Title: Acquired immunodeficiency syndrome (AIDS).
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Abstract: Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), a member of the lentivirus family of retroviruses. This virus is thought to have arisen in Africa in the early to mid-twentieth century from related viruses in the chimpanzee and the sooty mangabey monkey. The virus cannot survive long in the air and cannot be transmitted by casual contact. Individuals can be infected only by the exchange of certain body fluids, including semen, vaginal fluid, blood, and breast milk. Other body fluids such as sweat, tears, saliva, urine, and feces may contain HIV, but the virus exists in such low concentrations that these fluids are completely ineffective in transmitting an infection. The most common mode of transmission is through vaginal and anal sex; it is also possible to transmit HIV by performing oral sex, although this is less common than with vaginal or anal sex. The presence of other sexually transmitted diseases (STDs), such as gonorrhea, syphilis, chlamydia, genital herpes, or human papillomavirus, dramatically increases the risk of acquiring an HIV infection through sexual contact.

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Acquired immunodeficiency syndrome (AIDS)

Anatomy or system affected: Blood, brain, eyes, gastrointestinal system, immune system, intestines, liver, lungs, lymphatic system, mouth, reproductive system, respiratory system, skin, throat

Definition: A disease state caused by infection with human immunodeficiency virus (HIV), leading to a progressive deterioration of the immune system and characterized by development of any of a large number of opportunistic infections.

Causes: HIV infection through the exchange of certain body fluids and subsequent destruction of CD4 T-lymphocytes of the immune system

Symptoms: Initially, flulike or mononucleosis-like symptoms, then none until opportunistic infections (candidiasis, cytomegalovirus, ulcers, Pneumocystis carinii pneumonia, histoplasmosis, toxoplasmosis) and cancers (Kaposi’s sarcoma, Burkitt’s lymphoma) become common

Duration: Chronic, eventually fatal
**Treatments:** Surgery, chemotherapy, and radiation for cancers; antibiotics for bacterial and fungal infections; anti-HIV drugs (nucleoside analogues, reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors)

**Causes and Symptoms**

Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), a member of the lentivirus family of retroviruses. This virus is thought to have arisen in Africa in the early to mid-twentieth century from related viruses in the chimpanzee and the sooty mangabey monkey. The virus cannot survive long in the air and cannot be transmitted by casual contact. Individuals can be infected only by the exchange of certain body fluids, including semen, vaginal fluid, blood, and breast milk. Other body fluids such as sweat, tears, saliva, urine, and feces may contain HIV, but the virus exists in such low concentrations that these fluids are completely ineffective in transmitting an infection. The most common mode of transmission is through vaginal and anal sex; it is also possible to transmit HIV by performing oral sex, although this is less common than with vaginal or anal sex. The presence of other sexually transmitted diseases (STDs), such as gonorrhea, syphilis, chlamydia, genital herpes, or human papillomavirus, dramatically increases the risk of acquiring an HIV infection through sexual contact.

![SEM (low magnification) of AIDS infected lymphocytes CDCP](image)

The second most common mode of transmission is through the sharing of needles or syringes contaminated with HIV-positive blood. An HIV-positive pregnant woman may transmit the virus to her child in utero, or more commonly during childbirth. Mother-to-child transmission may also occur through breastfeeding in which the virus is present in the milk. Early in the AIDS epidemic and before a blood test for HIV was available, blood and blood products from blood banks were sometimes contaminated with HIV that subsequently infected recipients. Indeed, more than 90 percent of patients with hemophilia at this time became infected with HIV through injections of HIV-contaminated clotting factor VIII. Because of the development of a heat treatment for clotting factor VIII and the screening of the blood supply, patients with hemophilia and other blood-transfusion recipients are no longer at high risk for HIV infection. Although the blood supply is relatively safe today, a very low probability of acquiring HIV through a transfusion of contaminated blood still exists, as a recently infected donor may not yet test positive for HIV, although this is a phenomenon is extremely rare in developed countries.

Although HIV can infect virtually all cells of the body, it has a strong affinity for cells of the immune system. The virus uses a cell surface receptor called CD4 to bind to the membrane of a cell. The CD4 receptor is found on many cells in the body but is in relatively high concentrations on the surface of a class of T lymphocytes called T4 or CD4 cells. The virus uses a coreceptor called CXCKR4, also found on the membrane, that promotes the fusion of the membrane of the virus particle with the membrane of the cell, thereby allowing entry of the virus. Persons who lack the coreceptor on their cells appear to resist infection by the virus. The T4 cells are also known as T-helper cells, as they produce a series of chemical signals called lymphokines that are needed for the development and maintenance of the entire immune system. While the body constantly makes new T4 cells, HIV has a very small edge in the rate at which these T4
cells are infected and destroyed. Thus, there is a slow but progressive decrease in T4 lymphocytes in the body and loss of immune function. This process may take ten or more years.

The clinical course of infection occurs in three stages. Initially upon infection, HIV produces an acute retroviral syndrome referred to as the prodromal stage, beginning about three to four weeks after initial infection and lasting for two to three weeks. During a retroviral syndrome, the patient experiences flu-like or mononucleosis-like symptoms. The patient will believe that he or she simply has a moderate-to-severe case of influenza or, if the symptoms are prolonged, mononucleosis. During this period, HIV is rapidly proliferating, disseminating throughout the body and infecting lymphoid tissues. Viral load is high at this stage, and the patient is highly infectious. At the same time, the T4 cell count, which normally is about 1,000 per cubic millimeter, drops by about half. The patient’s immune system will mount an antibody response against HIV, but these antibodies are ineffective in stopping the infection. When such antibodies are detectable, the patient is then said to have seroconverted. Anti-HIV antibody detection by a simple blood test is the basis for assigning HIV-positive status. In most cases, seroconversion occurs between six to eighteen weeks after initial infection, although, in rare cases, antibodies may not be detectable until later. By three months, 95 percent of patients will have seroconverted; by six months, more than 99 percent will have detectable circulating antibodies to HIV.

The second stage is called the clinical latency period or asymptomatic stage. Without anti-HIV therapy, this period may last ten or more years. It is during this time that the patient usually has no AIDS symptoms. Early in the latent period, T4 cell counts usually recover somewhat during the first year of infection, averaging approximately 700 per cubic millimeter. After that, there is a very slow decline. In the meantime, viral loads, which were high during the acute retroviral syndrome stage, drop by several orders of magnitude as the T4 count rises. At about one year into the infection, the viral load very slowly increases as the latent period progresses.

The third phase of HIV infection is the development of AIDS. This usually occurs when the T4 count drops below 200 per cubic millimeter. Opportunistic infections and cancers become common, and patients may have several infections simultaneously. Many of these diseases are rare in healthy individuals. Most common is Pneumocystis jiroveci pneumonia, a form caused by a fungus that is virtually unseen in individuals with a normal immune system. Indeed, the fungus is present in a majority of the population yet almost never causes pneumonia unless the immune system is compromised or suppressed. As one of the functions of the immune system is to destroy cancer cells when they arise, patients with AIDS are at a substantially higher risk of developing some types of cancers compared to uninfected individuals of the same age. One of these cancers is Kaposi sarcoma, a normally very rare tumor of blood vessels characterized by pink to purple spots or slightly raised areas on the skin. These lesions may also arise on internal organs, where they can impair function. Kaposi’s sarcoma is caused by human herpes virus 8 (HHV8) and is sexually transmitted. Individuals with AIDS are several thousand times more likely to develop Kaposi sarcoma than uninfected individuals. The other cancer commonly associated with AIDS is non-Hodgkin’s lymphoma, often in the brain. Patients with AIDS are nearly seventy times more likely to be diagnosed with non-Hodgkin lymphoma.

In 1987, the US Centers for Disease Control (CDC) published the criteria for the diagnosis of AIDS, including the appearance of one or more opportunistic infections or cancers. Twenty-three different conditions were listed in the definition: candidiasis of the bronchi, trachea, or lungs; esophageal candidiasis; disseminated or extrapolmonary coccidiomycosis; extrapolmonary cryptococcosis; chronic Intestinal cryptosporidiosis (greater than one month in duration); cytomegalovirus disease (other than liver, spleen, or lymph nodes); cytomegalovirus retinitis (with loss of vision); HIV encephalopathy; herpes simplex causing chronic ulcers (greater than one month in duration) or bronchitis, pneumonitis, or esophagitis; disseminated or extrapolmonary histoplasmosis; chronic intestinal isosporiasis (greater than one month in
Kaposi sarcoma; Burkitt lymphoma; immunoblastic lymphoma; primary lymphoma of the brain; *Mycobacterium avium* complex or *M. kansasii*; extrapulmonary infection due to *Mycobacterium tuberculosis*; other or unidentified *Mycobacterium species*; *Pneumocystis jiroveci* pneumonia; progressive multifocal leukoencephalopathy (PML); recurrent *Salmonella* septicemia; toxoplasmosis of the brain; and wasting syndrome caused by HIV. In 1993, three conditions were added to the criteria: pulmonary tuberculosis, recurrent pneumonia, and invasive cervical carcinoma. Moreover, the definition was expanded to include any HIV-positive person whose T4 count had dropped to 200 per cubic millimeter or lower or whose level of T4 lymphocytes had fallen to 14 percent or less of total lymphocytes.

For the diagnosis of HIV infection, the CDC recommends laboratory evidence from a positive HIV antibody screening test, such as a reactive enzyme immunoassay, that is confirmed by a positive result from a supplemental HIV antibody test or a positive result from HIV nucleic acid detection test such as polymerase chain reaction (PCR) or HIV virologic tests such as HIV p24 antigen test or HIV viral culture. The Infectious Disease Society of America recommends diagnosing HIV infection by a rapid HIV test or conventional enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blot or indirect immunofluorescence assay; if the initial testing is negative or indeterminate it should be repeated four weeks later.

**Treatment and Therapy**

As of 2014, no effective vaccine had been developed to prevent HIV infection. While a number of candidate vaccines have been under development and in clinical trials, none has proven successful. The usual strategies used with most antiviral vaccines in the past, immunization with attenuated or inactivated viruses, have so far proven ineffective for HIV given its significant rate of mutation. Control of the epidemic has shifted significantly toward preventing exposure and decreasing infectivity by treating to reduce viral load, a measure of the number of viruses in blood and in body fluids.

AIDS treatment and therapy fall into two categories: prophylaxis and the prevention and treatment of opportunistic infections to slow progression to advanced AIDS. Treatment of opportunistic infections must follow established guidelines for the individual disease. Thus, in the treatment of Kaposi sarcoma, surgery, chemotherapy, and radiation treatment singly or in combination are utilized. Bacterial and yeast or other fungal infections are treated with antibiotics or antifungal agents. Although some medications may reduce the severity of viral infections, such infections are not easily treated. Because a person with AIDS might suffer from more than one opportunistic infection and/or cancer at the same time, simultaneous treatments often take a severe toll on the patient. Without treatment, individuals who progress to AIDS survive approximately three years. Death typically results from an opportunistic infection or cancer. However, HIV-positive individuals who undergo antiretroviral therapy (ART) to maintain a low viral load typically have a life expectancy similar to HIV-negative individuals and never progress to AIDS.

This strategy for HIV treatment involves interfering with the viral life cycle with the aim of slowing viral replication. Anti-HIV drugs target several steps in the life cycle, primarily at the levels of reverse transcription or assembly. In 1987, the first generation of drugs was developed to treat HIV. The first effective treatment utilized zidovudine (ZDV), commonly called azidothymidine (AZT), a drug originally developed for chemotherapy of cancer. ZDV inhibits the viral encoded enzyme, reverse transcriptase, involved in copying the RNA viral genome into a DNA copy. As a result, a nucleoside analogue is inserted into the growing DNA, which stops further synthesis of the DNA copy. Other nucleoside reverse transcriptase inhibitors (NRTIs) that have a similar effect include emtricitabine, tenofovir, and abacavir. In a similar manner, the nucleotide analogue tenofovir blocks DNA replication. Nevirapine and efavirenz are non-nucleoside drugs that bind directly to and inhibit reverse transcriptase. Although this group of drugs inhibits reverse transcriptase, their mode of action is different from nucleoside or nucleotide analogues.
The final step in HIV replication involves the cleavage of a large precursor protein into smaller structural proteins, an event taking place at the cell surface and followed by release of the completed virus. The cleaving enzyme is called a protease and is encoded by the virus. The second generation of anti-HIV drugs, which were developed in the 1990s, were protease inhibitors, drugs that interfere with cleavage of the precursor and prevent viral assembly. As a result, functional virions cannot be made. Atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, and ritonavir are approved drugs in this class. Other types of anti-HIV drugs called fusion inhibitors (for example, enfuvirtide) interfere with entry of the virus into a cell. In addition, integrase inhibitors, such as raltegravir, may be used. Integrase inhibitors prevent the DNA copy of the virus from inserting itself into one of the cell's chromosomes. Thus the anti-HIV arsenal includes drugs that act at different sites or stages in the HIV life cycle.

The HIV reverse transcriptase makes numerous mutations during the synthesis of DNA. Consequently, resistance to individual anti-HIV drugs arises easily and frequently. Beginning in 1995, a new strategy for anti-HIV therapy called highly active antiretroviral therapy (HAART), also known as AIDS cocktail therapy, was developed. HAART consists of using a combination of three or more anti-HIV drugs, including two reverse transcriptase inhibitors and at least one protease inhibitor. HAART therapy is very effective, as it has been estimated that it prolongs the life expectancy of a person with AIDS by three to ten years. Moreover, many patients with AIDS and in terminal stages of the disease have made remarkable recoveries when placed on HAART. In many cases, viral loads were dramatically reduced, T4 cells made some recovery, and the incidence of opportunistic infections was reduced. Another advantage of multiple drug therapy is that the probability of HIV developing simultaneous resistance to three or four different drugs is very low, extending the useful therapeutic life of the individual drugs.

The long-term effectiveness of HAART is underscored by an examination of the AIDS deaths in the United States. In 1981, the CDC began to track the number of AIDS deaths. Each year, the number of deaths climbed steadily, reaching a peak of 50,610 in 1995. In 1996, the first full year of widespread HAART therapy, AIDS deaths dropped by 25 percent, and they have continued to drop every year since. In 2012, an estimated 1.6 million people died of the disease worldwide, down from approximately 2.3 million in 2005.

Perspective and Prospects

AIDS was first recognized as a new disease in the United States in late 1980. Michael Gottlieb at the University of California, Los Angeles (UCLA) diagnosed men who have had sex with men with *Pneumocystis carinii* pneumonia and Kaposi sarcoma, diseases that in the past were extremely rare. In June 1981, the CDC alerted doctors in a report on this new epidemic for the first time in the *CDC Weekly Morbidity and Mortality Report*. Shortly thereafter, the *New York Times* reported on the new “gay cancer.” At first, the disease was called gay-related immunodeficiency (GRID). The name GRID was changed to acquired immunodeficiency syndrome, or AIDS, in an August 8, 1982, article in the *New York Times*, representing the first time that the term was used in a publication. The change reflected the fact that this new disease was not restricted to men who have had sex with men; cases involving intravenous drug users, individuals with hemophilia and other blood-transfusion recipients, and infants were being diagnosed. In January 1983, Luc Montagnier and colleagues at the Pasteur Institute in Paris were the first to isolate the virus causing AIDS. It was given the name human immunodeficiency virus, or HIV, in 1985; previously, the virus had been given several names by different researchers. With the isolation of the virus, a blood test could be developed.

Testing of blood and blood products started in March 1985. A test called enzyme-linked immunosorbent assay (ELISA) screens for the presence of anti-HIV antibodies. Results once took weeks, but the test is now automated and is performed within hours.
HIV has been confirmed in the United States since at least 1969. At that time, a physician in St. Louis, Missouri, had a young male patient with a variety of AIDS symptoms. After the patient died, the pathologist took samples of his tissues and froze them. Later, when tests to detect HIV became available, the tissue samples were tested and found positive for HIV. The oldest positively identified HIV sample came from blood collected from a male patient by a Belgian physician in Kinshasa, Democratic Republic of the Congo. The doctor had saved many blood samples taken between 1959 and 1982; thus, the earliest confirmation of HIV infection in Africa dates from 1959. The virus has probably been present in the human population for much longer, but without blood or tissue samples, this cannot be confirmed.

Two major classes of HIV have been identified: HIV-1, which arose in Central Africa, and HIV-2, which arose in Western Africa. HIV-1 and HIV-2 have long been known to be genetically similar to viruses known as simian immunodeficiency viruses (SIV) in chimpanzees (SIVcme) and the sooty mangabey monkey (SIVsm). In 2006, scientists determined that in all likelihood, HIV-1 originated in chimpanzees from regions of the nation of Cameroon; as many as one-third of chimpanzees from some colonies were found to carry SIV. The first confirmed human infection was that of a man from the nearby Congo, who developed AIDS in 1959. However, evidence suggests that HIV may have emerged in humans as early as 1930.

According to the CDC's HIV Surveillance Supplemental Report, 2011 (2013), an estimated 1.14 million persons aged thirteen and older are living with HIV infection in the United States, including nearly 181,000 people who are not aware of the infection; approximately 15,500 persons with an AIDS diagnosis died in the United States in 2010, although these deaths may or may not be related to AIDS. Worldwide, the World Health Organization (WHO) estimates that seventy-five million people have been infected with the HIV virus since the beginning of the epidemic and approximately thirty-six million people have died of HIV/AIDS. Worldwide, an estimated 36.7 million people were living with HIV infection at the end of 2015, while an estimated 1.6 million people died of AIDS-related illnesses in 2012. The WHO estimates that 0.8 percent of people aged fifteen to forty-nine years worldwide are living with HIV, although the vast majority of people with HIV live in low- and middle-income countries, where prevention and treatment efforts are limited. Sub-Saharan Africa is the most severely affected region of the world, with an estimated 24.9 million adults and children living with HIV in 2012. However, the number of people dying from AIDS-related causes in sub-Saharan Africa declined by more than 50 percent from 2004 and 2012, as prevention and treatment efforts in the region improve.

Several new medications in development will hopefully enlarge the arsenal of anti-HIV drugs, further extending the life expectancies of individuals with HIV/AIDS. The success of HAART promises to extend the life of persons with AIDS by many years, and with adequate treatment many HIV-positive individuals enjoy life expectancies equal to those of HIV-negative individuals. A significant issue is the high financial burden of HAART therapy. A typical HAART regimen may cost $1,500 to $2,000 per month. Although many people in high-income countries can purchase these drugs through insurance providers or government subsidy, this financial burden precludes the use of HAART and many anti-HIV drugs in low- and middle-income countries, where HIV prevalence is highest. Thus, effective prevention of HIV infections, through vigorous public education about HIV and AIDS, is absolutely critical. Such a program in Uganda dramatically reduced the incidence of HIV infections, showing the effectiveness of public education campaigns. According to the United Nations, although the number of individuals living with HIV/AIDS has risen between 2005 and 2013, the number of adults and children newly infected with HIV has declined from 2.9 million in 2005 to 2.1 million in 2013; the number of AIDS-related deaths has also declined from 2.4 million to 1.5 million in the same time period.

Bibliography


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