Immunodeficiency Syndromes
General classification

• Primary
  • Genetically determined

• Acquired
  • As complication of infections, other diseases

• Clinical symptoms
  • Main: infections
Primary immunodeficiencies

• Thought to be rare, indeed mild forms of genetic immune deficiency may be more frequent than expected

• Generally they manifest themselves in infancy
  • Susceptibility to infections

• They may affect
  • Innate immunity
  • B/T cells
  • May be associated with systemic diseases
## Defects in innate immunity

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<tr>
<td>Leukocyte adhesion deficiency 1</td>
<td>Defective leukocyte adhesion because of mutations in β chain of CD11/CD18 integrins</td>
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<tr>
<td>Leukocyte adhesion deficiency 2</td>
<td>Defective leukocyte adhesion because of mutations in fucosyl transferase required for synthesis of sialylated oligosaccharide (receptor for selectins)</td>
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<tr>
<td>Chèdiak-Higashi syndrome</td>
<td>Decreased leukocyte functions because of mutations affecting protein involved in lysosomal membrane traffic</td>
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<tr>
<td>Chronic granulomatous disease</td>
<td>Decreased oxidative burst</td>
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<tr>
<td>X-linked</td>
<td>Phagocyte oxidase (membrane component)</td>
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<td>Autosomal recessive</td>
<td>Phagocyte oxidase (cytoplasmic components)</td>
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<tr>
<td>Myeloperoxidase deficiency</td>
<td>Decreased microbial killing because of defective MPO-H$_2$O$_2$ system</td>
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<td>Defects in the Complement System</td>
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<td>C2, C4 deficiency</td>
<td>Defective classical pathway activation, results in reduced resistance to infection and reduced clearance of immune complexes</td>
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<tr>
<td>C3 deficiency</td>
<td>Defects in all complement functions</td>
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<tr>
<td>Deficiency of complement regulatory proteins</td>
<td>Excessive complement activation; clinical syndromes include angioedema, paroxysmal hemoglobinuria, others</td>
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The table lists some of the more common inherited immune deficiencies affecting phagocytic leukocytes and the complement system.

- Defects in leukocyte adhesion
  - Recurrent bacterial infection due to granulocytic defects

- Defects in phagolysosome function
  - Chèdiak-Higashi syndrome: autosomal recessive disease involving the gene LYST, encoding a protein that regulates lysosomal membrane traffic
    - Several abnormalities also affecting other systems (CNS, platelets, melanocytes)
    - Neutropenia, giant granules
    - Susceptibility to infections

- Chronic granulomatous disease
  - Defects in the enzyme responsible for the production of superoxide, and decreased oxidative burst
  - Decreased neutrophil function, resulting in a macrophage-rich chronic inflammatory reaction

- Defects of the complement system
  - C2-C4 deficiency
    - Susceptibility to infections, often compensated by activation of the alternative complement pathway
  - C1 INH deficiency
    - Hereditary angioedema due to hyperactivation of the system, and particularly of proteases of the kallikrein system that leads to the production of vasoactive peptides leading to edema, asphyxia, etc.
Defects in adaptive immunity
Severe Combined Immunodeficiency

• Severe combined immunodeficiency (SCID) represents a constellation of genetically distinct syndromes, all having in common defects in both humoral and cell-mediated immune responses

• Persons with SCID are extremely susceptible to recurrent, severe infections by a wide range of pathogens, including *Candida albicans*, *Pneumocystis jiroveci*, *Pseudomonas*, cytomegalovirus, varicella, and a whole host of bacteria.

• Without HSC transplantation, death occurs within the first year of life.
X-linked SCID

• Most common form (50% cases)

• **mutation in the common γ-chain (γc) subunit of cytokine receptors**

• This transmembrane protein is a signal-transducing component of the receptors for IL-2, IL-4, IL-7, IL-9, IL-11, IL-15, and IL-21

• IL-7: defect in T-cell development
  • Dramatic decrease in T cells
  • B cells may develop normally but they do not synthesize properly Ab, since there is a lack of T helper cell function

• IL-15 is important for the maturation and proliferation of NK cells, and because the common γ chain is a component of the receptor for IL-15, these individuals often have a deficiency of NK cells as well.
ADA deficiency

• Autosomal recessive SCID
• it has been proposed that deficiency of ADA leads to accumulation of deoxyadenosine and its derivatives (e.g., deoxy-ATP), which are toxic to rapidly dividing immature lymphocytes, especially those of the T-cell lineage.
• Hence there may be a greater reduction in the number of T lymphocytes than of B lymphocytes.
• (As in X-linked SCID) thymus is small and devoid of lymphoid cells
  • Other lymphoid tissues are hypoplastic as well
Gene therapy of X-linked SCID

• Hematopoietic stem cell (HSC) transplantation is the mainstay of treatment
• X-linked SCID is the first human disease in which gene therapy has been successful
• A normal γc gene is expressed using a viral vector in HSCs taken from patients, and the cells are then transplanted back into the patients
• The clinical experience is small, but some patients have shown reconstitution of their immune systems for over a year after therapy
• Unfortunately, however, about 20% of these patients have developed T-cell lymphoblastic leukemia, highlighting the dangers of this particular approach to gene therapy.
X-Linked Agammaglobulinemia (Bruton Agammaglobulinemia)

- characterized by the failure of B-cell precursors (pro-B cells and pre-B cells) to develop into mature B cells
- caused by mutations in a cytoplasmic tyrosine kinase, called Bruton tyrosine kinase (Btk)
- Btk is a protein tyrosine kinase that is associated with the Ig receptor complex of pre-B and mature B cells and is needed to transduce signals from the receptor. When it is mutated, the pre-B cell receptor cannot deliver signals, and maturation stops at this stage
- Because light chains are not produced, the complete antigen receptor molecule (which contains Ig heavy and light chains) cannot be assembled and transported to the cell membrane
- The disease usually does not become apparent until about 6 months of age, as maternal immunoglobulins are depleted
  - Several infections occur due to the lack of antibodies
- Therapy: in the past, most patients succumbed to infection in infancy or early childhood. Prophylactic intravenous Ig therapy allows most individuals to reach adulthood.
Acquired Immunodeficiency Syndrome (AIDS)

- AIDS is a disease caused by the retrovirus human immunodeficiency virus (HIV) and characterized by profound immunosuppression that leads to opportunistic infections, secondary neoplasms, and neurologic manifestations.
- AIDS is a global problem.
- The pool of HIV-infected persons in Africa and Asia is large and expanding.
  - The prevalence rate of infection in adults in sub-Saharan Africa is more than 8%.
- By the year 2011, HIV had infected 60 million people worldwide, and nearly 30 million adults and children have died of the disease.
Good news about AIDS

• the infection rate seems to be decreasing, and some authorities believe it may have peaked in the late 1990s
• Furthermore, improved antiviral therapies have resulted in fewer people dying of the disease.
Epidemiology of AIDS

- transmission of HIV occurs under conditions that facilitate exchange of blood or body fluids containing the virus or virus-infected cells

- The three major routes of transmission are sexual contact, parenteral inoculation, and passage of the virus from infected mothers to their newborns.
Epidemiology of AIDS

• Five groups of adults at high risk for developing AIDS. The case distribution in these groups is as follows
  • **Homosexual or bisexual men** constitute the largest group, accounting for more than 50% of the reported cases. This includes about 5% who were intravenous drug abusers as well. Transmission of HIV in this category appears to be on the decline
  • **Intravenous drug abusers** with no previous history of homosexuality are the next largest group, representing about 20% of infected individuals
  • **Hemophiliacs**, especially those who received large amounts of factor VIII or factor IX concentrates before 1985, make up about 0.5% of all cases.
  • **Recipients of blood and blood components** who are not hemophiliacs but who received transfusions of HIV-infected whole blood or components (e.g., platelets, plasma) account for about 1% of patients. (Organs obtained from HIV-infected donors can also transmit the virus.)
  • **Heterosexual contacts** of members of other high-risk groups (chiefly intravenous drug abusers) constitute about 20% of the patient population. Heterosexual transmission, although initially of less numerical importance in the United States, is globally the most common mode by which HIV is spread.

• The epidemiology of AIDS is quite different in children younger than 13 years. Close to 2% of all AIDS cases occur in this pediatric. In this group, the vast majority acquired the infection by transmission of the virus from mother to child
Epidemiology of AIDS

• Extensive studies indicate that HIV infection cannot be transmitted by casual personal contact in the household, workplace, or school.
• Spread by insect bites is virtually impossible.
• Regarding transmission of HIV infection to health care workers, an extremely small but definite risk seems to be present.
  • Seroconversion has been documented after accidental needle-stick injury or exposure of nonintact skin to infected blood in laboratory accidents.
  • After needle-stick accidents, the risk of seroconversion is believed to be about 0.3%, and antiretroviral therapy given within 24 to 48 hours of a needle stick can reduce the risk of infection eightfold.
    • By comparison, approximately 30% of those accidentally exposed to hepatitis B–infected blood become seropositive.
Etiology: HIV

- **HIV is a nontransforming human retrovirus belonging to the lentivirus family.** Included in this group are feline immunodeficiency virus, simian immunodeficiency virus, visna virus of sheep, bovine immunodeficiency virus, and the equine infectious anemia virus.

- Two genetically different but related forms of HIV, called *HIV-1 and HIV-2*, have been isolated from patients with AIDS.
  - HIV-1 is the most common type associated with AIDS in the United States, Europe, and Central Africa
  - HIV-2 causes a similar disease principally in West Africa and India.
Structure of HIV-1

- The HIV-1 virion is spherical and contains an electron-dense, cone-shaped core surrounded by a lipid envelope derived from the host cell membrane.
- **The virus core contains**
  - (1) the major capsid protein p24;
  - (2) nucleocapsid protein p7/p9;
  - (3) two copies of viral genomic RNA; and
  - (4) the three viral enzymes (protease, reverse transcriptase, and integrase).
- p24 is the most abundant viral antigen.
- The viral core is surrounded by a matrix protein called p17, which lies underneath the virion envelope.
- Studding the viral envelope are two viral glycoproteins, gp120 and gp41, which are critical for HIV infection of cells.
The HIV genome

- The products of the *gag* and *pol* genes are large precursor proteins that are cleaved by the viral protease to yield the mature proteins.
- In addition to these three standard retroviral genes, HIV contains several other accessory genes, including *tat*, *rev*, *vif*, *nef*, *vpr*, and *vpu*, which regulate the synthesis and assembly of infectious viral particles and the pathogenicity of the virus.
- For example, the product of the *tat* (transactivator) gene causes a 1000-fold increase in the transcription of viral genes and is critical for virus replication.
Variability of the HIV genome

• Molecular analysis of different HIV-1 isolates has revealed considerable variability in certain parts of the viral genome.

• Most variations are clustered in particular regions of the envelope glycoproteins. Because the humoral immune response against HIV-1 is targeted against its envelope, such variability poses problems for the development of a single antigen vaccine.

• On the basis of genetic analysis, HIV-1 can be divided into three subgroups, designated M (major), O (outlier), and N (neither M nor O). Group M viruses are the most common form worldwide, and they are further divided into several subtypes, or clades, designated A through K. Various subtypes differ in their geographic distribution; for example, subtype B is the most common form in western Europe and the United States, whereas subtype E is the most common clade in Thailand. Currently, clade C is the fastest spreading clade worldwide, being present in India, Ethiopia, and Southern Africa.
Pathogenesis of HIV Infection and AIDS

- The two major targets of HIV infection are the immune system and the central nervous system.
- Profound immune deficiency, primarily affecting cell-mediated immunity, is the hallmark of AIDS.
  - This results chiefly from infection and subsequent loss of CD4+ T cells as well as impairment in the function of surviving helper T cells.
  - Macrophages and dendritic cells are also targets of HIV infection.
  - HIV enters the body through mucosal tissues and blood and first infects T cells as well as dendritic cells and macrophages. The infection becomes established in lymphoid tissues, where the virus may remain latent for long periods. Active viral replication is associated with more infection of cells and progression to AIDS.
The life cycle of HIV consists of infection of cells, integration of the provirus into the host cell genome, activation of viral replication, and production and release of infectious virus.
Infection of cells

• **HIV infects cells by using the CD4 molecule as receptor and various chemokine receptors as coreceptors.** The requirement for CD4 binding explains the selective tropism of the virus for CD4+ T cells and other CD4+ cells, particularly monocytes/macrophages and dendritic cells.

• Binding to CD4 is not sufficient for infection, however. HIV gp120 must also bind to other cell surface molecules (coreceptors) for entry into the cell. Chemokine receptors, particularly CCR5 and CXCR4, serve this role. HIV isolates can be distinguished by their use of these receptors: R5 strains use CCR5, X4 strains use CXCR4, and some strains (R5X4) are dual-tropic. R5 strains preferentially infect cells of the monocyte/macrophage lineage and are thus referred to as M-tropic, whereas X4 strains are T-tropic, preferentially infecting T cells
  • Over the course of infection, T-tropic viruses gradually accumulate; these are especially virulent because T-tropic viruses are capable of infecting many T cells and even thymic T-cell precursors and cause greater T-cell depletion and impairment.

• The HIV envelope contains two glycoproteins, surface gp120 noncovalently attached to a transmembrane protein, gp41. **The initial step in infection is the binding of the gp120 envelope glycoprotein to CD4 molecules, which leads to a conformational change that results in the formation of a new recognition site on gp120 for the coreceptors CCR5 or CXCR4.**
  • Binding to the coreceptors induces conformational changes in gp41 that result in the exposure of a hydrophobic region called the fusion peptide at the tip of gp41. This peptide inserts into the cell membrane of the target cells (e.g., T cells or macrophages), leading to fusion of the virus with the host cell.
  • After fusion the virus core containing the HIV genome enters the cytoplasm of the cell.
  • polymorphisms in the gene encoding CCR5 are associated with different susceptibility to HIV infection. About 1% of white Americans inherit two defective copies of the CCR5 gene and are resistant to infection and the development of AIDS associated with R5 HIV isolates
Virus replication

- Once internalized, the RNA genome of the virus undergoes reverse transcription, leading to the synthesis of double-stranded complementary DNA (cDNA; proviral DNA).

- In quiescent T cells, HIV cDNA may remain in the cytoplasm in a linear episomal form. In dividing T cells, the cDNA circularizes, enters the nucleus, and is then integrated into the host genome. After this integration, the provirus may be silent for months or years, a form of latent infection. Alternatively, proviral DNA may be transcribed, with the formation of complete viral particles that bud from the cell membrane. Such productive infection, when associated with extensive viral budding, leads to death of infected cells.

- HIV infects memory and activated T cells but is inefficient at productively infecting naive (unactivated) T cells. Naive T cells contain an active form of an enzyme that introduces mutations in the HIV genome. This enzyme - APOBEC3G (for apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3G) - is a cytidine deaminase that introduces cytosine-to-uracil mutations in the viral DNA that is produced by reverse transcription. These mutations inhibit further DNA replication by mechanisms that are not fully defined. Activation of T cells converts cellular APOBEC3G into an inactive, high-molecular-mass complex, which explains why the virus can replicate in previously activated (e.g., memory) T cells and T-cell lines.

- Completion of the viral life cycle in latently infected cells occurs only after cell activation, and in the case of most CD4+ T cells virus activation results in cell lysis.

- Activation of T cells by antigens or cytokines upregulates several transcription factors, including NF-κB, which stimulate transcription of genes encoding cytokines such as IL-2 and its receptor. The long-terminal-repeat sequences that flank the HIV genome also contain NF-κB–binding sites that can be triggered by the same transcription factors.

- Imagine now a latently infected CD4+ cell that encounters an environmental antigen. Induction of NF-κB in such a cell (a physiologic response) activates the transcription of HIV proviral DNA (a pathologic outcome) and leads ultimately to the production of virions and to cell lysis. Furthermore, TNF and other cytokines produced by activated macrophages also stimulate NF-κB activity and thus lead to production of HIV RNA.

- HIV-infected people are at increased risk for recurrent exposure to other infections, which lead to increased lymphocyte activation and production of proinflammatory cytokines. These, in turn, stimulate more HIV production, loss of additional CD4+ T cells, and more infection. Thus, it is easy to visualize how in individuals with AIDS a vicious cycle may be set up that culminates in inexorable destruction of the immune system.
Mechanism of T-Cell Depletion in HIV Infection

- Loss of CD4+ T cells is mainly because of infection of the cells and the direct cytopathic effects of the replicating virus.

- In infected individuals, approximately 100 billion new viral particles are produced every day, and 1 to 2 billion CD4+ T cells die each day.

- Because the frequency of infected cells in the circulation is very low, for many years it was suspected that the immunodeficiency is out of proportion to the level of infection and cannot be attributed to death of infected cells.
  - In fact, many infected cells may be in mucosal and other peripheral lymphoid organs, and death of these cells is a major cause of the relentless, and eventually profound, cell loss.
  - Also, up to a point the immune system can replace the dying T cells, and hence the rate of T cell loss may appear deceptively low, but as the disease progresses, renewal of CD4+ T cells cannot keep up with their loss.

- Possible mechanisms by which the virus directly kills infected cells include increased plasma membrane permeability associated with budding of virus particles from the infected cells, and virus replication interfering with protein synthesis.

- Other mechanisms may contribute to T cell loss (inflammation and apoptosis of noninfected cells, etc.)
Abnormalities of Immune function in AIDS

<table>
<thead>
<tr>
<th>Lymphopenia</th>
<th>Predominantly caused by selective loss of the CD4+ helper T-cell subset</th>
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<tr>
<th>Decreased T-Cell Function In Vivo</th>
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<tr>
<td>Preferential loss of activated and memory T cells</td>
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<tr>
<td>Decreased delayed-type hypersensitivity</td>
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<tr>
<td>Susceptibility to opportunistic infections</td>
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<td>Susceptibility to neoplasms</td>
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<tr>
<th>Altered T-Cell Function In Vitro</th>
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<tr>
<td>Decreased proliferative response to mitogens, alloantigens, and soluble antigens</td>
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<tr>
<td>Decreased cytotoxicity</td>
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<tr>
<td>Decreased helper function for B-cell antibody production</td>
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<td>Decreased IL-2 and IFN-γ production</td>
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<th>Polyclonal B-Cell Activation</th>
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<tr>
<td>Hypergammaglobulinemia and circulating immune complexes</td>
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<tr>
<td>Inability to mount de novo antibody response to new antigens</td>
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<td>Poor responses to normal B-cell activation signals in vitro</td>
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<th>Altered Monocyte or Macrophage Functions</th>
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<tr>
<td>Decreased chemotaxis and phagocytosis</td>
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<tr>
<td>Decreased class II HLA expression</td>
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<tr>
<td>Diminished capacity to present antigen to T cells</td>
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CD4+ T cells play a key role in orchestrating the immune response.
Loss of CD4+ T cells has therefore multiple consequences and cripples almost every aspect of the immune function.

HLA, Human leukocyte antigen; IFN-γ, interferon-γ; IL-2, interleukin-2; TNF, tumor necrosis factor.
HIV Infection of Non–T Cells

- In addition to infection and loss of CD4+ T cells, infection of macrophages and dendritic cells is also important in the pathogenesis of HIV infection. Similar to T cells, the majority of the macrophages that are infected by HIV are found in the tissues. In certain tissues, such as the lungs and brain, as many as 10% to 50% of macrophages are infected. Although cell division is required for nuclear entry and replication of most retroviruses, HIV-1 can infect and multiply in terminally differentiated nondividing macrophages. This property of HIV-1 is dependent on the viral vpr gene. Even though macrophages allow viral replication, they are quite resistant to the cytopathic effects of HIV, in contrast to CD4+ T cells. Thus, in late stages of HIV infection, when CD4+ T-cell numbers decline greatly, macrophages may be an important site of continued viral replication.

- Macrophages may act as portals of infection.

- Even uninfected monocytes are reported to have unexplained functional defects that may have important consequences for host defense. These defects include impaired microbicidal activity, decreased chemotaxis, decreased secretion of IL-1, inappropriate secretion of TNF, and poor capacity to present antigens to T cells. Also, even the low number of infected blood monocytes may be vehicles for HIV to be transported to various parts of the body, including the nervous system.

- Studies have documented that, in addition to macrophages, two types of dendritic cells are also important targets for the initiation and maintenance of HIV infection: mucosal and follicular dendritic cells. It is thought that mucosal dendritic cells are infected by the virus and may transport it to regional lymph nodes, where the virus is transmitted to CD4+ T cells.

- Follicular dendritic cells in the germinal centers of lymph nodes are potential reservoirs of HIV. Although some follicular dendritic cells may be susceptible to HIV infection, most virus particles are found on the surface of their dendritic processes. Follicular dendritic cells have receptors for the Fc portion of immunoglobulins, and hence they trap HIV virions coated with anti-HIV antibodies. The antibody-coated virions localized to follicular dendritic cells retain the ability to infect CD4+ T cells as they traverse the intricate meshwork formed by the dendritic processes of the follicular dendritic cells.

- B Cell Function in HIV Infection.

- Individuals with AIDS also display profound abnormalities of B-cell function. Paradoxically, there is polyclonal activation of B cells, resulting in germinal center B-cell hyperplasia (particularly early in the disease course), bone marrow plasmacytosis, hypergammaglobulinemia, and formation of circulating immune complexes. This activation may result from multiple interacting factors: reactivation of or reinfection with cytomegalovirus and EBV, both of which are polyclonal B-cell activators, can occur; gp41 itself can promote B-cell growth and differentiation; and HIV-infected macrophages produce increased amounts of IL-6, which stimulates proliferation of B cells.

- Patients with AIDS are unable to mount antibody responses to newly encountered antigens. This could be due, in part, to lack of T-cell help, but antibody responses against T-independent antigens are also suppressed, and hence there may be other intrinsic defects in B cells as well. Impaired humoral immunity renders these patients prey to disseminated infections caused by encapsulated bacteria, such as S. pneumoniae and H. influenzae, both of which require antibodies for effective opsonization and clearance.
Pathogenesis of Central Nervous System Involvement

• the nervous system is a major target of HIV infection.

• Macrophages and microglia, cells in the central nervous system that belong to the macrophage lineage, are the predominant cell types in the brain that are infected with HIV.

• It is believed that HIV is carried into the brain by infected monocytes.

• The mechanism of HIV-induced damage of the brain, however, remains obscure. Because neurons are not infected by HIV, and the extent of neuropathologic changes is often less than might be expected from the severity of neurologic symptoms, most workers believe that the neurologic deficit is caused indirectly by viral products and by soluble factors produced by infected microglia. Included among the soluble factors are the usual culprits, such as IL-1, TNF, and IL-6. In addition, nitric oxide induced in neuronal cells by gp41 has been implicated. Direct damage of neurons by soluble HIV gp120 has also been postulated.
The initial infection starts in mucosal tissues, involving mainly memory CD4+ T cells and dendritic cells, and spreads to lymph nodes.

Viral replication leads to viremia and widespread seeding of lymphoid tissue.

The viremia is controlled by the host immune response, and the patient then enters a phase of clinical latency. During this phase, viral replication in both T cells and macrophages continues unabated, but there is some immune containment of virus (not illustrated).

There continues a gradual erosion of CD4+ cells and ultimately, CD4+ T-cell numbers decline, and the patient develops clinical symptoms of full-blown AIDS. CTL, Cytotoxic T lymphocyte.
Clinical history of HIV infection
Primary Infection, Virus Dissemination, and the Acute Retroviral Syndrome

- Acute (early) infection is characterized by infection of memory CD4+ T cells (which express CCR5) in mucosal lymphoid tissues, and death of many infected cells. Because the mucosal tissues are the largest reservoir of T cells in the body, and a major site of residence of memory T cells, this local loss results in considerable depletion of lymphocytes. Few infected cells are detectable in the blood and other tissues. Mucosal infection is often associated with damage to the epithelium, defects in mucosal barrier functions, and translocation of microbes across the epithelium.

- Mucosal infection is followed by dissemination of the virus and the development of host immune responses. Dendritic cells in epithelia at sites of virus entry capture the virus and then migrate into the lymph nodes. Once in lymphoid tissues, dendritic cells may pass HIV on to CD4+ T cells through direct cell-cell contact. Within days after the first exposure to HIV, viral replication can be detected in the lymph nodes. This replication leads to viremia, during which high numbers of HIV particles are present in the patient’s blood. The virus disseminates throughout the body and infects helper T cells, macrophages, and dendritic cells in peripheral lymphoid tissues.

- As the HIV infection spreads, the individual mounts antiviral humoral and cell-mediated immune responses. These responses are evidenced by seroconversion (usually within 3 to 7 weeks of presumed exposure) and by the development of virus-specific CD8+ cytotoxic T cells. HIV-specific CD8+ T cells are detected in the blood at about the time viral titers begin to fall and are most likely responsible for the initial containment of HIV infection. These immune responses partially control the infection and viral production, and such control is reflected by a drop in viremia to low but detectable levels by about 12 weeks after the primary exposure.

- The acute retroviral syndrome is the clinical presentation of the initial spread of the virus and the host response. It is estimated that 40% to 90% of individuals who acquire a primary infection develop this syndrome. This typically occurs 3 to 6 weeks after infection, and resolves spontaneously in 2 to 4 weeks. Clinically, this phase is associated with a self-limited acute illness with nonspecific symptoms, including sore throat, myalgias, fever, weight loss, and fatigue, resembling a flulike syndrome.

- The extent of viremia, measured as HIV-1 RNA levels, in the blood is a useful surrogate marker of HIV disease progression and is of clinical value in the management of people with HIV infection. The viral load at the end of the acute phase reflects the equilibrium reached between the virus and the host response, and in a given patient it may remain fairly stable for several years. This level of steady-state viremia, called the viral set point, is a predictor of the rate of decline of CD4+ T cells, and, therefore, progression of HIV disease. In one study, only 8% of patients with a viral load of less than 4350 copies of viral mRNA per microliter of blood progressed to clinical AIDS in 5 years, whereas 62% of those with a viral load of greater than 36,270 copies developed AIDS in the same period.

- For clinical management, blood CD4+ T-cell counts are perhaps the most reliable short-term indicator of disease progression. For this reason, CD4+ cell counts and not viral load are the primary clinical measurements used to determine when to start antiretroviral therapy.
Chronic Infection: Phase of Clinical Latency

• In the chronic phase of the disease, lymph nodes and the spleen are sites of continuous HIV replication and cell destruction. During this period of the disease, few or no clinical manifestations of the HIV infection are present. Therefore, this phase of HIV disease is called the clinical latency period.

• Destruction of CD4+ T cells within lymphoid tissues continues during this phase, and the number of circulating blood CD4+ T cells steadily declines. More than 90% of the body’s approximately $10^{12}$ T cells are normally found in lymphoid tissues, and it is estimated that HIV destroys up to $1 \times 10^5$ to $2 \times 10^6$ CD4+ T cells every day. Early in the course of the disease, the body may continue to make new CD4+ T cells, and therefore CD4+ T cells can be replaced almost as quickly as they are destroyed. At this stage, up to 10% of CD4+ T cells in lymphoid organs may be infected, but the frequency of circulating CD4+ T cells that are infected at any one time may be less than 0.1% of the total CD4+ T cells. Eventually, over a period of years, the continuous cycle of virus infection, T-cell death, and new infection leads to a steady decline in the number of CD4+ T cells in the lymphoid tissues and the circulation.

• Concomitant with this loss of CD4+ T cells, host defenses begin to wane, and the proportion of the surviving CD4+ cells infected with HIV increases, as does the viral burden per CD4+ cell. Not unexpectedly, HIV RNA levels increase as the host begins to lose the battle with the virus. How HIV escapes immune control is not entirely clear, but several mechanisms have been proposed. These include destruction of the CD4+ T cells that are critical for effective immunity, antigenic variation, and down-modulation of class I MHC molecules on infected cells so that viral antigens are not recognized by CD8+ CTLs. During this period the virus may evolve and switch from relying solely on CCR5 to enter its target cells to relying on either CXCR4 or both CCR5 and CXCR4. This coreceptor switch is associated with more rapid decline in CD4+ T-cell counts, presumably because of greater infection of T cells.

• In this chronic phase of infection, patients are either asymptomatic or develop minor opportunistic infections, such as oral candidiasis (thrush), vaginal candidiasis, herpes zoster, and perhaps mycobacterial tuberculosis (the latter being particularly common in resource-poor regions such as sub-Saharan Africa).
AIDS

• The final phase is progression to AIDS, characterized by a breakdown of host defense, a dramatic increase in plasma virus, and severe, life-threatening clinical disease. Typically the patient presents with long-lasting fever (>1 month), fatigue, weight loss, and diarrhea. After a variable period, serious opportunistic infections, secondary neoplasms, or clinical neurologic disease (grouped under the rubric AIDS indicator diseases, discussed later) emerge, and the patient is said to have developed AIDS.

• In the absence of treatment, most patients with HIV infection progress to AIDS after a chronic phase lasting from 7 to 10 years. Exceptions to this typical course are exemplified by rapid progressors and long-term nonprogressors.

  • In rapid progressors the middle, chronic phase is telescoped to 2 to 3 years after primary infection.
  • About 5% to 15% of infected individuals are long-term nonprogressors, defined as untreated HIV-1–infected individuals who remain asymptomatic for 10 years or more, with stable CD4+ T-cell counts and low levels of plasma viremia (usually less than 500 viral RNA copies per milliliter).
  • Remarkably, about 1% of infected individuals have undetectable plasma virus (<50-75 RNA copies/mL); these have been called elite controllers. Individuals with such an uncommon clinical course have attracted great attention in the hope that studying them may shed light on host and viral factors that influence disease progression. Studies thus far indicate that this group is heterogeneous with respect to the variables that influence the course of the disease. In most cases, the viral isolates do not show qualitative abnormalities, suggesting that the course of the disease cannot be attributed to a “wimpy” virus. In all cases there is evidence of a vigorous anti-HIV immune response, but the immune correlates of protection are still unknown. Some of these individuals have high levels of HIV-specific CD4+ and CD8+ T-cell responses, and these levels are maintained over the course of infection. The inheritance of particular HLA alleles seems to correlate with resistance to disease progression, perhaps reflecting the ability to mount antiviral T cell responses. Further studies, it is hoped, will provide the answers to this and other questions critical to understanding disease progression.
Clinical manifestations of HIV

<table>
<thead>
<tr>
<th>Infections</th>
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<tbody>
<tr>
<td>Protozoal and Helminthic Infections</td>
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<tr>
<td>Cryptosporidiosis or isosporidiosis (enteritis)</td>
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<tr>
<td>Pneumocystosis (pneumonia or disseminated infection)</td>
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<tr>
<td>Toxoplasmosis (pneumonia or CNS infection)</td>
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<tr>
<td>Fungal Infections</td>
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<tr>
<td>Candidiasis (esophageal, tracheal, or pulmonary)</td>
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<tr>
<td>Cryptococcosis (CNS infection)</td>
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<td>Coccioidiomycosis (disseminated)</td>
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<tr>
<td>Histoplasmosis (disseminated)</td>
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<tr>
<td>Bacterial Infections</td>
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<tr>
<td>Mycobacteriosis (&quot;atypical,&quot; e.g., Mycobacterium avium-intracellulare, disseminated or extrapulmonary; Mycobacterium tuberculosis, pulmonary or extrapulmonary)</td>
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<tr>
<td>Nocardiosis (pneumonia, meningitis, disseminated)</td>
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<tr>
<td>Salmonella infections, disseminated</td>
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<tr>
<td>Viral Infections</td>
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<tr>
<td>Cytomegalovirus (pulmonary, intestinal, retinitis, or CNS infections)</td>
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<tr>
<td>Herpes simplex virus (localized or disseminated infection)</td>
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<tr>
<td>Varicella-zoster virus (localized or disseminated infection)</td>
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<tr>
<td>Progressive multifocal leukoencephalopathy</td>
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<tr>
<td>Neoplasms</td>
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<tr>
<td>Kaposi sarcoma</td>
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<tr>
<td>Primary lymphoma of brain</td>
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<tr>
<td>Invasive cancer of uterine cervix</td>
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</table>

In addition, CNS symptoms may also be very important
Kaposi Sarcoma.

- Kaposi sarcoma, a vascular tumor that is otherwise rare in the United States, is the most common neoplasm in patients with AIDS. At the onset of the AIDS epidemic, up to 30% of infected homosexual or bisexual men had KS, but in recent years, with use of HAART there has been a dramatic decline in its incidence. In contrast, in areas of sub-Saharan Africa where HIV infection is both frequent and largely untreated, Kaposi sarcoma is one of the most common tumors.

- The lesions of KS are characterized by the proliferation of spindle-shaped cells that express markers of both endothelial cells (vascular or lymphatic) and smooth muscle cells. There is also a profusion of slitlike vascular spaces, suggesting that the lesions may arise from primitive mesenchymal precursors of vascular channels. In addition, KS lesions display chronic inflammatory cell infiltrates.

- Many of the features of KS suggest that it is not a malignant tumor (despite its ominous name). For instance, spindle cells in many KS lesions are polyclonal or oligoclonal, although more advanced lesions occasionally show monoclonality. The current model of KS pathogenesis is that the spindle cells produce proinflammatory and angiogenic factors, which recruit the inflammatory and neovascular components of the lesion, and the latter components supply signals that aid in spindle cell survival and growth.

- There is compelling evidence that KS is caused by the *KS herpesvirus* (KSHV), also called *human herpesvirus 8* (HHV8). Exactly how KSHV infection leads to KS is still unclear. Like other herpesviruses, KSHV establishes latent infection, during which several proteins are produced with potential roles in stimulating spindle cell proliferation and preventing apoptosis. These include a viral homologue of cyclin D and several inhibitors of p53. However, KSHV infection, while necessary for KS development, is not sufficient, and additional cofactors are needed. In the AIDS-related form, that cofactor is clearly HIV. (The relevant cofactors for HIV-negative KS remain unknown.) HIV-mediated immune suppression may aid in widespread dissemination of KSHV in the host.
Lymphomas

- Lymphoma occurs at a markedly increased rate in individuals with AIDS, making it one of several AIDS-defining conditions. With the advent of effective antiretroviral therapy, the incidence of lymphoma has fallen substantially in some HIV-infected populations. However, even in the era of retroviral therapy, lymphoma continues to occur in HIV-infected people at an incidence that is at least 10-fold greater than the population average.

- Based on molecular characterization of HIV-associated lymphomas, at least two mechanisms appear to underlie the increased risk of B-cell tumors in HIV infected individuals:
  - **Unchecked proliferation of B cells infected with oncogenic herpesviruses in the setting of profound T cell depletion (AIDS).** T-cell immunity is required to restrain the proliferation of B cells infected with oncogenic viruses such as EBV and KSHV. With the appearance of severe T-cell depletion late in the course of HIV infection, this control is lost. As a result, AIDS patients are at high risk of developing aggressive B cell lymphomas composed of tumor cells infected by oncogenic viruses, particularly EBV.
  - By adulthood, most normal individuals are infected by EBV. Once immunity is established, EBV persists in such individuals as a latent infection in approximately 1 in 100,000 B cells, most of which have a memory B-cell phenotype. Activation of such cells, by antigen or by cytokines, reawakens an EBV-encoded program of gene expression that drives B-cell proliferation. Patients with AIDS have high levels of several cytokines, some of which, including IL-6, are growth factors for B cells. These patients are also chronically infected with pathogens that may lead to B-cell stimulation. In the absence of T-cell immunity, these activated, EBV infected clones proliferate and eventually acquire additional somatic mutations, leading to their outgrowth as full-blown EBV-positive B-cell lymphomas.
  - **Germinal center B-cell hyperplasia in the setting of early HIV infection.** The majority of the lymphomas that arise in patients with preserved CD4 T-cell counts are not associated with EBV or KSHV. What then explains the continued increased risk of lymphoma? The answer is not known, but it may be related to the profound germinal center B-cell hyperplasia that occurs early in HIV infection. In germinal centers, B cells diversify their immunoglobulin genes via lesions introduced into their DNA by the enzyme activation-induced deaminase (AID). This process is imperfect, and there is experimental evidence showing that AID can cause mutations in oncogenes implicated in B-cell lymphomagenesis. Of note, the aggressive B cell tumors that arise outside of the setting of full-blown AIDS in HIV-infected individuals, such as Burkitt lymphoma and diffuse large B-cell lymphoma, are often associated with mutations in oncogenes such as MYC and BCL6 that bear the molecular hallmarks of “mistakes” made during attempted immunoglobulin class-switching and somatic hypermutations, two AID-dependent events that occur in germinal center B cells. Thus, the striking germinal center B-cell hyperplasia that occurs early in HIV infection may contribute to lymphomagenesis by simply increasing the number of B cells that are “at-risk” for acquiring potential lymphoma-initiating events.
Mechanisms of lymphomagenesis during HIV infection
Central Nervous System Disease.

- Involvement of the central nervous system is a common and important manifestation of AIDS.
- Ninety percent of patients demonstrate some form of neurologic involvement at autopsy, and 40% to 60% have clinically apparent neurologic dysfunction.
- Several virally determined neuropathologic changes occur. These include a self-limited meningoencephalitis occurring at the time of seroconversion, aseptic meningitis, vacuolar myelopathy, peripheral neuropathies, and, most commonly, a progressive encephalopathy designated clinically as HIV-associated neurocognitive disorder.
Effect of Antiretroviral Drug Therapy on the Clinical Course of HIV Infection.

• The advent of new antiretroviral drugs that target the viral reverse transcriptase, protease, and integrase has changed the clinical face of AIDS. These drugs are given in combination to reduce the emergence of mutants that develop resistance to any one; treatment regimens are commonly called highly active antiretroviral therapy (HAART) or combination antiretroviral therapy.

• When a combination of at least three effective drugs is used in a motivated, compliant patient, HIV replication is reduced to below the level of detection (<50 copies RNA per milliliter) and remains there indefinitely (as long as the patient adheres to therapy). Even when a drug-resistant virus breaks through, there are several second- and third-line options to combat the virus.

• Once the virus is suppressed, the progressive loss of CD4+ T cells is halted. Over a period of several years the peripheral CD4+ T-cell count slowly increases and often returns to a normal level.

• With the use of these drugs, in the United States the annual death rate from AIDS has decreased from its peak of 16 to 18 per 100,000 people in 1995-1996 to less than 4 per 100,000. Many AIDS-associated disorders, such as opportunistic infections with P. jiroveci and Kaposi sarcoma, are very uncommon now.

• Effective antiretroviral therapy has reduced the transmission of the virus, especially from infected mothers to newborns.

• However, because of the reduced mortality, more people are living with HIV, and since they are not virus-free, there is a fear that the risk of spreading the infection may increase if vigilance is relaxed. Indeed, there is compelling evidence that even treated patients who remain asymptomatic, with virtually undetectable plasma virus for years, develop active infection if they stop the treatment.

• Despite these dramatic improvements, several new complications associated with HIV infection and its treatment have emerged. Some patients with advanced disease who are given antiretroviral therapy develop a paradoxical clinical deterioration during the period of recovery of the immune system. This occurs despite increasing CD4+ T-cell counts and decreasing viral load. This disorder has been called the immune reconstitution inflammatory syndrome. Its basis is not understood but is postulated to be a poorly regulated host response to the high antigenic burden of persistent microbes. Perhaps a more important complication of long-term HAART pertains to adverse side-effects of the drugs. These include lipoatrophy (loss of facial fat), lipoaccumulation (excess fat deposition centrally), elevated lipids, insulin resistance, peripheral neuropathy, premature cardiovascular kidney and liver disease.
Considerations on therapy

• Despite spectacular advances in our understanding of HIV infection, the long-term prognosis of patients with AIDS remains dismal.

• Although with effective drug therapy the mortality rate has declined in the United States, the treated patients still carry viral DNA in their lymphoid tissues. Can there be a cure with persistent virus?

• Although a considerable effort has been mounted to develop a vaccine, many hurdles remain to be crossed before vaccine-based prophylaxis becomes a reality. Molecular analyses have revealed an alarming degree of variation in viral isolates from patients; this renders the task of producing a vaccine extremely difficult.

• Recent efforts have focused on producing antibodies against relatively invariant portions of HIV proteins. The task of developing an effective vaccine is complicated by the fact that the correlates of immune protection are not fully understood. At present, therefore, prevention, public health measures, and antiretroviral drugs remain the mainstays in the fight against AIDS.
The HIV Life Cycle

1. Binding (also called Attachment): HIV binds (attaches itself) to receptor on the surface of a CD4 cell.

2. Fusion: The HIV envelope and the CD4 cell membrane fuse (join together), which allows HIV to enter the CD4 cell.

3. Reverse Transcription: Inside the CD4 cell, HIV releases and uses reverse transcriptase to convert its genetic material—HIV RNA—into HIV DNA. This conversion of HIV RNA to HIV DNA allows HIV to enter the CD4 cell nucleus and combine with the cell's genetic material—cell DNA.

4. Integration: Inside the CD4 cell nucleus, HIV releases integrase (an HIV enzyme). HIV uses integrase to insert (integrate) its viral DNA into the DNA of the CD4 cell.

5. Replication: Once integrated into the CD4 cell DNA, HIV begins to use the machinery of the CD4 cell to make more copies of HIV proteins. The protein chains are the building blocks for more HIV.

6. Assembly: New HIV proteins and HIV RNA move to the surface of the cell and assemble into immature (noninfectious) HIV.

7. Budding: Newly formed immature (noninfectious) HIV buds off the host CD4 cell. The new HIV releases protease (an HIV enzyme). Protease acts to break up the long protein chains that form the immature virus. The smaller HIV proteins combine to form mature (infectious) HIV.

Reverse Transcriptase
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
Nucleoside reverse transcriptase inhibitors (NRTIs)
Integrase inhibitors
Fusion inhibitors
CD4 receptors
Reverse transcriptase
HIV DNA
Integrase
HIV RNA
CD4 cell DNA
Protease
HIV virions
HIV protease inhibitors (PIs)
What are the HIV drug classes?

HIV medicines are grouped into six drug classes according to how they fight HIV. The six drug classes are:

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Protease inhibitors (PIs)
- Fusion inhibitors
- CCR5 antagonists (CCR5s) (also called entry inhibitors)
- Integrase strand transfer inhibitors (INSTIs)

In general, a person's first HIV regimen includes two NRTIs plus an INSTI, an NNRTI, or a PI boosted with cobicistat (brand name: Tybost) or ritonavir (brand name: Norvir). Cobicistat or ritonavir increase (boost) the effectiveness of the PI.
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI and Nucleoside Reverse Transcriptase Inhibitor NRTI)

Antiretroviral (ARV) HIV drug class. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind to and block HIV reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.
Protease Inhibitor (PI)

Antiretroviral (ARV) HIV drug class. Protease inhibitors (PIs) block protease (an HIV enzyme). By blocking protease, PIs prevent new (immature) HIV from becoming a mature virus that can infect other CD4 cells.
Fusion Inhibitor

Antiretroviral (ARV) HIV drug class. Fusion inhibitors block the HIV envelope from merging with the host CD4 cell membrane (fusion). This prevents HIV from entering the CD4 cell.
Synonym(s): CCR5 Inhibitor, CCR5 Receptor Blocker
Antiretroviral (ARV) HIV drug class. CCR5 antagonists block the CCR5 coreceptor on the surface of certain immune cells, such as CD4 T lymphocytes (CD4 cells). This prevents HIV from entering the cell.
Integrase Strand Transfer Inhibitor (INSTI)

Synonym(s): Integrase Inhibitor
Antiretroviral (ARV) HIV drug class. Integrase strand transfer inhibitors (INSTIs) block integrase (an HIV enzyme). HIV uses integrase to insert (integrate) its viral DNA into the DNA of the host CD4 cell. Blocking integrase prevents HIV from replicating.