and premature rupture of membranes.[138] The risk is halved with delivery by elective cesarean section.[137] For mothers with HIV-2 infection, the rate of perinatal transmission is only 1 to 2%.[144] Breast feeding by HIV-infected mothers further increases the risk for transmission of HIV to an infant.[125]

The risk for development of opportunistic infections, encephalopathy, and death in these infected children is increased in the first 18 months of life when, at the time of birth, the mother had clinical AIDS, p24 antigenemia, or a CD4 lymphocyte count of <400/μL. Almost half of children die by 18 months of age if mother had clinical AIDS at birth.[856]

Zidovudine therapy in an HIV-infected mother has been shown to reduce the rate of perinatal transmission of HIV by two-thirds, and no association with birth defects has been reported from zidovudine therapy. Zidovudine decreases viral load and decreases the risk for perinatal transmission in late gestation and/or at the time of delivery.[140] Such therapy includes antenatal maternal oral administration of zidovudine starting at 14 to 34 weeks gestation and continuing throughout the pregnancy, intravenous maternal zidovudine therapy during labor and delivery, and

oral administration of zidovudine to the infant 8 to 12 hours after birth and continuing for 6 weeks following delivery.[142,857] However, even an abbreviated regimen of zidovudine is efficacious in reducing the risk for perinatal transmission of HIV.[236]

There appear to be two patterns of progression to AIDS with perinatal HIV infection. In about 10 to 25% of infections the infants and children manifest severe immunodeficiency with failure to thrive and encephalopathy in the first two years of life, with mortality of nearly 100% from AIDS by 4 years of age.[858] Rapid progression of perinatally acquired HIV-1 may be predicted by a number of factors. These include positive HIV-1 culture or polymerase chain reaction (PCR) assay during the first week of life, <30% CD4+T-lymphocytes at birth, and any or all of the following noted at birth: hepatomegaly, splenomegaly, lymphadenopathy.[859] Specific infectious diseases, severe bacterial infections, progressive neurologic disease, anemia, fever, cardiomyopathy, growth failure, hepatitis, and persistent oral candidiasis are all findings that correlate with shortened survival.[182] In the remaining 75 to 90% of cases, children with HIV infection have a much slower progression to AIDS over 10 years or more, often remaining asymptomatic through adolescence, and their morbidity and mortality more closely resembles adult AIDS.[858]

HIV-infected children, however, with hepatomegaly, splenomegaly, lymphadenopathy, parotitis, skin diseases, and recurrent respiratory infections tend to have longer survival. Children with lymphoid interstitial pneumonitis tend to have a survival intermediate between the above two groups. About half of children with perinatally acquired HIV infection are alive at age 9.[79] In any case, increased HIV viral replication is noted in the first 3 to 16 weeks of life, similar to acute HIV infection in adults. A higher viral load at this time suggests a more rapid pattern of progression.[858]

In developed nations, most of the mothers of infants with HIV infection have acquired HIV infection as intravenous drug users or as sexual partners of drug users, but increasing numbers of mothers have acquired HIV heterosexually. In addition, some sexually abused children have contracted AIDS, with symptoms often not appearing until adolescence. Transfusion-associated AIDS in the early 1980's accounted for about 10% of pediatric cases and transfusion of blood products for hemophilia about 5%. In places where screening of blood products for HIV has been employed, these percentages have decreased substantially. Death has occurred in over 75% of reported pediatric AIDS cases, usually with opportunistic infections similar to adult AIDS patients, but with a clinical course, on overall average, shorter than that of adult patients.[182]

FAILURE TO THRIVE.-- Poor growth may be seen in up to half of children infected with HIV. The decrease in growth continues over time, and appears to involve lean body mass. This effect may be present from birth, since it is noted that infants born to HIV-infected mothers (even those who do not acquire HIV) have a significantly lower mean birth weight and length. Micronutrient deficiencies, and vitamin A deficiency, may play a role, but dietary supplementation does not correct deficits in lean body mass or height. The levels of HIV-1 RNA are higher in children with poor growth.[860]

PULMONARY FINDINGS.-- Pulmonary problems include *Pneumocystis carinii* pneumonia (PCP), which occurs in more than half of pediatric patients with AIDS and has a high mortality rate in infants less than 2 months of age. Approximately 12% of infants with perinatally acquired HIV infection develop PCP in the first year of life. More than a third of pediatric AIDS patients die from PCP. Recurrent bacterial infections are common and account for about 20% of deaths from AIDS in children.[861] The histopathology is similar to that seen in adults. Prophylaxis is recommended for all infants with perinatal HIV exposure, beginning at 4 to 6 weeks of life, and continuing throughout the first year of life if HIV infection is confirmed. Despite prophylaxis, PCP may still occur.[251] The risk for PCP is increased when the CD4 count is declining or when maternal CD4 counts are lower, but does not appear to be related to HIV-1 RNA levels.[862]

Lymphoid interstitial pneumonitis (LIP) is not characteristic of adult AIDS but is seen at some point in about 20 to 30% of all children with AIDS. LIP rarely causes death and affected

children may have a better prognosis than that of HIV-infected children with AIDS-defining opportunistic infections and neoplasms. It usually develops when passively acquired maternal antibody begins to disappear. Corticosteroid therapy may be useful in treatment of LIP.[863] Bacterial pneumonias can be seen in the late stage of pediatric AIDS. Cytomegalovirus infection of the lungs is also common and may be associated with pulmonary failure and death. Mycobacterial and fungal infections are uncommon.[344,537]

A polyclonal B-cell lymphoproliferative disorder (PBLD) can affect the lungs in children with HIV infection, as well as other organ sites including liver, spleen, lymph nodes, and kidneys. Thus, hepatosplenomegaly and lymphadenopathy may be present. The lungs can demonstrate nodular infiltrates. PBLD is a more florid example of a pattern of pulmonary lymphoid hyperplasia (PLH) characterized by lymphoid follicles with or without germinal centers surrounding bronchioles. With PBLD there are nodular infiltrates of polyclonal B-lymphocytes and CD8+ T-lymphocytes. Other organs may also be involved by PBLD.[540]

CNS FINDINGS.-- The most common neurologic finding in pediatric AIDS is a progressive encephalopathy which appears to be caused by direct CNS infection by HIV. This encephalopathy may affect 30 to 60% of children with AIDS. There are three major patterns of AIDS dementia complex, or human immunodeficiency virus-associated dementia (HIVD) in children: (1) subacute progressive - patients at first develop normally but then social, language, and motor skills are lost, and microcephaly may be present; (2) plateau progressive - patients initially develop at a normal pace but then decline in their rate of developmental progress with little or no further acquisition of skills, and microcephaly may be present; (3) static encephalopathy - children are late to acquire motor and language skills, are cognitively impaired, and acquire skills slowly; radiographic scans are normal.[620]

Neuropathologic findings distinctive to pediatric HIV infection include acquired microcephaly. In such cases there is no gross or microscopic malformation, only decreased brain weight accompanied by cortical atrophy and ventriculomegaly. Gliosis is seen microscopically. Other frequent histologic findings include calcification in vascular walls of basal ganglia and deep cerebral white matter, and these changes are often progressive with age. As in adult AIDS cases, multinucleated giant cells are often present. Children with encephalopathy often have corticospinal tract degeneration from myelin loss, while the vacuolar myelopathy seen in spinal cords of adults is uncommon. An anoxic-ischemic encephalopathy with neuronal necrosis in cerebral cortex, hippocampus, and basal ganglia may be seen in association with systemic hypoxemia from cardiovascular disease. Although non-Hodgkin lymphoma can be seen in pediatric AIDS patients with focal CNS lesions, opportunistic infections such as toxoplasmosis, cryptococcosis, cytomegalovirus, and progressive multifocal leukoencephalopathy are uncommon in pediatric AIDS, as contrasted with adult AIDS cases.[864,865]

NEOPLASIA.-- Neoplasms are seen less frequently in cases of pediatric AIDS than in adult cases. About 2.5% will develop a malignant neoplasm. The most frequent neoplasm of HIV-infected children is high-grade non-Hodgkin lymphoma (NHL). A third of NHL's in children are of the intermediate (Burkitt) type and a fourth are seen to occur in the brain.[866] Clinical findings seen at presentation with NHL's in pediatric AIDS include fever, weight loss, jaundice, hepatosplenomegaly, abdominal distension, anemia, and neurologic abnormalities. Most patients are at stage III or IV on presentation. In children, NHL's are more likely to occur in boys who are Caucasians and who are older. Brain lymphomas tend to occur late in the course of AIDS. In addition to NHL's, mucosa-associated lymphoid tissue (MALT) lesions have been seen in association with pediatric HIV infection.[476] They are typically localized and found in lung, salivary gland, and tonsils.[485]

Kaposi's sarcoma has been reported in children with AIDS in both skin and visceral sites, but with far less frequency than in adults with HIV. The etiology of KS probably involves infection with human herpes virus 8 (HHV-8), but risk factors may be difficult to identify. The average age of onset is between 5 and 6 years.[866]

Next in frequency are smooth muscle tumors. These are either leiomyomas or leiomyosarcomas.[485] Leiomyosarcoma is the second leading cancer in children with HIV infection.[485] These smooth muscle tumors are generally visceral in location (gastrointestinal tract, lung, spleen, and liver). In lung, these lesions appear as multiple nodules; tracheobronchial involvement may lead to respiratory distress with wheezing.[867] Gastrointestinal lesions may produce bloody diarrhea, abdominal pain, and obstruction.[485] Epstein-Barr virus can be demonstrated in the cells of HIV-associated smooth muscle neoplasms, and EBV stimulated clonal proliferation may contribute to their pathogenesis in both children as well as adults.[868]

MISCELLANEOUS FINDINGS.-- An arteriopathy has been described at autopsy in children dying of AIDS in which there is either cerebral vasculitis or generalized fibrocalcific change in elastic lamina or media of arteries in brain, lung, heart, thymus, kidney, spleen, heart, and lymph node. Pathologic findings in large vessels consist of vasa vasora medial involvement with chronic inflammation. Coronary artery involvement is mainly calcific. The luminal narrowing may explain focal necrosis, atrophy, fibrosis, or gliosis.[869,870] In the brain, this arteriopathy is manifested as a diffuse dilation with ectasia of major arteries of the circle of Willis, with intimal fibroplasia, medial thinning, and elastic lamina destruction or reduplication. This arteriopathy can lead to hemorrhages in cerebrum, basal ganglia, and subarachnoid space. Infarctions may also occur. Though little inflammation is identified within these lesions at autopsy, the features suggest a prior vasculitis, and there is often a history of a prior opportunistic infection, particularly varicella zoster virus (VZV).[871,872]

Human immunodeficiency virus nephropathy (HIVN) can occur in children with HIV infection. Patients have excessive proteinuria or albuminuria. Focal and segmental glomerulosclerosis (FSGS) is seen in only half of cases, and other changes include mesangial hyperplasia or minimal change. The course in children is less fulminant than in adults, but progression to end-stage renal disease still occurs.[771]

The thymus in pediatric AIDS can undergo marked involution with irreversible injury that contributes to immunosuppression and rapid progression of disease from immune dysfunction. This occurs more often in children with HIV strains using CXCR4 as a coreceptor. Aggressive antiretroviral therapy may lead to thymic recovery in children without extensive thymic damage.[873] In other organs, *Candida* infection of the esophagus or lung has been seen in 10% of pediatric cases. Recurrent oral thrush, a frequent finding in infants with AIDS, may give rise to invasive or systemic candidiasis. Systemic, recurrent bacterial infections are seen with frequency and may satisfy definitional criteria for diagnosis of AIDS.[319]

Diarrhea can be a serious problem in HIV-infected infants and appears more frequently, tends to be more persistent, and has an onset earlier in life than in infants who are not HIV-infected. Fever, vomiting, anorexia, and dehydration often accompany the diarrheal illness. In many cases, a pathogen cannot be found. The most common pathogens identified are cytomegalovirus (particularly involving the cecum), rotavirus and *Salmonella* species.[874]

The lipodystrophy described in adults, with dyslipidemia, fat redistribution, and insulin resistance, also occurs in children receiving highly active antiretroviral therapy (HAART).[875]

Granulomas are seen less frequently in children and fewer organisms are present with either mycobacterial or fungal infections than in adult AIDS patients. The large macrophages containing *Mycobacterium avium*-complex (MAC) found throughout the reticuloendothelial system in some cases may mimic the cells observed with some storage diseases such as Gaucher disease and Niemann-Pick disease.[876]

CHAPTER 6 - SAFETY PROCEDURES WITH AIDS

EDUCATIONAL GOALS

Human immunodeficiency virus (HIV) and other infectious agents may be encountered in the daily routine of workers employed in health care. There is concern by workers about exposure to infected persons or specimens. Questions may arise about the hazards, risks, and consequences of job-related exposure to infectious agents--and HIV in particular.

All health care providers have a basic responsibility to attend all patients, regardless of disease. Physicians in particular have a special responsibility to model professional behavior and display their willingness to provide competent, sensitive, and compassionate care to all patients. Failure to properly care for and attend HIV-infected patients violates a basic tenet of the medical profession: to place the patient's interest and welfare first.[877]

Educational efforts provide health care workers with the means to understand the nature of AIDS and to cope with their fears and prejudices in treating HIV-infected patients. Educational goals should include: (1) dissemination of accurate information concerning the true risks involved in health care, (2) understanding the modes and risks of transmission of HIV, (3) training in the protective procedures, techniques, and equipment for infection control, (4) use of monitoring for compliance with infection control measures, and (5) understanding the procedures to be followed in the event of potential exposure.

UNIVERSAL PRECAUTIONS

The Centers for Disease Control (CDC) now recommends universal precautions for all health care workers when dealing with all patients and specimens at all times. The rationale for this is supported by a study which indicated that the prevalence of HIV-1 was 1.1% and hepatitis B virus (HBV) was 4.9% in routine unlabeled serum or plasma specimens sent to the clinical chemistry laboratory of an urban teaching hospital.[878] In another study of patients seen in a large metropolitan hospital emergency room, a 7.8% rate of HIV-1 seropositivity was found, but even after initial HIV-1 testing by EIA and WB assays, 0.3% additional HIV infections were found by HIV-1 p24 antigen and HIV-1 plasma RNA testing.[281,879] Thus, potentially contaminated specimens are received by a hospital's laboratories and, despite the very high sensitivity of current testing methods for HIV, limitations of testing methods mean that it is not possible to identify with certainty all infectious specimens.[275,277]

Despite increasing prevalence of HIV infection, the numbers of reported seroconversions in health care workers have not risen significantly during the AIDS epidemic. Most of the documented cases of occupational HIV transmission have occurred in nurses and laboratory technicians performing many procedures with needles or other sharps that carry a risk for accidental exposure. Percutaneous injury, usually inflicted by a hollow-bore needle, is the most common mechanism of occupational HIV transmission. In a few instances, inapparent inoculation through mucous membranes or inapparent breaks in the skin may occur. Contact with saliva, urine, and feces carries little risk. Infection with HIV or hepatitis viruses from aerosols has not been demonstrated.[880,119]

The risk of HIV infection in hospitals, though very small, does exist, as with other infectious agents, especially with failure to follow proper procedures or with accidents. The risk for HIV seroconversion from inadvertent occupational exposures with bloodborne transmission is only about 0.3%. However, the risk for transmission for hepatitis B virus (HBV) ranges from <6% to at least 30% based upon the absence or presence of hepatitis B e antigen. The risk for hepatitis C seroconversion ranges up to 7%, with an average risk of 1.8%. Risk is primarily based upon the number of virions present in blood, which is higher for hepatitis than for HIV, and body fluids other than blood contain far fewer virions. The average volume of blood inoculated during a needlestick injury with a 22-gauge needle is approximately 1 μL, a quantity sufficient to contain up to 100 infectious doses of hepatitis B.[880,118,119]

Every facility that handles the blood, body fluid, or tissue of AIDS patients must develop safety procedures that are routinely employed on a daily basis. In-service or continuing education programs should address the facts about AIDS and the proper approach of the laboratory in dealing with it. Every laboratory worker has an important responsibility to promote infection control. The real safety factor depends upon the least amount of precaution that will routinely be taken, because any specimen could contain an infectious agent.

On hospital wards, AIDS patients should not require strict isolation when universal precautions are employed, and legal actions have been taken against hospitals that did so. Precautions used for patients with hepatitis are more than adequate. Segregation of HIV-infected persons or specimens in specific areas is impractical, leading to inefficient duplication of facilities or services and undermining the philosophy and benefits of universal precautions. However, HIV-infected patients should not be placed in close proximity to immunosuppressed patients, such as those undergoing chemotherapy or those with lymphoreticular malignancies, who are at risk, not for contracting HIV, but for spread of opportunistic infections from the AIDS patient.

The most common form of parenteral exposure to infectious agents in the hospital setting is needlestick injury. Disposable syringes have the lowest rate of injuries and those devices that required disassembly have higher rates of injury. Needleless intravenous access can also be instituted to decrease injuries to health care workers. One third of needlestick injuries are related to recapping needles. Therefore, attention should be given to evaluation and development of equipment with shielded or retracting needles along with ongoing training programs and

implementation of procedures that help to avoid these penetrating injuries. Use of needleless systems or resheathable needles results in a marked reduction in needlestick injuries.[119]

The risk to surgeons from accidental exposure to HIV in the operating room is low, with a percutaneous injury rate of 1.7% per operative procedure in a hospital with a high HIV prevalence population.[881] There is no evidence to suggest a higher rate of HIV infections for surgeons performing surgery in moderate to high AIDS incidence areas, and the risks for hepatitis B and hepatitis C are greater.[882] The potential risk to a patient undergoing an invasive procedure by a physician infected with HIV is also extremely low, particularly with use of universal precautions. By contrast, the risk of death from homicide in the United States is 1 in 10 000 per year and from vehicular accident 1 in 7000 per year, and more health care workers have died from firearms injuries incurred at work than from AIDS.[883]

OSHA REGULATIONS

The Federal Occupational Safety and Health Administration (OSHA) of the United States have adopted standards to be followed to protect workers against exposure to blood-borne pathogens, particularly hepatitis B virus and HIV.[884] These rules have as their basis the Centers for Disease Control (CDC) guidelines for universal precautions for bloodborne pathogens. These rules require that the following standards be followed in the health care delivery setting:

1. Vaccines and post-exposure treatment be made available free of charge to all employees at risk of exposure on the average of one or more times per month.

2. Routine tasks are to be evaluated for potential exposure, without consideration of protective equipment, and personnel at risk are to be identified and documented. Standard operating procedures are recommended.

3. A written control plan be implemented, including:

    a. exposure determination
    b. proper and appropriate use of safety equipment, work practice and engineering controls
    c. schedule and method of implementation for each provision
    d. a summary of education and training procedures
    e. review and update of infection control plan as needed to reflect any changes in policy

4. Personal protective clothing and equipment must be appropriate and fit properly and must be readily available at all times. The employer shall clean, launder, repair, or replace all such items as necessary. Disposable gloves may not be disinfected or washed for re-use but must be removed immediately upon leaving the work area and placed in an appropriate container for disposal. Masks, eye protection, or face shields must be worn whenever there are splashes, sprays, spatter, droplets, or aerosol of blood or other potentially infectious materials and the possibility of eye, nose, or mouth contamination.

    Fluid resistant clothing must be worn in the event of splashing or spraying. Fluid-proof clothing, including shoe covers, must be worn if there is the potential for soaking with blood or other infectious material.

5. No work area with the potential for occupational exposure will be exempt from following universal precautions.

Used needles and other sharp objects shall not be sheared, bent, broken, recapped, or resheathed by hand. Used needles shall not be removed from disposable syringes. Mouth pipetting is prohibited.

Work areas where there is the potential for exposure to infectious material must be free of food or drink. Smoking, cosmetics or lip balm, and handling contact lenses in work areas are prohibited.

6. Signs and warning labels--including the name of the infectious agent, requirements for entering the area, and the name and telephone number of the responsible person--must be posted at entrances to work areas that contain biohazards.

   Warning labels shall be placed on all storage containers, refrigerators, freezers, and disposal facilities that are used to store or transport potentially infectious fluids or materials.

7. All at risk employees shall participate in an annual training program that provides information regarding risks of exposure, transmission, and necessary precautions. An explanation of the employer's infection control plan, meaning of all signs and warnings, and the appropriate actions to take and person to contact in an emergency must also be provided.

   A training program must be provided for employees inexperienced in the handling of human pathogens or tissue cultures. Persons without such training or experience shall be prohibited from working with HIV or HBV materials.

8. Employers shall maintain individual medical records that include vaccinations, circumstances of exposure incidents, results of medical testing and follow-up procedures, and any copies of physicians' written opinions. These records must be kept confidential except where reporting is required by law.

   Training records must also be maintained that include dates of sessions, summary of contents, persons conducting the training, and attendance of all personnel.

These OSHA regulations do not require that all employees use all possible barrier precautions. Rather, the employer must make the determination as to which employees need to wear gloves, which require face protection, which need impermeable gowns, etc. This is to be done on a job by job or task by task basis. Guidelines promulgated by the CDC are similar and also discuss or reference disposal methods for contaminated waste.[118]

With regard to prevention of transmission of *Mycobacterium tuberculosis* (MTB) in health care settings, particularly in view of increasing numbers of MTB cases in the United States and also increasing incidence of multiple drug resistant MTB strains, OSHA have promulgated inspection and enforcement criteria which are based upon Centers for Disease Control (CDC) recommendations. First, the CDC supports use of administrative measures to reduce risk of exposure to persons with infectious MTB through policies that insure rapid detection, isolation, evaluation, and treatment of persons likely to have MTB. Second, the CDC recommends engineering controls in the workplace to reduce the concentration of infective droplet nuclei. This can be achieved through proper ventilation. Use of ultraviolet light can also aid in disinfection. Third, the CDC supports use of personal respiratory protective equipment by health care workers when engineering controls alone will not provide adequate protection. Such a respirator must filter particles 1 micron in size with 95% efficiency and have a face-seal leakage of no more than 10%. A NIOSH-certified respirator with a HEPA filter meets the CDC criteria.[885]

High risk settings for exposure to MTB may include:

1. Entering a room occupied by a known or suspected infectious tuberculosis patient;

2. Performing certain high hazard medical procedures such as aerosol administration of medication, bronchoscopy, and sputum induction; and

3. Transporting patients with tuberculosis.

Institutions utilizing respirators must implement a comprehensive respiratory protection program with written standard operating procedures, medical screening of health care workers who will use the respirators, employee training, and equipment inspection, cleaning, maintenance, and storage checks. Each institution must have a tuberculosis infection control program, assign supervisory responsibility to persons with expertise in infection control, and evaluate the risk for transmission of tuberculosis in the workplace. The risk for transmission in a work area is assessed as low, intermediate, or high based upon the number of patients with MTB admitted to the work area along with the number of health care workers who become PPD positive.[885]

Develop and display leadership in implementing infection control practices. Review routine tasks and procedures to determine the potential risks for exposure to infectious agents. A reasonable approach should be taken, recognizing that risks cannot be completely eliminated and that unwieldy, complicated measures to prevent exposure are unlikely to add any additional measure of safety. In fact, institution of additional complex procedures or use of cumbersome equipment may increase the potential for accidents. Develop and practice the skills necessary to safely perform tasks as a routine that never varies. The true meaning of "universal precautions" is the safety afforded by the most minimal level of infection control in routine procedures.

DISINFECTION PROCEDURES

Retroviruses, including HIV, are extremely susceptible to environmental degradation. The titer of HIV is reduced from 90 to 99% within several hours after drying, though hepatitis B virus has been found to be stable on environmental surfaces for at least 7 days.[119] HIV is highly susceptible to common routine chemical disinfectants and fixatives used in medical practice. These include quaternary ammonium compounds, isopropanol (rubbing alcohol), ethanol, hydrogen peroxide, sodium hypochlorite (bleach), cytologic specimens received in 95% ethanol, tissues received in a formalin-containing fixative (such as 10% (v/v) neutral buffered formalin, Zenker's, B-5, or Bouin's fixatives), and glutaraldehyde. Heat treatment of serum specimens at 56^0 C for 10 minutes also inactivates HIV.[886,887,888] Pasteurization of human breast milk has been demonstrated to inactivate HIV.[889] Pasteurization by heat treatment for 10 hours in a stabilized aqueous solution at 60^0 C will inactivate not only HIV, but also hepatitis A virus, hepatitis B virus, and hepatitis C virus in human plasma derivatives.[890]

Table 9 details many commonly available disinfectants and/or laboratory reagents effective against HIV. Recommended concentrations of these agents are based upon a sufficient safety margin, given additional factors of absorption, dilution, evaporation, or other loss of potency in the application of these disinfectants.[888] One reason for the relatively poor infectivity of HIV from contact in the environment is that in blood there are only about 10^7/L infective HIV virions as compared to 10^{16}/L infective hepatitis B virions.[887]

Highly concentrated retroviral preparations can have recoverable virus after more than 1 week in an aqueous environment at temperatures ranging from room to body temperature (23^0 C to 37^0 C). Five hours of heating to 56^0 C are needed to eliminate HIV in aqueous solutions. One week of drying at room temperature also results in loss of infectivity. Thus, spills of body fluids and specimen bottles or containers contaminated with patient fluid or tissue should be disinfected with 0.5% hypochlorite (bleach). Work areas can be routinely disinfected with the same solution. Equipment or surfaces sensitive to bleach can be cleaned with alternative disinfectants.[126,886,887,888]

ACCIDENTAL EXPOSURES

Transmission of HIV from infected patients to health care workers by accidents involving parenteral exposure is highly unlikely--a risk of about 0.3% per exposure[119] Since this figure represents the findings of studies of exposures in high risk situations to patients with advanced AIDS with higher viral titers, the average risk in most health care delivery settings is much less. The risk for HIV seroconversion is increased with a deep injury, injury with a device visibly contaminated with patient blood, injury involving a procedure in which a needle is placed in a patient's artery or vein, and injury involving a patient progressing to death from AIDS within two months of the injury. Health care workers who seroconvert are less likely to have had postexposure zidovudine prophylaxis. These findings are consistent with the observations that the risk for HIV infection after a percutaneous exposure increases with a larger volume of blood and with a greater HIV viremia in the patient's blood.[119]

However, rare inadvertent exposures to HIV or other infectious agents may occur despite the best practices of health care workers. When such incidents occur, the situation that led to the exposure must be documented, reported as an industrial accident, and investigated to determine why it happened and how it could be prevented in the future. Persons exposed to HIV should have serologic testing carried out immediately for baseline determination of serologic status and followed by additional testing at 3 months, and 6 months after initial exposure. Persons with work-related exposure to HIV can still acquire HIV infection outside of the workplace, and persons in known risk groups with exposure to HIV may be employed in settings of occupational exposure. There is no laboratory method for making a distinction among the means for HIV exposure.

There is experimental and epidemiologic evidence that administration of antiretroviral therapy beginning soon after exposure to HIV and continuing for several weeks may prevent HIV infection from occurring. There is insufficient data in humans to fully verify this observation, and persons accidentally exposed to HIV have seroconverted despite immediate prophylaxis, but a risk reduction of 81% with post-exposure prophylaxis with zidovudine following percutaneous injuries has been reported. The standard 4week regimen consists of two drugs (zidovudine and lamivudine, lamivudine and stavudine, or stavudine and didanosine) started as soon as possible after HIV exposure through percutaneous or mucosal routes. If the source person is determined to be HIV negative, treatment should be discontinued. Antiretroviral treatment is not indicated for contact between intact skin and blood or other body fluids contaminated by HIV.[880]

Adverse side effects of such prophylaxis are frequent, but minor, with about three fourths of persons reporting nausea, malaise or fatigue, and headache. The serious side effect of bone marrow suppression is less frequent. Post-exposure combination therapy with ZDV plus may be recommended because of the greater antiretroviral activity of this combination of drugs. The degree of risk of exposure may be stratified to determine the appropriateness of using postexposure prophylaxis.[119,891]

Recommended procedures following an exposure by a health care worker to blood or body fluids that contain HIV may include:[119,891]

1. Administer first aid as needed to the injured health care worker.

2. Decontaminate the exposure site when the safety of the health care worker permits.

3. Wash open wounds first with soap and water and then irrigate with sterile saline or a disinfectant.

4. Flush exposed mucosal surfaces extensively with water.

5. Exposed eyes should be irrigated with clean water, saline, or sterile eye irrigants.

6. Promptly report the exposure to the institutional occupational medicine department.

7. Counsel the exposed health care worker regarding the risks and benefits of antiretroviral chemoprophylaxis and then offer chemoprophylaxis.

8. If chemoprophylaxis is accepted, then the first dose should be administered as soon as possible, preferably within an hour of the time of exposure.

9. The chemoprophylactic drug regimen may be altered if the source and the drug resistance pattern is known.

10. Follow up at 6 weeks, 3 months, 6 months, and 1 year (note: HIV seroconversion will typically occur in the first 6 months if chemoprophylaxis has failed).

Though testing of the person or specimen suspected of being the potential source of exposure may be done, such testing will not always resolve the issue of transmission because: (1) even if the source is found to be positive for HIV, this does not prove that transmission to the exposed worker occurred; (2) the laboratory tests employed, though they are extremely good, are not 100% accurate; (3) a small number of HIV-infected persons cannot be detected by current methods of laboratory testing; and (4) persons recently infected by HIV may not be detected by routine testing for several weeks or months.

Cost alone would preclude routine screening of all patients, persons, bodies, or specimens, nor would the detection of specific sources for HIV infection lessen the need for routine infection control. Remember that other important infectious diseases such as hepatitis also exist! If testing of a specific source specimen or patient of HIV exposure is undertaken, it should be carried out in conformity with local statutes.

Hepatitis continues to be the greatest risk to workers exposed to blood or body fluids, though the incidence of infection declined markedly in the last decade of the 20th century. In 1985 there were over 300 000 cases of hepatitis B reported in the United States, with 12,000 health care workers infected, but this declined to 400 cases of hepatitis B in health care workers in 1995.[119]

Vaccination for hepatitis B virus (HBV) is recommended for workers in areas with potential exposure. This would include persons employed in health care with potential exposure to blood or blood products in the performance of routine duties. Post-exposure prophylaxis for HBV consists of testing for antibody to HBsAg in persons whose immune status is not known. Persons previously vaccinated against HBV should also be tested if their immune status has not been assessed in the preceding 2 years. If no immunity to HBV is found, then exposed workers should receive HBV vaccine as well as hepatitis B hyperimmune serum globulin (HBIG).[118,119,880]

INVASIVE AND SURGICAL PROCEDURES

A variety of diagnostic and therapeutic procedures may be performed in the management of patients with HIV infection and with AIDS. Procedures can be as routine as phlebotomy to as complex as major surgery. About 15% of HIV-infected persons will have one or more surgical procedures performed during the course of their infection and about 3 to 4% of patients with AIDS will require major surgery.[881] In order for health care workers to avoid risk of exposure to HIV during performance of procedures, adherence to universal precautions is a must. Procedures must have written guidelines, personal protective equipment must be readily available, and personnel must be trained. Equipment as simple as latex gloves can reduce by 50% the volume of blood transmitted in a needlestick injury. Solid needles used in surgery do not carry as much blood through barriers as do hollow core needles. Avoidance of injury-prone techniques, such as recapping of needles, would eliminate many injuries. Nurses and laboratory personnel, particularly phlebotomists, have the greatest number of occupational infections.[119]

Risk of infection through reduction in blood contacts in the operating room may be decreased by:

1. Use of double gloves
2. Use of cut-resistant gloves
3. Use of instruments and not fingers to hold or retract tissues
4. Not picking up dropped or broken sharps with fingers
5. Keeping needle use to a minimum
6. Keeping track of sharp instruments in use
7. Use of blunt instruments where applicable
8. Use of fluid-resistant gowns when blood splashing to the body may occur
9. Use of face protection when blood splashing to the face may occur
10. Requiring non-operating room personnel to wear gloves and gowns while in the operating room

Surgical procedures in the operating room are associated with a 1.7 to 5% risk for blood exposure for personnel in that setting. The majority of these exposures are to skin and eye, and the majority could be avoided by use of gloves, face protection, and fluid-resistant gowns. Surgeons and scrub staff have the highest risk for percutaneous exposures, about 1 incident per 100 procedures. Blood contacts are more frequent when performing emergency procedures, when patient blood loss exceeds 0.25 L, and when personnel are in the operating room longer than 1 hour. The greatest number of needle sticks occur on the surgeon's non-dominant hand, indicating that injuries could be significantly reduced if maneuvers such as palpation of a suture needle and use of a retractor rather than fingers to hold tissues were avoided.[881,892,893]

Adherence to universal precautions requires an ongoing effort on the part of all personnel. Ironically, lack of compliance is most acute in situations where risk of exposure is greatest--in emergency situations with profuse bleeding. The most common factors cited for lack of adherence in use of protective equipment include: insufficient time to put on protective equipment, interference

with skillful maneuvers by protective equipment, and uncomfortable feel of protective equipment. The first excuse requires a reordering of priorities and a need to keep protective materials close at hand. The second and third excuses can be approached in training. Persons who begin their careers with proper training and routinely employ protective equipment are unlikely to encounter difficulties with use of such equipment.[881,894]

THE SURGICAL PATHOLOGY LABORATORY

Pathologists receive the greatest potential exposure to infectious agents in surgical pathology activities. Many specimens are received fresh from surgery without fixation. Surgical pathology activities should take place in a separate, well-lighted and ventilated room out of the main flow of traffic. The cutting bench and adjacent sink should be large enough for adequate manipulation of all submitted fresh or fixed tissues, including amputation and exenteration specimens. Provide a puncture-proof container for disposal of sharps--blades and needles. Work surfaces should be designed for easy cleanup and to withstand 0.5% sodium hypochlorite (bleach) disinfection.[895]

Specimens sent to the laboratory for routine tissue processing should be in sealed, leak proof containers with fixative and within a second sealed, leak proof container. Requisition forms that accompany specimens should be handled in a manner that avoids contamination. If contaminated, copy the information on to a clean form. Avoid contamination of materials or equipment--reports, tapes, floppy disks, keyboards, telephones, etc.--that are used by others or are carried to non-contaminated clerical areas. Use dictation equipment that allows "hands-off" operation or that can be disinfected.

Personnel handling the surgical specimens should wear a gown, protective mask and eyewear (or face shield), and disposable gloves. Practice careful dissection technique with good equipment and do not be hurried or distracted. Clean-up and decontamination can be accomplished with detergents, followed by disinfection with bleach. Determine procedures and equipment for use when accidental spills or splashes occur. The barrier provided by latex gloves is compromised by disinfectants and fixatives, so that heavy duty or utility gloves may be needed for jobs with exposure to these chemicals.

Consider the cryostat a contaminated area. Wear the same protective gear as when dissecting a fresh specimen. Remember that freezing propellants can potentially spread infectious agents outside of the cryostat. Decontaminate the cryostat at regular intervals, using recommended disinfectants that will not harm sensitive surfaces or seals.

Specimens for histopathologic examination can be routinely fixed in 10% (v/v) neutral buffered formalin, or alternatively in mercurial fixatives (such as B5 or Zenker's) or Bouin's fixative. Cytologic smears can be fixed with 95% ethanol. HIV will be rendered inactive in tissues or smears by proper fixation. Fixatives may not thoroughly penetrate large tissue specimens. If specimens arrive in the histology laboratory in containers whose outer surfaces are contaminated with blood or body fluids, the surfaces can be disinfected by application of 0.5% sodium hypochlorite.

Saved tissues not blocked and embedded can be stored in fixative before discarding either via a tissue grinder attached to a sink or via incineration. Large specimens not suitable for fixation or tissues saved fresh must be placed in containers or bags marked as hazardous infectious waste before disposal in accordance with local statutes.

THE AIDS AUTOPSY

The CDC has recommended protective masks and eyewear (or face shields), laboratory gowns, gloves, and waterproof aprons be worn when performing or attending all autopsies.[118] All autopsy material should be considered potentially infectious for both HIV and HBV. Onlookers with an opportunity for exposure to blood or fluid splashes should be similarly protected. Routine standard infection control practices should be employed for all cases. Use a detergent to clean bloody or soiled work surfaces, followed by 0.5% sodium hypochlorite as a disinfectant in ALL areas of the autopsy department, except on sensitive equipment, where alternative disinfectants are used (Table 9).[896]

The best defense against accidents is good technique. Though many dissection skills in autopsy are similar to surgical pathology, some are unique and require specific training, such as evisceration of abdominal and thoracic organs or brain and spinal cord removal. A protective face shield is recommended with use of an oscillating saw, as with any power tool. Also available for use are hand protectors such as steel mesh gloves or "fishing" gloves of tough fabric which may provide additional security with evisceration of organs.

Although disposable latex or vinyl gloves are quite reliable, leakage can occur, so double gloving is recommended.[897] If cuts or abrasions on potentially exposed skin surfaces are present, they should be taped or covered before protective gear is put on. Persons performing frozen sections on HIV contaminated tissues using a cryostat designated for this purpose must be protected similarly to when handling fresh tissue.

Fixed tissues or fluids may be disposed of in a routine fashion through a tissue grinder to sanitary sewer or through incineration. Fresh tissues, blood, and body fluids can be autoclaved or placed in fixatives prior to disposal in accordance with local statutes. Formalin is the most cost-effective and efficacious fixative. Other contaminated wastes can be collected into marked, leak proof plastic bags and incinerated. Housekeeping personnel handling this material should use protective gear. Needles should never be recapped, and all needles or other sharp objects such as scalpel blades should be discarded into specifically designated containers.

Disposable paper scrub suits and gowns are often easier to work with and more cost-effective than cloth materials. If linen or other cloth scrub suits, gowns, or aprons are used they may be collected into bags that can be directly laundered without removal of the contents (bag dissolves in water).

The experience of the past decade in public hospitals and other centers performing large numbers of AIDS autopsies has shown that AIDS is not a threat to pathologists or other laboratory workers. There is no such thing as a "high risk" autopsy because the autopsy room environment can be well-controlled. It is also unlikely that requirements for unusual, extraordinary, or unwieldy procedures will add a definable margin of safety, but such procedures may lead to accidents or failure of compliance. A system of standard, routine procedures should be followed at all times.[898]

MORTUARY AND FORENSIC LABORATORY PROCEDURES

There is minimal risk of exposure to HIV for funeral directors and licensed embalmers with use of proper precautions. Bodies they receive should be handled in designated work areas that can be routinely disinfected. Personnel handling the bodies should wear a protective waterproof gown or apron, mask and protective eyewear (or face shield), and disposable gloves. Needles and other sharp objects require careful handling with proper disposal into puncture-proof containers. A waterproof, leak proof shroud or body bag should be used for transport of bodies.

The CDC has made the following specific recommendations for personnel working in forensic laboratories:[118]

Blood from ALL individuals should be considered potentially infective. In order to supplement other work site precautions, the following precautions are recommended for workers in forensic laboratories.

1. All specimens of blood should be put in a well-constructed, appropriately labeled container with a secure lid to prevent leaking during transport. Care should be taken when collecting each specimen to avoid contaminating the outside of the container and the laboratory form accompanying the specimen.

2. All persons processing blood specimens should wear gloves. Masks and protective eyewear or face shields should be worn if mucous-membrane contact with blood is anticipated (e.g., removing tops from vacuum tubes). Hands should be washed after completion of specimen processing.

3. For routine procedures, such as histologic and pathologic studies or microbiological culturing, a biological safety cabinet is not necessary. However, biological safety cabinets (Class I or II) should be used whenever procedures are conducted that have a high potential for generating droplets. These include activities such as blending, sonicating, and vigorous mixing.

4. Mechanical pipetting devices should be used for manipulating all liquids in the laboratory. Mouth pipetting must not be done.

5. Use of needles and syringes should be limited to situations in which there is no alternative, and the recommendations for preventing injuries with needles outlined under universal precautions should be followed.

6. Laboratory work surfaces should be cleaned of visible materials and then decontaminated with an appropriate chemical germicide after a spill of blood, semen, or blood-contaminated body fluid when work activities are completed.

7. Contaminated materials used in laboratory tests should be decontaminated before reprocessing or be placed in bags and disposed of in accordance with institutional and local regulatory policies for disposal of infective waste.

8. Scientific equipment that has been contaminated with blood should be cleaned and then decontaminated before being repaired in the laboratory or transported to the manufacturer.

9. All persons should wash their hands after completing laboratory activities and should remove protective clothing before leaving the laboratory.

10. Area posting of warning signs should be considered to remind employees of continuing hazard of infectious disease transmission in the laboratory setting.

Workers in the forensic sciences or law enforcement officers routinely collect and preserve forensic specimens including needles, knives, or other sharp objects that may be contaminated with blood from a crime victim. Such objects represent a potential hazard to persons handling this evidence. These specimens also require handling through a proper chain of custody procedure to be used as evidence in court, so there is a need to preserve blood or fluids or specimens without decomposition, precluding the use of airtight containers for some specimens.

The following basic guidelines are recommended:

1. Use puncture-proof, non-airtight containers for transportation of potentially contaminated evidence with sharp or cutting edges. Clearly mark these containers, HANDLE WITH CARE.

2. Sharp or pointed objects such as needles that are confiscated but not needed as evidence should be properly discarded into designated puncture-proof containers that are clearly labeled for use with infectious materials.

3. Each department should adopt standard safety procedures for search and seizure or collection of evidence to include initial handling, transportation, booking in evidence, storage, display, and disposal of potentially contaminated objects.

Specimens collected and transported in sealed containers that could undergo decomposition or degradation, such as blood for toxicologic studies, should be processed without delay. Such tissues or fluids obtained at the scene should be transported to the laboratory in sealed containers such as plastic bags, tubes with tight-fitting stoppers, or jars with screw-cap lids. These containers should be placed within a second sealed, leak proof container. Once in the laboratory, the specimens should be initially handled in a specified area by persons wearing protective clothing appropriate to the amount of manipulation of the specimen.[899]

ATHLETICS AND HIV INFECTION

HIV infection and sports participation has raised issues regarding risks for participants. Sports participation is not a risk for transmission. Recommendations for prevention of transmission of blood-borne pathogens during sports have included education of athletes about approaches to prevention of sexually transmitted diseases and the risks associated with injectable drugs. When resources permit, hepatitis B vaccination should be made available. Athletes should not be excluded from participation in sports solely because they are infected with HIV or hepatitis virus.[900,901] Persons with early to moderately advanced HIV infection can engage in moderate sport without risk to themselves or other participants. With the onset of AIDS, the ability to exercise can be compromised by disease conditions, and intensive bouts of competitive exercise should be avoided.[902]

For athletes participating in sports that involve person-to-person contact, it is recommended that skin wounds and potentially infectious skin lesions should be securely covered with bandages or simple wraps to prevent leakage of blood or serous fluid during sports activity. Injuries with bleeding should be promptly treated, blood should be washed off the skin, and the injured athlete permitted to return to sports activity only after the wound has been securely covered or wrapped. Contaminated equipment or uniforms wet with blood should be changed. Athletic trainers should use disposable gloves to prevent exposure to blood when treating injured athletes who are bleeding.[900]

In the United States, the National Football League has also determined that a player with HIV infection poses virtually no threat to others or himself by athletic participation. The long latent period between initial HIV infection and the development of AIDS means that athletic performance is unlikely to be affected for many years.[903]

A complete set of guidelines regarding bloodborne pathogens and sporting events have been adopted by the American Medical Society for Sports Medicine (AMSSM) and the American Academy of Sports Medicine (AASM).[904] The American Academy of Pediatrics have adopted similar guidelines as follows:[905]

- Athletes with human immunodeficiency virus, hepatitis B virus or hepatitis C virus infection should be allowed to participate in all competitive sports.

- The infection status of patients should be kept confidential. Confidentiality about an athlete's infection with a blood-borne pathogen is necessary to prevent exclusion of the athlete from sports because of inappropriate fear among others in the program.

- Athletes should not be tested for blood-borne pathogens because they are sports participants.

- Physicians should counsel athletes who are infected with human immunodeficiency virus, hepatitis B virus and hepatitis C virus that they have a very small risk of infecting other athletes. These athletes can then consider choosing a sport with a low risk of virus transmission. This will not only protect other participants from infection but also will protect the infected athletes themselves by reducing their possible exposure to blood-borne pathogens other than the one(s) with which they are infected. Wrestling and boxing, a sport opposed by the AAP, probably have the greatest potential for contamination of injured skin by blood.

- Athletic programs should inform athletes and their families that they have a very small risk of infection, but that the infection status of other players will remain confidential.

- Physicians and athletic program staff should aggressively promote hepatitis B virus immunization of all persons who may be exposed to athletes' blood. If possible, all athletes should receive hepatitis B virus immunization; more than 95 percent of persons who receive this immunization will be protected against infection.

- Coaches and athletic trainers should receive training in first aid and emergency care, and in the prevention of transmission of pathogens in the athletic setting.

- Coaches and health care team members should teach athletes about the precautions listed above and about high-risk activities that may cause transmission of blood-borne pathogens. Sexual activity and needle sharing during the use of illicit drugs, including anabolic steroids, carry a high risk of viral transmission. Athletes should be told not to share personal items, such as razors, toothbrushes and nail clippers, that might be contaminated with blood.

- In some states, depending on state law, schools may be required to comply with the Occupational Safety and Health Administration (OSHA) regulations for the prevention of transmission of blood-borne pathogens. The rules that apply must be determined by each athletic program. Compliance with OSHA regulations is a reasonable and recommended precaution, even if it is not required by the state.

- The AAP committee also recommends that the following precautions be taken in sports with direct body contact and sports in which an athlete's blood or other bodily fluids may contaminate the skin or mucous membranes of other participants or staff members of the athletic program.

- Athletes should cover existing cuts, abrasions, wounds or other areas of broken skin with an occlusive dressing before and during participation. Caregivers must also cover their own damaged skin to prevent transmission of infection to or from an injured athlete.

- Disposable, water-impervious vinyl or latex gloves should be worn to avoid contact with blood or other bodily fluids visibly tinged with blood and any object contaminated with these fluids. Hands should be cleaned with soap and water or an alcohol-based antiseptic hand wash as soon as gloves are removed.

- Athletes with active bleeding should be removed from competition immediately and bleeding should be stopped. Wounds should be cleaned with soap and water or skin antiseptics. Wounds should be covered with an occlusive dressing that remains intact during further play before athletes return to competition.

- Athletes should be told to report injuries and wounds in a timely fashion before or during competition.

- Minor cuts or abrasions that are not bleeding do not require interruption of play but can be cleaned and covered during scheduled breaks. During breaks, if an athlete's equipment or uniform is wet with blood, the equipment should be cleaned and disinfected and the uniform should be replaced.

- Equipment and playing areas contaminated with blood should be cleaned and disinfected with an appropriate germicide. The decontaminated equipment or area should be in contact with the germicide for at least 30 seconds. The area may be wiped with a disposable cloth after the minimum contact time or be allowed to air dry.

- Emergency care should not be delayed because gloves or other protective equipment is not available. If the caregiver does not have appropriate protective equipment, a towel may be used to cover the wound until a location off the playing field is reached and gloves can be obtained.

- Breathing bags and oral airways should be available for giving resuscitation. Mouth to mouth resuscitation is recommended only if this equipment is not available.

- Equipment handlers, laundry personnel and janitorial staff should be trained in the proper procedures for handling washable or disposable materials contaminated with blood.

CHAPTER 7 - MEDICOLEGAL ISSUES AND AIDS

DEATH INVESTIGATION AND CERTIFICATION IN AIDS

The medical examiner-coroner may need to conduct a comprehensive investigation, including an autopsy, in some deaths of HIV-infected persons. When an established diagnosis of AIDS by definitional criteria can be documented, an autopsy with histological confirmation of diagnosis may not always be necessary.[319,320] However, in cases in which the diagnosis is in doubt or in which death occurred under suspicious circumstances an autopsy should be performed. Investigation of deaths with HIV infection from job-related or accidental parenteral exposure to blood or blood products require an autopsy with histopathologic and/or laboratory confirmation of findings to prepare for possible litigation by surviving family who may challenge the medical examiner's determination of the cause and mode of death.

A thorough external examination of the body may reveal typical findings with AIDS such as cachexia, needle tracks of intravenous narcotism, onychomycosis of nails, or skin lesions typical of Kaposi's sarcoma. However, not all skin lesions appearing to be KS on gross examination are confirmed by microscopy. Use routine CDC criteria for AIDS as a guide in death investigation to search for data to confirm or exclude AIDS.[319,320] The presence of a medical record may document specific clinical findings, laboratory testing, or tissue diagnoses. In some states, reporting of laboratory testing for HIV may be strictly regulated, limiting availability of medical data. In the absence of definitive documented findings in available records, an internal examination should still be performed when doubt exists concerning either mode or underlying cause of death.[896]

Additional information may be obtained either from autopsy with microscopic examination and/or postmortem microbiologic cultures of tissues or fluids or from postmortem laboratory testing for HIV infection, or both. Postmortem testing for HIV infection can be done on sera from blood, vitreous humor from the eye, and bile from gallbladder. Samples are stable at room temperature for at least one month. Testing by enzyme immunoassay and Western blot (WB) for antibodies to HIV is performed similarly to screening pre mortem samples.[906,907]

Viral culture of blood, fluids, or tissues for HIV is definitive for diagnosis of infection, but is difficult to perform and has very limited availability. If specimens for enzyme immunoassay or other serologic testing are not obtained at the time of autopsy, then HIV detection by *in situ* hybridization, polymerase chain reaction, and immunohistochemical methods can be carried out in formalin-fixed and paraffin embedded tissues--even years later. Microbiologic culture of opportunistic infectious agents in tissues or fluids is typically available in many laboratories for all agents except *Pneumocystis carinii*, *Toxoplasma gondii*, *Isospora belli*, and *Cryptosporidium*. Most of the remaining agents require special media, complex procedures, and several weeks' time for definitive results.[308,309,296]

DETERMINATION OF CAUSE AND MODE OF DEATH WITH HIV INFECTION

Not all deaths in which HIV is present are caused by HIV. The proportion of deaths from AIDS-related causes has decreased when highly active antiretroviral therapy (HAART) is widely available, and non-AIDS conditions may account for at least a third of deaths, and may include non-natural causes such as drug overdose, suicide, and violence.[908] The mode or manner in which HIV was acquired is of particular importance. Always investigate for risk factors for HIV infection along with information obtained from scene investigation and postmortem examination of tissues and fluids.[896]

Deaths of HIV-infected persons who have not developed the clinical syndromes of HIV infection and AIDS by definitional criteria are usually due to causes other than HIV. HIV-infected persons with a CD4 lymphocyte count >200/μL, or those with stages A and B of HIV-infection, are

generally not at great risk for death. As a rule, HIV infection should lead to clinically apparent consequences of immune deficiency meeting diagnostic criteria for AIDS in order to cause death.

The proximate causes of death in 565 cases with AIDS in a large autopsy series are given in Table 10. Over half of the deaths were due to pneumonia, either *Pneumocystis carinii* pneumonia, cytomegalovirus pneumonia, or bacterial bronchopneumonias. *Cryptococcus neoformans*, Kaposi's sarcoma, and malignant lymphomas also frequently involved the lungs. Thus, the single most important organ to examine is lung, and the commonest mechanism of death in AIDS is respiratory failure (in two thirds of cases). Central nervous system lesions lead to death in one fifth of AIDS patients, so it is important to remove and examine the brain at autopsy. Gastrointestinal diseases lead to death in one seventh of cases. Over 90% of the immediate causes of death in AIDS can be determined from histological examination alone.[342]

The differentiation of natural versus accidental mode of death with HIV infection and AIDS is made primarily by risk factors. If HIV was a sexually transmitted disease, including perinatal deaths in which the mother acquired HIV sexually, then the mode is natural. Identification of intravenous narcotism as the source of HIV infection establishes an accidental mode of death. If transmission occurred from administration of blood or blood products in the course of therapy for natural disease (e.g., treatment of hemophilia, hemorrhage, or bone marrow failure) then the mode is natural. If HIV was acquired from transfusion of blood or blood products in the course of treating a victim of accident, suicide, or homicide, and the victim later died from HIV infection or AIDS as a result, then the mode is not altered from accident, suicide, or homicide. Death from HIV infection or AIDS as a consequence of HIV transmission through job-related exposure is an accidental mode also qualifying for workman's compensation benefits.

Proper death certification in AIDS has been and will continue to be important for generation of appropriate vital statistics upon which understanding of the epidemiology and extent of HIV infection will depend.[909]

ETHICAL ISSUES ARISING FROM THE AIDS EPIDEMIC

HIV will continue to spread in the population due to several factors: (1) there is a large reservoir of millions of HIV-infected persons who may not know they are infected. (2) knowledge of infection may not modify sexual behavior or other practices such as intravenous drug use. (3) there is no effective vaccine or curative treatment available. (4) even with knowledge of infection, basic human rights cannot be restricted enough to curb the spread of this disease.

In spite of mandatory testing of blood and blood products, cases of accidental exposure to HIV from these sources will rarely occur. Complex testing schemes have eliminated much of the risk, but the testing systems are not perfect. Additional HIV subtypes, such as HIV-2, may become prevalent. These problems will require even more complex screening programs, particularly in blood banking, and medical liability problems with blood products will continue to exist.

The adoption of the criterion that a CD4 lymphocyte count of <200 cells/μL is indicative of AIDS when HIV infection is present has significance because the low CD4 count itself implies a high probability of HIV infection. Thus, laboratories and other agencies performing CD4 lymphocyte count must be aware of the implications of the test results and provide for confidentiality of testing, as with tests for HIV, where appropriate.

Discrimination against HIV-infected persons on the job or in the community will lead to conflicts. Recent court cases in the United States have established the rights of HIV-infected persons against discrimination on the job, in housing, and at school. This protection against discrimination has even been extended to health care workers who, though not infected by HIV, provide essential services for persons who are HIV-infected. The courts have not generally condoned discriminatory practices by health care workers against patients with HIV by refusing to offer treatment or by refusal to accept occupational hazards.[910,911]

Access of AIDS patients to new treatments not yet approved by governmental agencies will be debated. HIV-infected persons may knowingly donate blood or commit purposeful acts in an attempt to transmit the infection to others, prompting criminal charges. Clinical diagnosis or death certification of congenital AIDS may have implications for surviving family members with regard to placement of children in foster homes and investigation of parents. Death certification in cases of suspected AIDS may have profound sociopsychological and socioeconomic implications for surviving family members (i.e., insurance claims or risks of exposure relating to HIV infection).

The CDC have adopted guidelines which indicate that there is no basis either for mandatory HIV testing of health care workers or for restricting the practice of HIV-infected health care workers who perform non-exposure prone invasive procedures using recommended technique with adherence to universal precautions. Exposure prone procedures are to be delineated by organizations and institutions which oversee medical or dental practice, and health care workers who perform such procedures should know their HIV status. HIV-infected health care workers should not perform exposure prone invasive procedures unless they have sought counsel from an expert review panel and have informed the patient. HIV-infected health care workers should, it is recommended, be provided opportunities to continue appropriate patient-care activities through career counseling and job retraining.[912]

The risk for HIV infection from infected patients to health care workers, or from health care workers to patients, cannot be completely eliminated, but remains negligible. Screening of health care workers for HIV is not cost-effective.[913] The risk for transmission of HIV to a patient from an infected surgeon has been estimated to be comparable to the risk of HIV transmission after transfusion of blood screened for HIV and less than the risk from general anesthesia. To date, only two health care workers (a dentist and a surgeon) have been implicated in transmission of HIV to patients. For the future, risk reduction will be best accomplished via thorough infection control measures rather than reliance upon workplace restrictions or upon mandatory HIV testing.[119,914,915]

HIV TESTING AND COUNSELING

Testing for HIV infection in patients has become an important issue for health care professionals in many disciplines and locations, not just for those in large metropolitan areas. Patients must receive adequate HIV test counseling and education. The mainstay of initial HIV testing in developed nations is the EIA test for HIV antibody, with all initial positives confirmed by a second more specific test, usually a Western blot. False positive EIA tests or indeterminate Western blot tests can occur but will constitute a smaller fraction of the total positives as the prevalence of HIV infection increases in the population tested. In addition to initial testing, the patient should be informed that additional testing at 3 and 6 months may be warranted because HIV antibodies may not appear for 6 to 12 weeks (and rarely longer) after primary infection or because indeterminate results may appear. The patient should be provided with counseling and support as necessary to deal with the stress involved in testing and waiting for results.[195,275,285]

Persons to be tested should be identified primarily on the basis of a history of risk factors for HIV infection (Table 2). The history-taking must include very frank, but non-judgmental and open-ended questions which are asked in order to elicit specific risks related to sexual behavior and drug use. In the course of taking a history and performing a physical examination, findings that suggest the presence of sexually transmitted diseases, opportunistic infections or neoplasms characteristic of HIV infection, or physical findings of acute or advanced HIV infection should suggest the need for HIV testing. Health care professionals who display compassionate care and allow the patient to ask questions and express feelings through open communication will provide the best setting in which testing can proceed in the best interests of the patient as well as allow for educational efforts to be successful. Patient education should include information about: how HIV is spread, what can be done to decrease the risk of HIV infection, how HIV infection affects the body, what danger exists to others from an infected person, what treatments are available, and what the course of the disease is to the final outcome--death.[80,95,115,123,125,195]

Patients should be informed that some facilities may offer "anonymous" HIV testing in which no specific identifying information about them is collected. Such anonymous testing will provide the patient only with a positive or negative result outside of the context of continuing medical care, and additional care will require informing a physician about such results. Patients should be informed that "confidential" testing by most health care facilities requires specific patient consent and that positive results will be reported to public health officials as required by law. Health care professionals should obtain consent for such confidential testing according to local statutes and should be aware of the minimum age at which persons can legally give consent. Physicians should also be aware of the need to maintain confidentiality of additional test results such as total lymphocyte or CD4 lymphocyte counts, microbiologic cultures, or tissue diagnoses (e.g., Kaposi's sarcoma) which have strong implications concerning possible HIV infection.[916]

Persons who have been tested should be provided with the opportunity to obtain and freely discuss the results with the physician.[917,918] Even if the result is negative, such a session provides an opportunity to reinforce the educational information about HIV. A positive result should be discussed in regard to understanding what this result means about life expectancy, the need for eventual medical care and treatment, the need to inform others who have been exposed to HIV, the need to modify behaviors to reduce the risk for spread to others, and the need for psychological and social support services.[195] A significant problem is the failure of persons tested to return for results. The use of rapid HIV testing for screening (results in less than an hour) leads to a greater number of new HIV infections detected and in fewer patients leaving before test results are obtained.[919]

Pregnant women represent an important group for whom HIV testing can provide considerable benefit. This is because of the significant reduction in perinatal HIV transmission that can be accomplished by giving mothers-to-be antiretroviral therapy.[142]

Mandatory testing remains controversial. The stigma associated with a diagnosis of HIV infection continues to prevent infected persons from being treated similar to patients with most

other illnesses. This makes HIV testing less than routine. In the U.S., mandatory testing has been applied to personnel in the armed forces, foreign service personnel, immigrants, and certain sex offenders. Other jurisdictions, including some of the individual states in the U.S., have mandated testing for additional populations, including prisoners and newborns. Many states provide for compulsory testing of patients to determine their HIV status when an injury to a health care worker may involve possible HIV transmission.[910]

In the U.S., the results of HIV testing for medical purposes are generally held to be confidential. Most states have laws protecting confidentiality of HIV-related information. However, all states require reporting of all patients diagnosed with AIDS to governmental health departments, though little more than half of the states require similar reporting for HIV infection. A "duty to warn" other persons, including spouses and sex partners, regarding a patient's HIV positivity by health care providers is specifically permitted by law in some states, though the courts have ruled that the health care provider has a duty to warn persons at risk for infection.[910]

BLOOD AND TISSUE BANKING AND AIDS

The AIDS epidemic has markedly modified screening procedures in blood and tissue banks. Transfusion-associated AIDS early in the epidemic accounted for some cases of AIDS, particularly in persons with hemophilia. Current and future retroviral laboratory screening tests for HIV, first initiated in 1985 in the U.S., have eliminated virtually all of the risk. In the U.S. blood products are currently screened for antibodies to HIV1/2, HTLVI/II, hepatitis B, hepatitis C (HCV) and syphilis. Testing is also performed for donor ALT (SGOT) levels, for the presence of hepatitis B surface antigen, human immunodeficiency virus (HIV) p24 antigen and, using nucleic acid amplification testing (NAT), for HIV and HCV nucleic acids. Despite excellent methodology, however, the tests employed are not perfect, and blood containing HIV may very rarely be released for transfusion. Since patients receiving transfusions may die from their primary disease or other causes prior to onset of AIDS, then the overall risk for transmission HIV infection from transfusion is extremely small---on average only 1 case in 1 900 000 single donor units of screened blood in the U.S.[120] This risk remains low with repeat blood donors.[920] Behavioral risk factor screening appears to be effective in reducing the risk for HIV infection through blood products.[921]

In populations with a low prevalence of HIV, including most developed nations, the risk for HIV transmission by blood products is very low, while in some larger metropolitan areas or in parts of Africa or Asia, the risk is higher. In developing nations where blood screening is not rigorous, 5 to 10% of HIV infections may be acquired through use of blood products. Despite economic hardships in many regions, the screening of blood donors for HIV is a cost-effective strategy to prevent the spread of HIV, particularly in areas where seroprevalence of HIV is >5%. Additional strategies to reduce the spread of transfusion-associated HIV infection include: elimination of paid donors, reduction in use of family members to donate blood for a patient, institution of guidelines for judicious use of transfusion therapy, and prevention of severe anemias.[121]

Current screening tests include EIA for both HIV-1 and HIV-2 (though the prevalence of the latter outside of West Africa is very low) and HIV-1 p24 antigen.[922] Addition of testing for HIV-1 p24 antigen, which can detect some newly HIV-infected persons in the EIA seronegative "window," is estimated to find approximately one infected blood donor per 6 million donations in the U.S.[121] As EIA screening test performance improves, the seronegative window period becomes more important. Nucleic acid amplification tests (NAT) for HIV RNA have reduced the window period more than p24 testing, reducing the risk of HIV transmission from blood products to less than 1 in 1 900 000, but show poor cost-effectiveness.[923] The cost effectiveness of NAT-based screening is estimated to be $4.7 to 11.8 million U.S. dollars per quality-adjusted life-year.[924] In populations where the incidence of new HIV infections is increasing, this potential window error becomes more important.[925] Testing by donor centers in the U.S. since 1989 is also routinely performed for HTLV I and HTLV II.[73]

In addition, screening questions applied to potential donors are aimed at determination of possible high risk behaviors which exclude them as donors (sex with another man even once, intravenous drug use, etc.) and symptoms of infection (generalized lymph node enlargement, mucocutaneous lesions, weight loss, etc.). Blood collection facilities also employ a confidential unit exclusion form which provides donors who are under duress to donate, but do not want to resist or answer truthfully for fear of being detected with HIV infection, to designate their blood as unsuitable for transfusion. Such donor self-deferral is effective in reducing the risk of HIV transmission through transfusion of blood products.[926] Autologous donations for elective surgical procedures have been encouraged, but directed donations have been found to be no safer than the routine blood supply.[73,927]

Liability problems for blood banks stem from the few blood products that have transmitted HIV to recipients. In the U.S., courts in some jurisdictions have held that as long as blood suppliers meet professional standards of practice they are immune from liability. However, in other jurisdictions, blood suppliers have been found negligent despite meeting the established standard of

care for the time period in which transmission of HIV occurred, implying that by maintaining liability there should be an incentive to adopt new precautionary measures to increase the safety level of the blood supply. Blood banks have also been held accountable for maintaining confidentiality of testing donors and for maintaining records of such testing. Many jurisdictions also require mandatory reporting of HIV positive donors. Thus, potential donors should be advised of the confidentiality protections as well as the circumstances under which test results will be disclosed.[928]

AIDS patients may require transfusion therapy for cytopenias resulting from progression of their disease and from bone marrow suppression resulting from drug therapy for infections or neoplasms associated with AIDS. Additionally, zidovudine (ZDV) chemotherapy against HIV has as a side effect significant severe cytopenias in about 12% of patients who take this drug. Blood products administered to AIDS patients have the potential for graft versus host reactions, but there have been no significant studies to suggest that this occurs frequently. There is no evidence that viral or cytokine activation occurs following blood transfusion in patients with advanced HIV infection, and leukoreduction appears to have no clinical benefit.[929].

Transplantation of human tissues and organs also carries the potential risk for HIV transmission. Transplantation involving kidney, liver, heart, pancreas, bone, and skin have been reported to be associated with this risk. Autologous transplants do not carry this risk, except potentially via administrative errors. In addition, HIV transmission via artificial insemination from banked sperm has occurred. Human milk also carries a potential risk.[930,931]

Screening of potential donors through assessment of risk factors and through testing for HIV (enzyme immunoassay with Western blot confirmation) should be performed similar to that for blood donation. In the case of cadaveric donors, a history must be obtained from available family or friends. In either case, HIV screening must be completed within 12 to 24 hours to allow for viability of the transplant tissues. Recipient testing for HIV is recommended just prior to transplantation and 3, 6, and 12 months thereafter in order to identify and offer therapies to persons who may become infected.[930,931]

There is no current method for inactivating HIV in whole organs. Use of gamma irradiation will not eliminate HIV from in vitro samples.[932] Human breast milk can be pasteurized to inactivate HIV.[889,930,931]

TABLES 1 - 10

Table 1 - Body Fluids Containing HIV

Fluids routinely associated with transmission of HIV

- Blood and blood components
- Semen
- Vaginal fluid
- Breast milk

Fluids not associated with transmission of HIV

- Saliva
- Urine
- Tears
- Sweat
- Cerebrospinal fluid

Table 2 - Behavioral Risks for HIV Infection

Sexual Intercourse: The following are associated with greater risk for HIV infection for both men and women, if one or both partners, either male or female, are infected:

Practices that result in lacerations, tears, or denudation of penile, vaginal, rectal, or oral epithelia
Increasing the number of sexual partners
Presence of genital, rectal, or oral ulcers from other sexually transmitted diseases
Not wearing a condom
Being under the influence of alcohol or drugs which impair judgment and decision-making
Engaging in sexual intercourse with a person whose stage of HIV infection is primary or advanced
More specific risks for a particular style of intercourse include:

Vaginal Intercourse:

Lack of circumcision in the male
Cervical ectopy
Oral contraceptive use
Pregnancy
Menstrual bleeding

Anal Intercourse:

Receptive anal intercourse > insertive anal intercourse, though either style is a risk
Use of douches or lubricants

Oral Intercourse

Presence of oral mucosal lesions
Use of cocaine (e.g., "crack pipes")

Lesbian Intercourse

Inclusion of male partners in sexual activities
Practices (e.g., mutual use of dildos) that allow exchange of blood or vaginal fluid

Blood Exposure: Any practice that allows for exchange of HIV-infected blood from one person to another, regardless of age, sex, race, or state of health, represents a risk for HIV exposure:

Intravenous drug use with sharing of needles or other "works"
Use of needles "cleaned" with a disinfectant other than bleach
Tattooing with sharing of devices (e.g., needles) used
Blood rituals (e.g., "blood brothers") with commingling of blood
Transfusion with inadequately screened or tested blood or blood products

Congenital Exposure: The fetus or infant of a mother who is infected with HIV is at risk for acquiring HIV infection, but this risk is increased with:

Maternal elevated CD8+ lymphocyte count
Maternal decreased CD4+ lymphocyte percentage
Maternal chorioamnionitis or funisitis
Persistent maternal fever
Breast feeding of the infant

Table 3 – Pharmacologic Agents for Antiretroviral Therapy

Nucleoside Reverse Transcriptase Inhibitors (NRTI's)

- Zidovudine (ZDV, or AZT)
- Zalcitabine (ddC)
- Didanosine (ddI)
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)

Nucleotide Reverse Transcriptase Inhibitors

- Adefovir (ADV)
- Tenofovir (PMPA)
- Cidofovir (CDV)
- Emtricitabine (FTC)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI's)

- Nevirapine (NVP)
- Delavirdine (DLV)
- Efavirenz (EFV)

Protease Inhibitors (PI)

- Saquinavir (SQV)
- Indinavir (IDV)
- Ritonavir (RTV)
- Nelfinavir (NFV)
- Amprenavir (APV)
- Lopinavir (LPV)
- Tipranavir (TPV) – non-peptidic
- Atazanavir (ATV)

Cell Fusion Inhibitors

- Enfuvirtide

Table 4 - Definitive Diagnostic Techniques for Diseases Indicative of AIDS

Indicator Disease for AIDS	Microscopy (cytology, histology)	Microbiologic Culture	Serum Serology	Clinical Criteria
Candidiasis	H&E,PAS,GMS	-	-	Gross Appearance
Cervical cancer	H&E	-	-	-
Coccidioides immitis	H&E,PAS,GMS	Fungal	Antigen	-
Cryptococcus neoformans	H&E,PAS,GMS	Fungal	Antigen	-
Cryptosporidium	H&E,AFB	-	-	-
Cytomegalovirus	H&E,IPX	Viral	Antigen	-
Encephalopathy, HIV	-	-	-	Clinical Features
Herpes simplex virus	H&E,IPX	Viral	Antigen	-
Histoplasma capsulatum	H&E,PAS,GMS	Fungal	Antigen	-
HIV wasting syndrome	-	-	-	Clinical Features
Isosporiasis	H&E,AFB	-	-	-
Kaposi's sarcoma	H&E	-	-	-
LIP	H&E	-	-	-
Malignant Lymphoma	H&E,IPX	-	-	-
Mycobacteria	-	Mycobacterial	-	-
PML	H&E,IPX	-	-	-
Pneumocystis pneumonia	GMS,Giemsa,IPX	-	-	-
Pneumonia, recurrent	-	Routine	-	Clinical Features
Salmonellosis	-	Routine	-	-
Toxoplasma gondii	H&E,IPX	-	-	-

Key: H&E=routine hematoxylin and eosin stain; IPX=immunohistochemical method with specific monoclonal antibody; GMS=Gomori methenamine silver stain; PAS=periodic acid-Schiff stain; AFB=Ziehl-Neelsen or Kinyoun acid fast stain; Giemsa=Giemsa stain; LIP=lymphoid interstitial pneumonitis; PML=progressive multifocal leukoencephalopathy

Table 5 - Documented Opportunistic Infections and Neoplasms in the Clinical Course and at Autopsy by Organ System in 565 Patients with AIDS: 1982-1993
AIDS Autopsy Program, LAC+USC Medical Center, Los Angeles, California

	PCP	CMV	CAND	KS	MAI	HERP	LYM	CRYP	MTB	TOXO	HIST	COCCI
TOTAL CASES	308	286	240	138	104	92	81	78	76	51	13	10
HEART	2	5	13	6	3	-	13	13	5	5	4	3
LUNG	305	133	44	56	30	1	27	47	63	6	10	10
UPPER RESP	-	6	18	41	2	1	-	3	1	2	1	-
ORAL CAVITY	-	3	144	37	1	10	1	4	1	1	-	-
ESOPHAGUS	-	41	55	27	1	10	3	3	-	-	2	-
STOMACH	-	34	18	46	2	-	14	8	5	2	2	-
SM. INTESTINE	-	40	8	61	27	-	18	7	9	-	5	1
COLON-RECTUM	-	43	6	45	9	5	17	6	4	1	4	-
PERIANAL	-	4	3	-	1	27	-	-	-	-	-	-
FEMALE GENITAL	-	1	3	-	-	2	1	2	-	-	-	-
MALE GENITAL	1	11	4	16	2	2	6	15	3	2	3	-
LOWER URINARY	1	6	5	3	1	-	9	-	-	1	-	-
KIDNEY	3	12	19	5	8	-	19	23	15	-	3	5
LIVER & GB	3	16	4	28	44	-	27	25	19	2	8	6
PANCREAS	2	16	1	9	1	-	10	18	4	2	2	-
SPLEEN	4	16	8	15	65	-	19	31	27	-	9	6
LYMPH NODE	12	8	6	59	86	-	31	43	40	-	11	8
BONE MARROW	1	-	2	2	25	-	17	12	9	2	7	3
BRAIN	-	40	9	-	3	3	22	65	5	44	-	2
EYE	2	49	1	1	-	3	-	1	-	1	1	-
PITUITARY	2	5	-	-	-	-	4	11	1	2	-	-
THYROID	2	15	5	1	2	-	3	14	4	-	2	4
ADRENAL	3	209	2	11	15	-	18	20	6	2	5	-
SKIN	1	6	16	110	1	65	5	6	1	-	-	1

Table 6 - Average Number of Organs or Organ Systems Involved by AIDS Diagnostic Diseases

Coccidioidomycosis	6.2
Histoplasmosis	4.4
Malignant Lymphoma	3.8
Cryptococcosis	3.7
M. tuberculosis	3.3
M. avium-complex	3.3
Kaposi's Sarcoma	2.8
Cytomegalovirus	1.9
Candidiasis	1.4
Herpes	1.4
Toxoplasmosis	1.4
Pneumocystis carinii	1.1
Cryptosporidiosis	1.1

Table 7 - Therapies for Diseases Indicative of AIDS

Disease Process	Clinical Therapy
Candidiasis, oral	Clotrimazole troches, topical nystatin
Candidiasis, esophageal	Clotrimazole troches, topical nystatin, fluconazole, ketoconazole
Candidiasis, vulvovaginal	Miconazole, clotrimazole suppositories
Cervical cancer	Surgical therapy
Coccidioides immitis	Amphotericin B
Cryptococcus neoformans	Amphotericin B with or without flucytosine; or fluconazole or itraconazole
Cryptosporidium	Paromomycin
Cytomegalovirus	Ganciclovir, foscarnet
Herpes simplex or zoster	Acyclovir
Histoplasma capsulatum	Amphotericin B, or itraconazole, or fluconazole
Isosporiasis	Trimethoprim-sulfamethoxazole
Microsporidium	Albendazole (for *Septata intestinalis*)
Giardia lamblia	Metronidazole
Kaposi's sarcoma	Surgical therapy, chemotherapy, radiation therapy
LIP	None effective
Malignant Lymphoma	Chemotherapy, radiation therapy, surgical therapy
M tuberculosis	Isoniazid, rifampin, pyrazinamide, plus ethambutol for resistance
M avium complex	Rifabutin, clarithromycin, ethambutol
PML	Cytosine arabinoside
P carinii pneumonia	Trimethoprim-sulfamethoxazole, or pentamidine, trimetrexate
Pneumonia, recurrent	Antibiotic therapy appropriate to sensitivity of bacteria cultured
Salmonellosis	Amoxicillin, trimethoprim-sulfamethoxazole, ciprofloxacin
Toxoplasma gondii	Pyrimethamine with sulfadiazine and folinic acid

Key: LIP=lymphoid interstitial pneumonitis; PML=progressive multifocal leukoencephalopathy

Table 8 - Patterns of Pulmonary Involvement with AIDS-diagnostic Diseases

Alveolar	Pneumocystis carinii Cytomegalovirus Candida
Interstitial	Cryptococcus neoformans Histoplasma capsulatum M. avium-complex Lymphoid interstitial pneumonitis
Bronchovascular	Kaposi's sarcoma Malignant lymphoma Lymphoid interstitial pneumonitis
Tracheobronchial	Candida Kaposi's sarcoma
Pleural	Kaposi's sarcoma M. tuberculosis
Granulomatous	M. tuberculosis Cryptococcus neoformans Histoplasma capsulatum

Table 9 - Laboratory Disinfectants and Fixatives Effective Against HIV (adapted from Tierno, 1986)

	Minimum Effective Concentration	Common Concentration to Use
Household bleach (sodium hypochlorite)	0.02 %	0.5 %
Hydrogen peroxide	0.3 %	1-3 %
Rubbing alcohol (isopropyl alcohol)	30 %	50 %
Lysol	1 %	1 %
Quaternary ammonium chloride	0.08 %	1 %
Nonidet P-40	1 %	1 %
Ethanol (ethyl alcohol)	25 %	50-95 %
Beta-proprionolactone	1:400	1:400
Formalin	2 %	4-10 %
Glutaraldehyde	0.1 %	1-2 %

Table 10 - Immediate Causes of Death by Disease and Organ Failure in 565 Patients with AIDS at Autopsy: 1982-1993
AIDS Autopsy Program, LAC+USC Medical Center, Los Angeles, CA

Organ System Involved	Resp	CNS	GI	Endo	Liver	Heart	GU	BM	Skin	Totals
Pneumocystis carinii	170	-	-	-	-	-	-	-	-	170
Bronchopneumonia	52	-	-	-	-	-	-	-	-	52
Cytomegalovirus	31	9	4	4	-	-	-	-	-	48
Malignant Lymphoma	11	16	10	1	3	4	1	1	1	48
Cs neoformans	13	22	1	-	-	-	1	-	-	37
M tuberculosis	14	1	-	-	1	-	1	-	-	26
Septicemia	-	-	-	-	-	-	-	-	-	32
Kaposi's sarcoma	19	-	6	-	-	-	-	-	-	25
T gondii	1	19	-	-	-	1	-	-	-	21
Encephalopathy	-	16	-	-	-	-	-	-	-	16
M avium-intracellulare	4	-	5	1	-	-	-	-	-	10
H capsulatum	6	1	1	-	1	-	-	-	-	9
Candida	6	2	-	-	-	-	1	-	-	9
Cs immitis	5	1	-	-	-	-	-	-	-	6
Aspergillosis	6	-	-	-	-	-	-	-	-	6
Cryptosporidium	-	-	5	-	-	-	-	-	-	5
HIV nephropathy	-	-	-	-	-	-	2	-	-	2
Miscellaneous	12	5	9	2	4	6	1	1	3	43
Total Occurrences									565	

Key: Resp=respiratory system from epiglottis to lung; GI=gastrointestinal system; Endo=endocrine system; LN=lymph nodes; CNS=central nervous system; GU=genitourinary system; BM=bone marrow; PML=progressive multifocal leukoencephalopathy; HIV=human immunodeficiency virus

Encephalopathy includes: HIV encephalopathy 8, Progressive multifocal leukoencephalopathy 7, acute hemorrhagic leukoencephalopathy 1. Septicemia includes: Bacterial organisms 25, MAC 4, Candida 3

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