DRUGS
The Straight Facts

HIV/AIDS Treatment Drugs

Brigid M. Kane

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School of Pharmacy and Pharmaceutical Sciences
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The Use and Abuse of Drugs

For thousands of years, humans have used a variety of sources with which to cure their ills, cast out devils, promote their well-being, relieve their misery, and control their fertility. Until the beginning of the twentieth century, the agents used were all of natural origin, including many derived from plants as well as elements such as antimony, sulfur, mercury, and arsenic. The sixteenth-century alchemist and physician Paracelsus used mercury and arsenic in his treatment of syphilis, worms, and other diseases that were common at that time; his cure rates, however, remain unknown. Many drugs used today have their origins in natural products. Antimony derivatives, for example, are used in the treatment of the nasty tropical disease leishmaniasis. These plant-derived products represent molecules that have been "forged in the crucible of evolution" and continue to supply the scientist with molecular scaffolds for new drug development.

Our story of modern drug discovery may be considered to start with the German physician and scientist Paul Ehrlich, often called the father of chemotherapy. Born in 1854, Ehrlich became interested in the ways in which synthetic dyes, then becoming a major product of the German fine chemical industry, could selectively stain certain tissues and components of cells. He reasoned that such dyes might form the basis for drugs that could interact selectively with diseased or foreign cells and organisms. One of Ehrlich's early successes was development of the arsenical "606"—patented under the name Salvarsan—as a treatment for syphilis. Ehrlich's goal was to create a "magic bullet," a drug that would target only the diseased cell or the invading disease-causing organism and have no effect on healthy cells and tissues. In this he was not successful, but his great research did lay the groundwork for the successes of the twentieth century, including the discovery of the sulfonamides and the antibiotic penicillin. The latter agent saved countless lives during World War II. Ehrlich, like many scientists, was an optimist. On the eve of World War I, he wrote, "Now that the liability to, and danger of, disease are to a

large extent circumscribed—the efforts of chemotherapeutics are directed as far as possible to fill up the gaps left in this ring." As we shall see in the pages of this volume, it is neither the first nor the last time that science has proclaimed its victory over nature only to have to see this optimism dashed in the light of some freshly emerging infection.

From these advances, however, has come the vast array of drugs that are available to the modern physician. We are increasingly close to Ehrlich's magic bullet: Drugs can now target very specific molecular defects in a number of cancers, and doctors today have the ability to investigate the human **genome** to more effectively match the drug and the patient. In the next one to two decades, it is almost certain that the cost of "reading" an individual genome will be sufficiently cheap that, at least in the developed world, such personalized medicines will become the norm. The development of such drugs, however, is extremely costly and raises significant social issues, including equity in the delivery of medical treatment.

The twenty-first century will continue to produce major advances in medicines and medicine delivery. Nature is, however, a resilient foe. Diseases and organisms develop resistance to existing drugs, and new drugs must constantly be developed. (This is particularly true for anti-infective and anticancer agents.) Additionally, new and more lethal forms of existing **infectious diseases** can develop rapidly. With the ease of global travel, these can spread from Timbuktu to Toledo in less than 24 hours and become pandemics. Hence the current concerns with avian flu. Also, diseases that have previously been dormant or geographically circumscribed may suddenly break out worldwide. (Imagine, for example, a worldwide pandemic of Ebola disease, with public health agencies totally overwhelmed.) Finally, there are serious concerns regarding the possibility of man-made epidemics occurring through the deliberate or accidental spread of disease agents—including manufactured agents, such as smallpox with enhanced lethality. It is therefore imperative that the search for new medicines continue.

All of us at some time in our life will take a medicine, even if it is only aspirin for a headache. For some individuals, drug use will be constant throughout life. As we age, we will likely be exposed to a variety of medications—from childhood vaccines to drugs to relieve pain caused by a terminal disease. It is not easy to get accurate and understandable information about the drugs that we consume to treat diseases and disorders. There are, of course, highly specialized volumes aimed at medical or scientific professionals. These, however, demand a sophisticated knowledge base and experience to be comprehended. Advertising on television is widely available but provides only fleeting information, usually about only a single drug and designed to market rather than inform. The intent of this series of books, Drugs: The Straight Facts, is to provide the lay reader with intelligent, readable, and accurate descriptions of drugs, why and how they are used, their limitations, their side effects and their future. It is our hope that these books will provide readers with sufficient information to satisfy their immediate needs and to serve as an adequate base for further investigation and for asking intelligent questions of health care providers.

The present volume, *HIV/AIDS Treatment Drugs*, illustrates admirably some of the problems in modern therapy. Initially there was little understanding of the origin of this newly emergent disease—or of the significance of its symptoms. Today, multiple drug treatments are available to control the disease. The development of drug resistance, however, means that there is a constant challenge to develop new medicines, with the attendant costs of research and clinical trials. In turn, this means that the issue of equitable availability of treatment for people in industrialized countries and in the developing world is a serious social problem. And HIV/AIDS remains incurable.

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1

Acquired Immunodeficiency Syndrome(AIDS): A Late-Twentieth-Century Infectious Disease

In many ways one can think of the middle of the twentieth century as the end of one of the most important social revolutions in history, the virtual elimination of infectious disease as a significant factor in social life.

—Sir F. Macfarlane Burnet, M.D., Nobel Laureate, 1962

Not so fast, doctor. In 1981, reports of clusters of an unusual and difficult-to-treat type of pneumonia occurring in previously healthy young men began to send ripples through the medical establishment. These case reports were intriguing but also worrisome. The pneumonia was often accompanied by other infections, some of which were considered exotic because they were seen only in patients who had traveled to remote, mostly tropical, Asian or African destinations

where such infections were known to occur. By 1983, the numbers of cases of unusual life-threatening infections in otherwise healthy young men, those receiving blood transfusions, and injection drug users, as well as male and female sexual partners of people with these infections had the medical community on edge and researchers scrambling. Public health officials were getting nervous, but determined not to send out alarmist messages. By 1985, the general public was anxious about these bizarre infections and paying rapt attention to any news about them. Why? Let's rewind and put the reports in context.

Prior to 1981, it was generally believed that medical science in industrialized countries had advanced to the point where infections and infectious diseases were no longer a threat. For one thing, several effective **antibiotics** were available. Penicillin and related antibiotic drugs (e.g., ampicillin) that destroy bacteria—as well as newer, more powerful, antibiotics—were able to tame infections that had been at one time life-threatening diseases (e.g., tuberculosis, pneumonia, and syphilis). In addition, strep throat (an infection caused by the **bacterium** *Streptococcus pyogenes*), common ear infections, and **dermatologic** (skin) infections could all be handled by a 7- or 10-day course of antibiotics taken at home in the form of pills, a liquid solution, or ear drops. Other **antimicrobial** drugs to fight **microorganisms** other than bacteria were available or would be soon. For example, **antiviral** drugs that attack viruses were just coming to the fore in the early 1980s. The antiviral drug acyclovir, in particular, was almost revered as a wonder drug by physicians and medical researchers. Acyclovir could halt the herpes viruses that cause cold sores, chicken pox, and genital herpes, leading to the disappearance of outward signs of infection. Just prior to 1981, newly discovered **antifungals** were found capable of inhibiting the growth of yeast and molds responsible for fungal infections that affected diabetics, organ or bone marrow transplantation recipients, and frail elderly patients.

Also contributing to the overriding sense of security concerning disease-causing **microbes** in the 1960s and 1970s was the widespread use and general success of **vaccines** to prevent outbreaks of contagious infectious diseases. Effective vaccines could prevent the disabling or disfiguring effects of such bacterial and viral infections as polio, tetanus, measles, and mumps.

So that was where medicine and society stood in the developed world in 1981. The complacency about infections and infectious diseases that was pervasive in the 1960s and 1970s was continuing into the 1980s. Physicians, other health care professionals, and the general public were ill prepared for what was about to hit.

THE WAKE-UP CALL

Beginning in June 1981 with the first report of an unusual pneumonia (caused by the ***Pneumocystis carinii*** parasite), the confidence of modern medicine began to crumble. The pneumonia was found in five previously healthy young homosexual men in Los Angeles.[1] One month later, there was a report of 10 additional cases of *Pneumocystis carinii* pneumonia, as well as 16 cases of a rare cancer—all in homosexual men in New York City, Los Angeles, and San Francisco.[2] The cancer, known as **Kaposi's sarcoma**, had previously been seen only in central Africa or in 50- to 60-year-old men of Mediterranean or Eastern European descent. It had never before been seen in young American men, and the cancer seemed to be more aggressive in young gay men. (A sarcoma is a tumor or cancer of the body's connective tissue and/or vascular tissue; Kaposi's sarcoma affects the blood vessel walls.) Kaposi's sarcoma manifests itself as round or oval pinkish, red, deep-purple, or dark-brown spots on the face, neck, trunk, hands, or feet. This outward manifestation of Kaposi's sarcoma would wreak havoc in the lives of many young gay men: The skin patches, appearing as either single spots or in clusters, were stigmatizing in the early years of the AIDS epidemic.

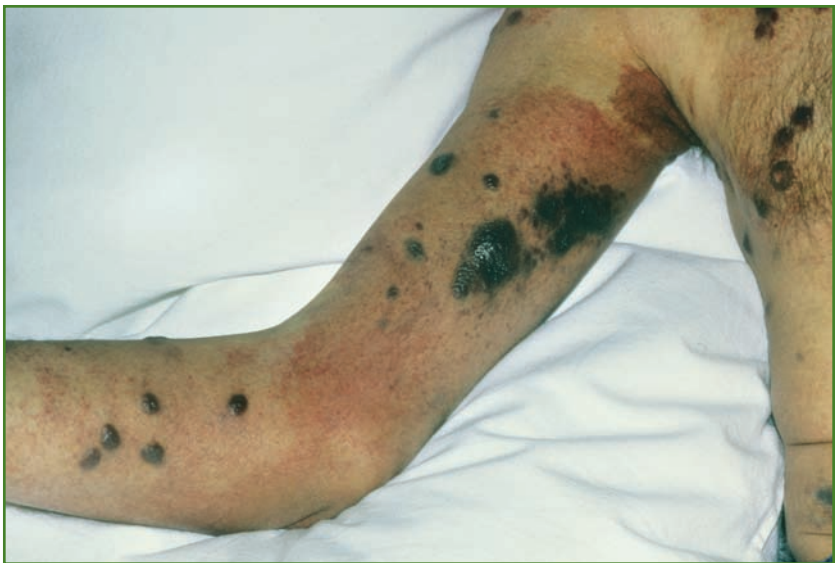


Figure 1.1 In AIDS patients, lesions from Kaposi's sarcoma can spread aggressively. In recent years however, improvements in HIV/AIDS treatment drugs has led to a decrease in the disease's incidence. *(© SPL / Photo Researchers, Inc.)*

The initial reports of 1981, including the full-length articles published in the prestigious and widely read *New England Journal of Medicine* in December 1981, described other odd infections.[3,4,5] These infections were so uncommon in industrialized countries that most physicians in the United States had never heard of them. Nevertheless, they were serious, aggressive, and deadly. Doctors and public health officials were trying to grasp what was happening—vigorous young men were being hospitalized for and dying from infection in the latter part of the twentieth century. It just was not computing.

CLUES TO THE MYSTERY CASES

Doctors caring for patients with these rare infections and researchers studying the mysterious cases were keenly aware of the obvious gay connection between the first clusters of cases.

It was not long before scientists found an important clue as to why these patients were suffering from atypical, aggressive infections that led to their total physical deterioration: The patients' blood tests showed an exceptionally low number of **T lymphocytes**, or T cells, which are a type of white blood cell. This suggested that their immune system—the body's natural defense against invading microorganisms and abnormal cells, such as cancerous cells—had been profoundly weakened.[3, 4] The laboratory finding of extremely low numbers of T cells was consistent with the clinical finding of persistently swollen lymph nodes under the jaw, in the armpits, or in the groin of these patients; such **lymphadenopathy** also suggested a besieged immune system. It was all beginning to make sense. It appeared that the body's immunity against the routine onslaught of microorganisms had become compromised, leading to a state

PHILADELPHIA

The 1993 movie *Philadelphia* dealt with some of the tragic consequences of AIDS. In his Academy Award-winning performance, Tom Hanks portrayed Andrew Beckett, a big-league Philadelphia lawyer who was hiding his homosexuality and AIDS from his bosses. He used makeup to hide the Kaposi's sarcoma skin lesions, but eventually they could not be masked. When fired shortly after being promoted to senior associate at his law firm, Beckett suspects that his sexual orientation and disease condition were the true cause of his dismissal. Personal injury lawyer Joe Miller (Denzel Washington), despite his own distaste for and fears about homosexuality, takes on the battle for justice in the workplace. Fairness in life eludes Beckett, however, as his physical condition deteriorates and he succumbs to the ravages of AIDS. *Philadelphia* succeeded in stirring compassion for those with AIDS and enlightening viewers about the discrimination homosexuals with AIDS were experiencing.

of immunodeficiency. When the human body is saddled with a failing, defective, or deficient immune system, any infectious agent (bacteria, viruses, fungi, or parasites) to which the body is exposed will take advantage and invade.

In the bizarre cases of 1981, the patients' weakened immune defenses provided the opportunity for rare and exotic **pathogens** (disease-causing infectious agents) as well as some common microbes to colonize specific organs or tissues, such as the lungs, brain, eyes, skin, or vascular tissue—and destroy them. No such opportunity exists in those with a healthy, functional immune system. Infections that are caused by microorganisms that do not usually lead to disease in healthy individuals are called **opportunistic infections**. (See Table 1.1) The question remained, however: What was causing the immunodeficiency that allowed these infections to flourish?

The two undeniable links among the very early cases of *Pneumocystis carinii* pneumonia, Kaposi's sarcoma, and myriad aggressive opportunistic infections—male homosexuality and immunodeficiency—led to the erroneous naming of the new disease. In the United States it was called GRID, for gay-related immune deficiency, and in Britain it was known as gay compromise syndrome. By 1982, however, reports of this new immunodeficiency disorder occurring in men who were not gay or bisexual and in women and children led to the more appropriate name of AIDS, or acquired immunodeficiency syndrome.[6] (The use of the word "acquired" distinguishes the disease from genetic or inherited immunodeficiency diseases.) A similar pattern of diseases was soon documented in hemophiliacs and other recipients of blood transfusions, intravenous drug users, and infants.[4,7,8,9,10] In early 1983, AIDS was documented in female sexual partners of men with AIDS.[11]

During this same time, AIDS cases in all these different populations (called risk groups) were also being diagnosed by physicians in Copenhagen, Paris, Berlin, Geneva, and Brussels.[12] Within a few years, reports from other continents—Australia,

AIDS MEMORIAL QUILT

In the early years of the AIDS epidemic, the number of deaths was mounting but awareness, facts, and compassion were sorely lacking. In 1985, Cleve Jones, a gay rights activist, rallied friends and acquaintances to hang placards, each with the name of a person who had died from AIDS, on the San Francisco Federal Building. The group put together more than 1,000 placards that, together, resembled a huge quilt. This resemblance inspired Jones and other dedicated people to create the AIDS Memorial Quilt.

Work on the quilt began in June 1987, when Jones crafted the first panel in remembrance of his friend Marvin Feldman. Other panels (each 3 feet by 6 feet) were added so that upon the initial display on October 11, 1987, at the National Mall in Washington, D.C., the quilt had 1,920 panels and covered an area a little larger than a football field. So many panels were added in the following years that by the time of the quilt's last display in 1996, the entire National Mall was covered. This massive memorial was constructed from more than 45,000 panels. Today, the quilt weighs 54 tons and would be more than 52 miles long if the panels were laid end-to-end. More than 83,440 names—slightly less than 20 percent of all U.S. AIDS-related deaths through 2005—are sewn into the AIDS Quilt. While some names are recognizable by the public, most are not. The goals of the AIDS Memorial Quilt, a mission of the NAMES Project Foundation, are to increase AIDS awareness, promote healing and remembrance, and encourage action to fight this disease. Since its first display, approximately 15 million people have viewed the quilt (either in Washington, D.C., or during tours of other cities worldwide), and many of these people have listened to the reading of AIDS victims's names. In 1989, the quilt was nominated for a Nobel Peace Prize and was the subject of the Academy Award-winning documentary *Common Threads: Stories from the Quilt*.

Figure 1.2 *The 1996 display of the AIDS quilt on the Mall in Washington, D.C. (© AP Images)*

Today, the work of The NAMES Project Foundation continues through more than 20 chapters in the United States and in 40 international organizations. Portions of the quilt can be found on display throughout the world. Tour schedules, general information, photographs of the quilt, and access to name searching may be found at http://www.aidsquilt.org.

THE IMMUNOCOMPROMISED STATE

The immune system of a healthy individual generally does not allow bacteria, viruses, fungi, or parasites to penetrate its many layers of defense. A healthy, functional immune system denies entry to a dizzying number of invading potentially infectious agents every day. If a breach does occur, the various cells and molecules of the immune system rally to expel the invader from the body. It is quite a different story for individuals with a dysfunctional immune system. Immunocompromised patients, as they are called, are susceptible to a wide range of microorganisms that, given free reign (i.e., no immune cells chasing after them), can spread throughout the body, possibly causing irreversible organ damage and even life-threatening disseminated disease.

Immunocompromised patients include those undergoing organ transplantation, who are given drugs to suppress the immune system's response to the new organ: Without immunosuppressive drugs, the immune system would attack what it detects as a foreign substance in the body. Such immunosuppressive therapy is also given to recipients of bone marrow transplants to prevent the body from rejecting the newly transplanted bone marrow tissue (which, similarly, would be detected as foreign and therefore slated for destruction and removal). Immunosuppressive drugs, however, leave the body susceptible to life-threatening opportunistic infections. Other immunocompromised patients include infants born with a genetic defect in their immune system, severe-burn patients, patients receiving heavy-duty cancer treatments (i.e., chemotherapy) that indiscriminately kill healthy cells of the immune system along with cancerous cells, and AIDS patients.

Africa, South America, and eventually Asia—confirmed that AIDS had gone global.[13,14] The global reality was that this new devastating, seemingly fatal disease was not restricted

to homosexual men. Indeed, more women than men were affected by AIDS in sub-Saharan Africa.

Several pieces of the puzzle were beginning to fit together by the end of 1983, due in large part to the accumulating epidemiologic data—i.e., the circumstances and factors affecting the emergence of new AIDS cases, the numbers of cases in defined risk groups, survival times, and death rates. The root cause of the immunodeficiency, however, was not readily established. From the outset, the clustering of cases suggested an infectious disease that could be spread through person-to-person contact—but how? Once AIDS was diagnosed in intravenous drug users who shared needles and syringes and in recipients of blood transfusions, it was clear that an infectious agent transmissible through blood was responsible. It was not at all clear, however, *which* agent was responsible since AIDS patients were typically infected with a variety of bacteria, viruses, fungi, and parasites. Also, it was not at all clear whether the infectious agent was transmissible through bodily fluids other than blood.

A "NEW" VIRUS

Physicians, biomedical researchers, and public health scientists were exploring all possibilities, searching diseased tissue of AIDS patients for known pathogens that might be acting individually or together to unravel the immune system so completely. Some known viruses were suspected as the cause of AIDS: Epstein-Barr virus, cytomegalovirus, and herpes simplex virus. In the final analysis, however, none of these was found to be responsible for inducing immunodeficiency. At the time, it was inconceivable that the culprit could be an agent that had never before been encountered. Nevertheless, several research teams were on the prowl for something new. Sure enough, in May 1983, a previously unknown virus was isolated from a homosexual male patient with lymphadenopathy, a hallmark of AIDS.[15] Researchers at the Pasteur Institute in Paris identified the virus from a lymph node biopsy sample

Table 1.1 AIDS-Defining Opportunistic Infections and Cancers

• Candidiasis: A yeast infection, caused by *Candida albicans* or other candidal species, affecting esophagus, bronchi, trachea, or lungs.	• Kaposi's sarcoma: Cancer of blood vessel walls caused by infection with human herpes virus-8; occurs on any area of the skin, including mucous membranes such as in the mouth.
• Cervical cancer, invasive: Cancer of the cervix or lower part of the uterus caused by infection with certain types of human papilloma virus (HPV), especially HPV 16 and 18.	• **Lymphoma** (brain lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma, or immunoblastic lymphoma): A cancer of lymphatic tissue or vessels.
• Coccidioidomycosis (disseminated or extrapulmonary): A fungal infection caused by *Coccidioides immitis* that can spread from the lungs to other sites such as lymph nodes, liver, spleen, and bone marrow.	• Mycobacterial disease: Infection caused by any species of this bacterial family, including *Mycobacterium tuberculosis* (pulmonary or extrapulmonary), *Mycobacterium avium intracellulare*, also called mycobacterium avium complex (MAC), and M. kansasii.
• Cryptococcosis (extrapulmonary): A fungal infection caused by *Cryptococcus neoformans* that can infect the brain, often leading to meningitis	• *Pneumocystis carinii* pneumonia: Inflammation of the lungs caused by the protozoal parasite *Pneumocystis carinii.*
• Cytomegalovirus disease (disseminated) or cytomegalovirus retinitis: An infection, caused by a herpes virus, that can lead to loss of vision when it infects the eye.	• Pneumonia (recurrent): A bacterial infection of the lungs caused by any microorganism occurring two or more times within a 12-month period.
• Encephalopathy (HIV-specific): HIV infection of the brain, also called HIV-associated or AIDS-related dementia.	• Progressive multifocal leukoencephalopathy: A disease that destroys the myelin sheath surrounding nerve fibers of the central nervous system. Caused by the JC virus.
• Herpes simplex virus infection: Chronic ulcers lasting more than one month or bronchitis, pneumonitis, or esophagitis caused by herpes simplex virus type 1 (HSV1) or herpes simplex virus type 2 (HSV2).	• Salmonella septicemia (recurrent): A bacterial infection of the blood caused by such strains of Salmonella as *S. enteritidis* and *S. typhimurium.*
• Histoplasmosis (disseminated or extrapulmonary): A fungal disease caused by infection with *Histoplasma capsulatum* that can spread from the lungs to bone marrow, liver, skin, and central nervous system.	• Toxoplasmosis: An infection of the brain (encephalitis) caused by the parasite *Toxoplasma gondii.*

Table 1.1 continued

• Isosporiasis (chronic, lasting more than one month): An intestinal disease caused by infection with the parasite *Isospora belli* that can lead to chronic diarrhea and malnutrition.	• Wasting syndrome due to HIV: Profound involuntary weight loss, with all other possible causes ruled out.

Source: Centers for Disease Control and Prevention (CDC). "1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS for Adolescents and Adults." *Morbidity & Mortality Weekly Report* 41/RR-17 (1992): 1-19, Appendix B.

from the AIDS patient; they named the virus lymphadenopathy-associated virus, or LAV. Another team of researchers at the National Institutes of Health (NIH) in Bethesda, Maryland, also reported finding a previously unknown virus recovered from adult and pediatric AIDS patients.[16] The NIH team named "their" virus human T-cell leukemia virus type III, or HTLV-III, because it was found inside and bursting forth from immune cells called T cells. Later, in 1984, another laboratory, at the University of California, San Francisco, published its findings of a "new" virus isolated from AIDS patients. This virus was called AIDS-associated retrovirus (ARV).[17] Ultimately, after lengthy study by numerous laboratories with expertise in **virology**, these three viruses—LAV, HTLV-III, and ARV—were found to be one and the same. It was not until 1986, however, that the nomenclature was officially cleared up and the name human immunodeficiency virus, or HIV, was ascribed to this previously unknown pathogen.[18]

HIV AND THE IMMUNE SYSTEM

The identification and isolation of the virus responsible for AIDS was followed by a period of heady research into the nature of the beast. While one research effort focused on the physical, biochemical, and molecular characteristics of HIV, another focused on determining exactly *how* HIV causes such profound immunosuppression. Using tissue from AIDS patients, laboratory investigations revealed that HIV knocks

out key cells in the body's defense system—CD4+ T lymphocytes, the very cells that sound the alarm when an infectious agent or abnormal cells are detected. By disabling or killing off these **CD4+ T cells**, HIV is able to elude detection. This means that other immune elements are not even aware there has been a breach in the system's security. The doors are open to other microbes, which, given the opportunity, waltz right in. It's a microbial takeover.

HIV has very cleverly "chosen" CD4+ T cells as its prey. Whether circulating in the blood or **lymph** (the fluid that bathes the body's tissues) or situated in a lymphoid organ, CD4+ T cells are responsible for sending out signals to the entire immune network when unauthorized personnel are

HIV: DISCOVERY VERSUS ORIGIN

An ongoing debate has surrounded the origins of the human immunodeficiency virus. Phylogenetic, or evolutionary genetic, studies clearly show that although HIV did emerge in the twentieth century, it was hardly new when it was discovered in 1983. That was simply our first face-to-face meeting with the enemy. Although the virus's exact origins are still being investigated, scientists have solid evidence that HIV originated from two monkey viruses that repeatedly infected chimpanzees of the forests of the Guinea-Bissau region of western Africa. It is thought that the chimpanzees acquired the viruses when they fed on monkeys (red-capped mangabeys and greater spot-nosed monkeys) and that in turn humans acquired the viruses when they fed on the chimpanzees or used their blood ritualistically. The molecular rearrangement of the genetic material of the two monkey viruses in the chimpanzee produced a simian immunodeficiency virus strain (SIVcpz) that could cross the species barrier and infect humans. Over time, SIV, which does not cause immunodeficiency or any illness in simians, mutated to HIV, which we know causes disease in humans. It appears that simian viral strains

detected on the premises. CD4+ T cells have also been called T helper cells because they send out chemical messengers to coordinate help from all other immune cells to set in motion a highly concerted immune response against a specific invader.

Visual evidence of HIV infecting and bursting forth from CD4+ T cells was consistent with the extremely low counts of CD4+ T cells found in the blood test results of AIDS patients. CD4+ T cells are susceptible to HIV infection because of two **receptor** molecules on their surface that act as docking stations for HIV. One of the receptors, known as CD4, is actually used to identify CD4+ T cells (T cells that possess or "are positive for" the CD4 marker). The **CD4 receptor** allows HIV

may have crossed the species barrier to humans several times. This is suggested by the development of two types of HIV, HIV-1 (chimpanzee origin) and HIV-2 (sooty mangabey origin), and the multiple groups of viruses within these types. Precisely when the "jump" from simians to humans occurred in Africa is part of the continuing scientific debate, but genetic studies indicate that it was around 1940 (give or take 20 years), which is consistent with tracking of previously unrecognized human AIDS cases and stored blood samples containing a virus now known to be HIV. Although HIV has its roots in SIV, human contact with SIV has occurred over thousands of years while development of HIV is relatively recent. Clearly, there is more to the story of AIDS emergence than simply human exposure to SIV. What researchers do know is that, unlike rabies (an example of a disease, not just a viral infection, acquired by humans from an animal), AIDS does not cross the species barrier, so humans cannot "catch" AIDS from monkeys or chimpanzees.

Source: Marx, P.A. "Unsolved Questions over the Origin of HIV and AIDS." *ASM News* 71, (January 2005): 15–20.

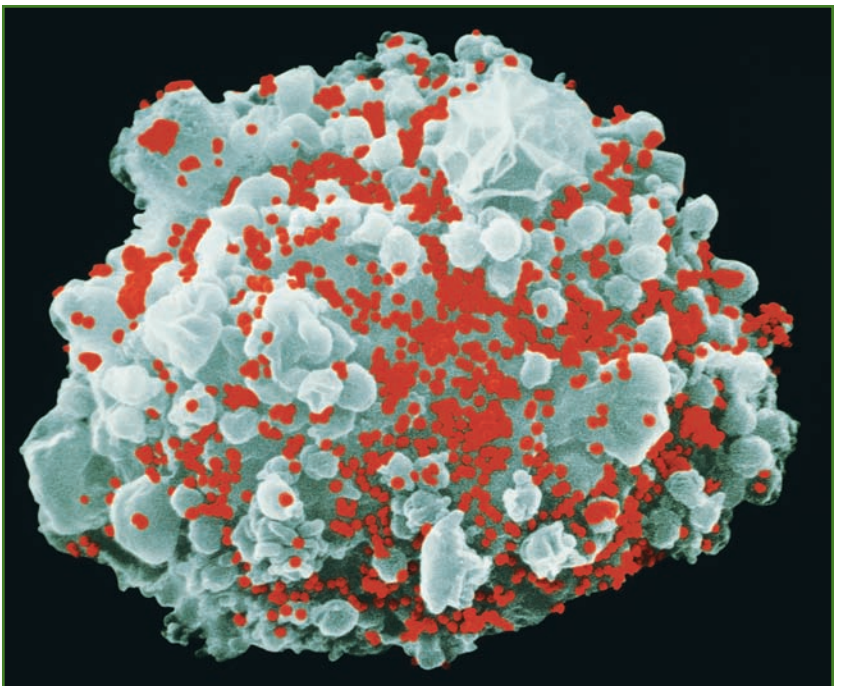


Figure 1.3 This color scanning electron micrograph (SEM) shows a T cell that has been infected with the AIDS virus. In this image the virus shows up as red dots. *(© NIBSC / Photo Researchers, Inc.)*

to latch on to susceptible cells. To gain access to the interior of the cell, the cell's **cytoplasm**, HIV must also bind with another receptor, a co-receptor. The co-receptor varies depending on the immune cell type: It may be one of two receptors—the CXCR4 receptor or the CCR5 receptor—embedded in the cell membrane. Binding to the CXCR4 or CCR5 receptor is necessary for viral entry into CD4+ T cells. In short, HIV needs a primary receptor (CD4) and an accessory co-receptor (either CCR5 or CXCR4) to infect a cell.

Because rules are meant to be broken, some immune system cells other than CD4+ T cells also possess CD4 receptors on their surface. These other immune cells—**monocytes**,

macrophages, **dendritic cells**, and **microglia** in the brain—also have the CCR5 receptor on their surface and therefore are susceptible to HIV infection. These **phagocytic** cells are also critical immune system cells; they literally eat foreign invaders, harmful substances, and abnormal cells.

CD4+ T CELL COUNTS

Blood test results provide "counts" of the different types of blood cells. The unit of measurement for such counts is the number of cells per cubic millimeter (cells/mm^3). The most common blood test ordered by doctors for their HIV-infected patients is a complete blood count (CBC) with lymphocyte subsets. CBC test results include red and white blood cell counts, platelet count, and differential white blood cell count, which is the total white blood cell count broken down into subsets. Lymphocyte subset results include the CD4+ T cell count, CD4+ T cell percentage, CD8+ T cell count, and the T-cell ratio (the number of CD4+ T cells divided by the number of CD8+ T cells). For HIV-infected patients, the white blood cell counts are almost always high, indicating that the immune system is fighting an infection in the body. The CD4+ T cell count is used to assess the overall health of the immune system in people with HIV. A low CD4+ T cell count is indicative of immunosuppression.

HIV INFECTION VERSUS AIDS

The identification of HIV quickly led to the development of blood tests for the presence of **antibodies** to HIV, which would indicate that someone has been infected with the virus and that the immune system is attempting to rid the body of it. Antibodies are large protein molecules, secreted by immune system cells called **B cells** that bind to the surface of an invading microorganism, thereby marking it for death by other immune system components. Antibody-coated microbes might as well have a sign on them that reads, "Time to get rid of me."

Once antibody tests for HIV became available, physicians were able to make a definitive diagnosis of AIDS. The criteria

for such a diagnosis were as follows: confirmation of HIV infection by a positive antibody test and the presence of at least one of more than 20 AIDS indicator illnesses, or "AIDS defining conditions" (opportunistic infections or cancers).[19] The formal definition of AIDS used by clinicians, **epidemiologists**, and public health professionals has been revised several times since 1985 to account for the changing dynamics of the epidemic (e.g., growing number of infected women) and the knowledge gained from accumulated clinical experience.

The current criteria for diagnosing AIDS in adults and adolescents,[20] and in children younger than 13,[21] are laboratory confirmation of HIV infection (an initial and confirming positive blood test) and one of the following:

1. CD4+ T cell count less than 200 cells per cubic millimeter or CD4+ percentage (of all circulating T lymphocytes) less than 14 percent.

2. Diagnosis of one of 26 clinical conditions (see Table 1.1).

AIDS is not synonymous with HIV infection. A person can be infected by HIV without having symptoms or without having dangerously low CD4+ T cell counts. Indeed, an individual can be HIV infected for years before any overt clinical signs become apparent. Many clinicians use the phrase *HIV disease*

Table 1.2 CD4+ T Cell Counts

	CD4+ T Cell Range
For a healthy person (normal)	500–1500 cells/mm^3
For an HIV-positive patient (typical)	<50–500 cells/mm^3

Source: AIDS Community Research Initiative of America (ACRIA). "Understanding Your Lab Results." Available online. URL: http://www.acria.org/treatment/treatment_edu_lab_results.html. Accessed May 17, 2007.

for their patients who are HIV infected and have some signs or symptoms of immune dysfunction, but who do not fulfill the criteria for AIDS (e.g., they have a CD4+ T cell count > 200 cells/mm^3). Many prefer using HIV disease rather AIDS because of the stigma that persists in society.

DRUGS CHANGED THE FACE OF AIDS

Back when the AIDS epidemic broke out, before anyone knew that a previously unknown virus (HIV) was punching holes in patients' immune systems by killing CD4+ T cells, previously healthy young men sought the attention of physicians well after one or more opportunistic infections or a cancer had become well established. Many patients seeking medical attention had a ghostly appearance due to rapid physical deterioration (known as **wasting syndrome**), and many suffered from neurological symptoms due to HIV infection of the brain (originally called AIDS dementia complex). The short time course from overt disease to death and the growing AIDS-related mortality rate in the early years spurred on the race to find effective therapies and therapeutic strategies. Experts debated, "Treat the opportunistic infection or the underlying immunosuppression?" "Can the body withstand treatment regimens aimed at the opportunistic pathogen and the newly identified AIDS-causing virus?" "How should AIDS-associated cancers be treated?" (Conventional chemotherapy would be too toxic for patients with already suppressed blood counts.)

Two clinical strategies helped change AIDS from a death sentence to a manageable, but still extremely challenging, disease. The first strategy, in use by the early 1990s, was to give antimicrobial drugs for the most difficult-to-treat opportunistic infections (namely *Pneumocystis carinii* pneumonia, mycobacterial disease, and cytomegalovirus retinitis) to HIV-infected patients who were symptom-free but had low CD4+ T cell counts (100 to 200 cells/mm^3). Such prophylactic, or preventive, therapy, kept at-risk patients free from these specific diseases, allowing some respite for an already-taxed immune system. This strategy

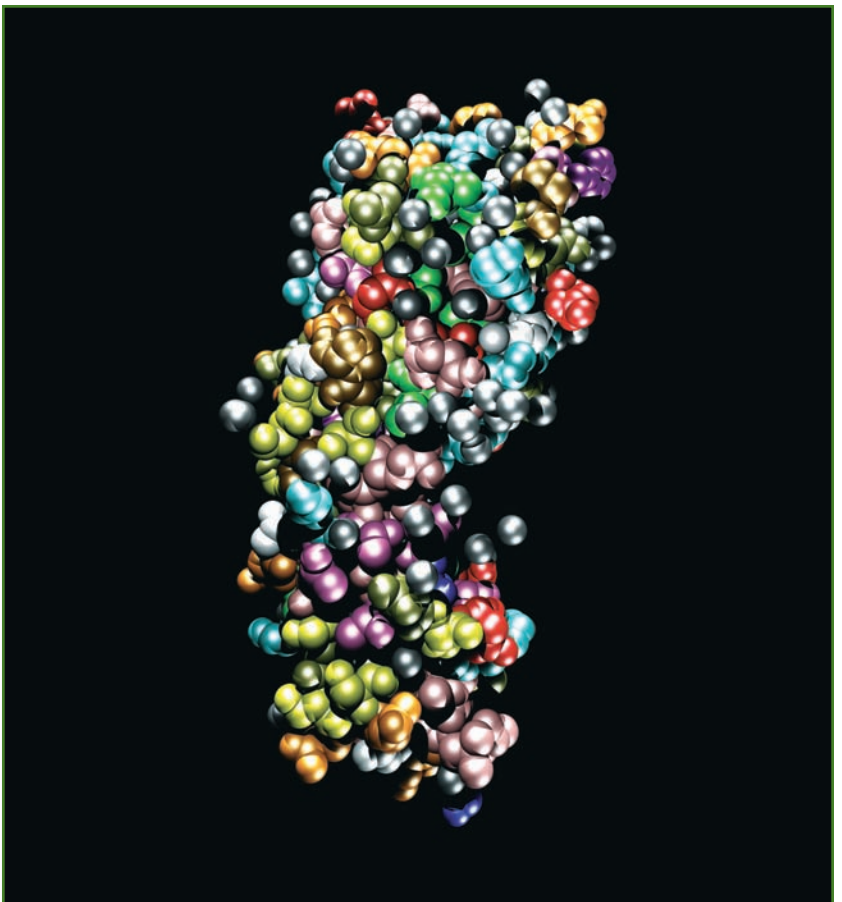


Figure 1.4 CD4 protein, shown here in a computer model, helps T cells to identify foreign bodies and trigger an immune response. The HIV virus binds itself to this protein and uses it to target and destroy the body's own T cells. *(© Dr. Tim Evans / Photo Researchers, Inc.)*

was responsible for AIDS patients remaining disease-free for significantly longer periods and prolonging survival.

The second clinical strategy was developed in the mid-1990s and involved the experimental use of three AIDS drugs in combination, rather than one drug alone or dual therapy.

2

Targeting HIV, The Causative Virus

A virus is ". . . a piece of bad news wrapped in protein."
—Sir Peter Medawar, British biologist and Nobel laureate

Before examining the drugs used to treat HIV infection and AIDS, it is helpful to know the enemy, inside and out. Since its discovery in late 1983, HIV has been photographed hundreds of times by electron microscopes that can magnify objects up to 400,000 times their actual size. Like most viruses, HIV is quite small: approximately one ten-thousandth of a millimeter in diameter!

All viruses, including HIV, are intracellular parasites, which means they depend on a host cell (animal or plant cell) to survive.[22] There are also viruses, known as bacteriophages, that infect bacteria. Viruses lack any independent metabolism and therefore cannot reproduce or replicate themselves without borrowing their host cell's protein-making machinery. One of the most intriguing things about viruses is the way they gain access to a cell's interior. As discussed in Chapter 1, HIV uses two receptor molecules on the surface of CD4+ T cells and other immune system cells for docking and subsequent entry into its host cell.

HIV is a member of the **retrovirus** family, which consists of viruses whose genetic material is ribonucleic acid (RNA) rather than **deoxyribonucleic acid (DNA)**, the genetic material of all other organisms.[23] The prefix "retro" in retrovirus refers to the pathway that these viruses use for making proteins (RNA to DNA), which is the reverse of the pathway used by all other organisms (DNA to

VIROLOGY: THE STUDY OF VIRUSES

The word *virus* is derived from Latin, and means venom or poisonous emanation. Viruses were first defined as infectious agents that could pass through filters capable of trapping bacteria. The Russian scientist Dmitri Ivanovski discovered these "filterable viruses" in the laboratory in 1892. Actually, Ivanovski didn't know whether he had isolated a substance, such as a toxin, or a life form smaller than bacteria; he only knew that whatever was causing disease in tobacco plants could pass through pores in a filter through which bacteria could not. Six years later, the Dutch scientist Martinus Beijerinck reproduced Ivanovski's experiments and showed that his viruses were indeed very small venomous microbes, not poison. It was not until the 1920s and 1930s that scientists were able to see large viruses by using more sophisticated microscopy techniques (dark field light microscopes and experimental ultraviolet microscopes). In 1938, the first electron microscopic view of a virus—a poxvirus—was published.

RNA). Retroviruses are an exception to the central dogma of molecular biology, which states that proteins are synthesized from DNA through an RNA intermediary molecule.[24] According to the central dogma, the first step in protein synthesis is the transcription of DNA to RNA (the DNA code is transcribed into an RNA code). For retroviruses, the first step is **reverse transcription**, whereby the virus's RNA is reverse transcribed into DNA.

Antiviral drugs that specifically act on retroviruses are called **antiretrovirals**. There are several classes of antiretroviral drugs that use different strategies to thwart the seemingly irrepressible presence of HIV in infected individuals. To date, there are no drugs that are able to eradicate HIV from the body.

HIV: HOW SMALL ARE WE TALKING?

Viruses are *really* small! The diameter of HIV is 100 nanometers (nm), or 1/10,000 of a millimeter (mm). Here are some reference units of measure to help put the size of this virus in perspective:

Millimeter: *mm*

- $1x10^{-3}$ meters or 0.001 meters

One inch is equivalent to 25.4 mm

Micrometer or micron: *µm*

- $1x10^{-6}$ meters or 0.000001 meters
- Bacteria are generally measured in µm
- Human hair (diameter) is approximately 20 µm

Nanometer: *nm*

- $1x10^{-9}$ meters or 0.000000001 meters
- Viruses (diameter) are generally measured in nm

Angstrom: *Å*

- $1x10^{-10}$ meters or 0.0000000001 meters
- Atomic diameters range between 1 and 2 Å

In general, viruses are roughly 1,000 times smaller than bacteria and cannot be seen using conventional light microscopes. Viruses are visualized with electron microscopes, which can magnify objects by 200,000 to 400,000 times and can resolve objects as small as 10 Angstroms (Å), or 1/1,000,000 (1×10^{-6}) of a millimeter. Viruses that infect animal cells (animal viruses) range from 18 to 450 nanometers (nm), or 0.000018 to 0.00045 mm or, at the other end of the "ruler," 180 to 4,500 Å. Retroviruses, the family of animal viruses to which HIV belongs, are 80 to 100 nm in diameter.

By comparison, conventional light microscopes magnify up to 2,000 times and can resolve objects as small as 0.2 µm. Thus, bacteria, which range from 0.5 to 1.0 µm in diameter, are visible under a light microscope.

HIV STRUCTURE AND COMPONENTS

In the mid-1980s, HIV was quickly stripped down to its basic elements. Laboratory researchers studied HIV as it latched onto susceptible host cells, as it penetrated and infected cells, and as hundreds of new (progeny) viruses burst forth from infected cells. Researchers also scrutinized HIV as a single virus particle or **virion**, the term that describes a virus "living" outside a host cell.

Outside of a cell, circulating in the blood or lymph, HIV exists as a spherical particle whose outermost layer, called an **envelope**, surrounds an inner core. HIV's genetic material—two linear single strands of RNA—is encased in the core along with the virus's three **enzymes**. Like a cell membrane, HIV's envelope is made up of two layers of lipoprotein (fat + protein). The envelope surface is studded with rather large protruding knobs that are actually sticky protein molecules—more specifically, glycoprotein (carbohydrate + protein) molecules. One portion of the glycoprotein molecule, the larger portion located exclusively outside the viral envelope, is called gp120; the smaller stick-like portion that traverses the inner and outer aspects of the envelope is called gp41.

Each HIV viral particle is fully loaded with all the genetic information needed for the virus to replicate itself, and with all three enzymes to make replication happen inside a host cell: **reverse transcriptase**, **integrase**, and **protease**.[25] These enzymes are indispensable to viral replication and the continued infection of additional susceptible cells. Therefore, these enzymes are the perfect targets for HIV/AIDS medicines. If one or more of these enzymes were knocked out or crippled, HIV would not be able to hold its offensive stance in the war against its host.

HIV LIFE CYCLE

In trying to understand how HIV causes AIDS, researchers have thoroughly dissected the life cycle or replicative cycle of HIV—

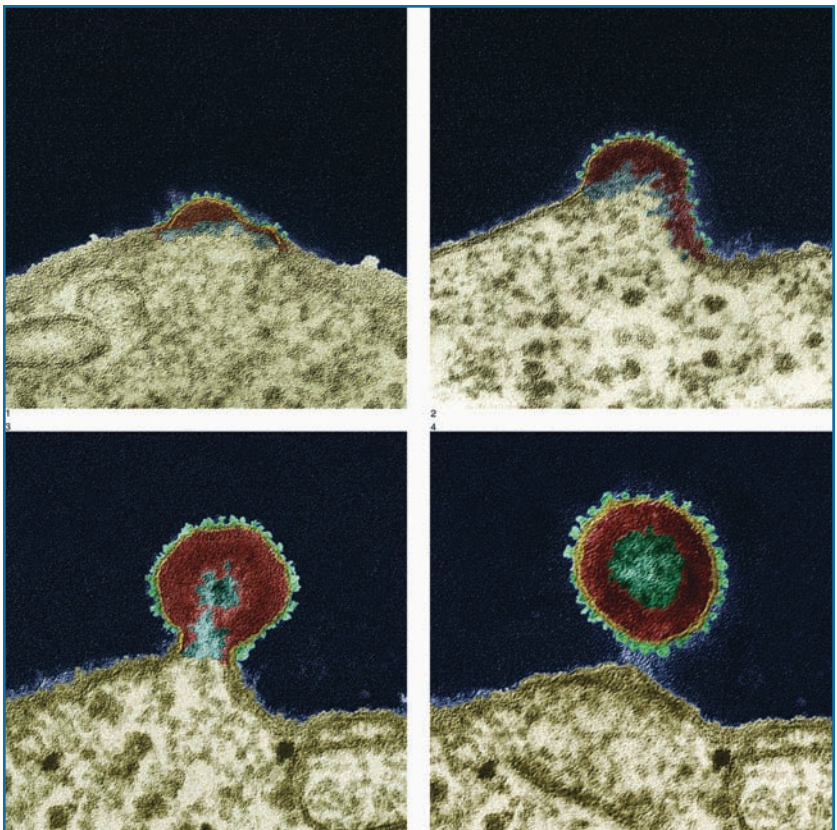


Figure 2.1 This color transmission electron micrograph (TEM) shows an HIV virus budding from an infected T cell. This new virus will then infect another T cell and force it to reproduce copies of the virus, until the T cell ruptures, releasing these copies to repeat the process. *(© Eye of Science / Photo Researchers, Inc.)*

the series of events from the virus's attachment to a susceptible host cell to the budding (release) of newly formed virions from the cell illustrates the major events in the HIV life cycle:

- Attachment or binding of HIV surface protein, gp120, to a CD4+ receptor and a co-receptor on the surface of certain immune system cells.

- Membrane fusion (between HIV envelope and cell membrane) and viral entry into the interior of the cell.
- Uncoating of HIV core, exposing the viral RNA in the cell's cytoplasm.
- Reverse transcription, whereby single-stranded HIV RNA is reverse transcribed, or converted, into double-stranded viral DNA.
- Transport of viral DNA into the cell's nucleus.
- **Integration** of viral DNA into the host cell's DNA (in the nucleus, cellular DNA is packaged in thread-like compact structures called chromosomes that unwind during periods of cell growth and division. Viral DNA is integrated at a specific site in the cellular DNA molecule when chromosomes are in their unwound or relaxed formation).
- Production of large, nonfunctional viral proteins (i.e., protein synthesis) from the genetic code carried in the integrated viral DNA.
- Production of new viral RNA is (this occurs during the cell's normal DNA-to-RNA transcription phase of protein synthesis).
- Assembly of the large, nonfunctional viral proteins and new viral RNA molecules near the cell membrane.
- Cleavage, or splitting, of the large viral proteins into smaller, functional viral proteins; this phase may occur after the new viral particle is fully assembled outside of the cell.
- Budding, or release, of new viral particles from the cell membrane.

Researchers involved in antiretroviral drug design and development have largely honed in on the three essential steps in the HIV life cycle: (1) reverse transcription (the

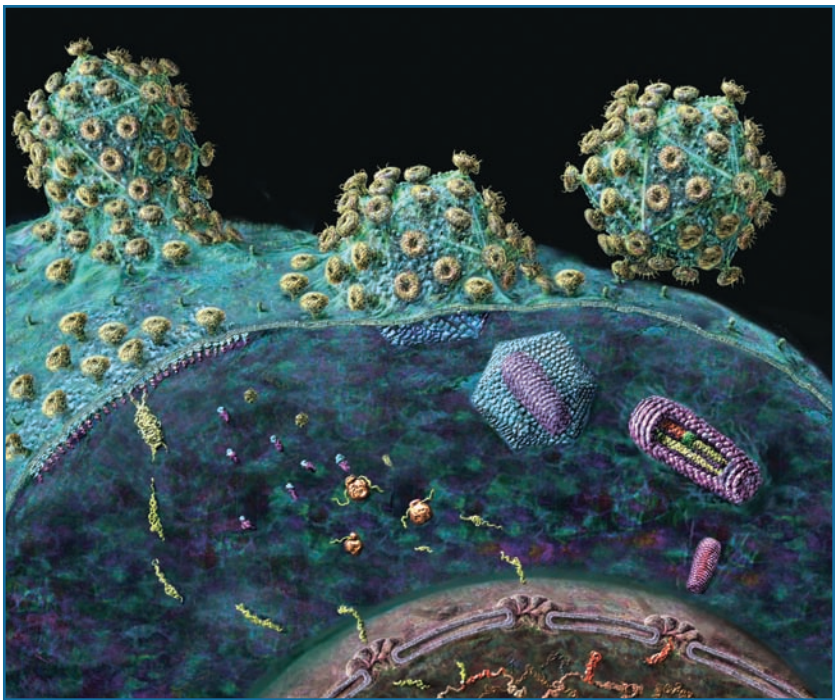


Figure 2.2 The life cycle of an HIV virus. The incoming virus *(center)* invades the T cell. The virus's capsule *(pink)* holds RNA *(yellow)*, which converts to DNA through reverse transcription. The viral DNA enters the nucleus *(brown)* and creates new RNA that make new viral proteins. These proteins make new copies of the virus, which are then released *(left)*. *(© Russell Kightley / Photo Researchers, Inc.)*

reverse transcriptase-driven conversion of viral RNA into viral DNA), (2) integration (the integrase-driven insertion of viral DNA into cellular DNA), and (3) polyprotein processing (the protease-driven cleaving of large, inactive viral proteins into smaller, functional viral proteins). Each one of these processes provides a unique opportunity for interrupting HIV replication and infection of susceptible cells. Since the discovery and characterization of HIV, medicinal chemists, pharmacologists, and others working to develop drugs to

fight HIV have focused their efforts on inhibiting the action of HIV enzymes.

THERAPEUTIC TARGETS, STRATEGIES, AND CHALLENGES

The first drugs used to treat AIDS patients were inhibitors of the HIV reverse transcriptase enzyme. Because daily treatment with one reverse transcriptase inhibitor drug (monotherapy) was effective only for a relatively short period of time, scientists decided to test the effectiveness of using two of these drugs simultaneously in combination or intermittently. The rationale was that lower doses of each drug would reduce the intolerable side effects while possibly putting more punch in the mix. Unfortunately, although dual therapy with two reverse transcriptase inhibitors appeared to be an improvement, the combination still lacked the staying power necessary to fight HIV for more than a few years. Physicians and researchers agreed that HIV was the toughest of enemies and they further agreed that a multipronged attack, using drugs aimed at multiple targets, may be the best way to knock out HIV.

Although different combinations of three or more antiretroviral drugs with long-lasting effectiveness are available today, these drug regimens cannot suppress HIV replication and infection of susceptible cells forever. The inability of potent antiretroviral drugs to maintain high levels of virologic suppression indefinitely is related to Darwin's natural selection theory, which says that organisms must adapt to survive. Like all populations of microbes exposed to long periods of continual antimicrobial therapy, HIV can escape the inhibitory action of antiretroviral drugs by mutating. To use Darwin's phraseology, the selection pressure of chronic exposure to a drug forces HIV to adapt by changing, or mutating. Indeed, molecular biologists have documented that HIV has an amazingly high genetic mutation rate, which ensures its survival.[26] American virologist and Nobel laureate Howard Temin noted, "To humans, variety is the spice of life. To a virus, it is survival." HIV strains that are resistant (less sensitive

CO-RECEPTORS

For more than 10 years, the CD4 receptor molecule was believed to be *the* receptor used by HIV to gain entry into a susceptible cell. In 1996, a second accessory receptor on CD4+ T cells and other CD4-bearing cells was found to be necessary for HIV to penetrate the membrane of a susceptible cell. The co-receptor may be one of two proteins: CXCR4, which is found on activated CD4+ T cells, or CCR5, which is found on unactivated CD4+ T cells, microglia in the brain, monocytes, macrophages, and dendritic cells (patrolling immune system cells). Critical studies have shown that if there is an alteration in the natural three-dimensional shape of a cell's co-receptor that renders the co-receptor nonfunctional, HIV is unable to infect that cell. People with a genetic mutation that codes for an altered nonfunctional co-receptor molecule may be resistant to HIV infection (if they possess two copies of the mutation) or they may remain symptom-free or experience delayed disease progression after becoming HIV-infected (if they possess one copy of the mutation). Interestingly, genetic studies have revealed that this mutation actually arose in humans long before the HIV/AIDS epidemic. Scientists are studying the frequency of this mutation in populations (it is more common in Europeans than all other populations) to establish how and why this particular mutation arose and whether the mutation confers any evolutionary advantage.

Sources:

Agrawal, L., Q. Jin, J. Altenburg, L. Meyer, R. Tubiana, I. Theodorou, and G. Alkhatib. "CCR5Delta32 Protein Expression and Stability are Critical for Resistance to Human Immunodeficiency Virus Type 1 in vivo." *Journal of Virology* 81, 15 (August 2007): L8041-8049.

Cohn, S.K., and L.T. Weaver. "The Black Death and AIDS: CCR5-Delta32 in Genetics and History. *Quarterly Journal of Medicine* 99, 8 (August 2006): 497-503.

or less susceptible) to the effects of a drug frequently emerge in HIV-infected patients taking antiretroviral medications. At the molecular level, select HIV **genes** in the viral RNA mutate,

thereby altering the interaction between virus and drug. HIV is said to develop **drug resistance**—in this case, resistance to the drug's anti-HIV action. Over time, a drug may become ineffective due to drug resistance.

Drug resistance is a major obstacle to the successful treatment of HIV/AIDS. Physicians, researchers, and even patients have come to realize that it is not a matter of *if* drug resistance will emerge, but a matter of *when*. This is also true with other infectious agents and the drugs used to treat them: Bacteria, for example, develop resistance against specific antibiotics. Patients harboring drug-resistant HIV strains will experience **virologic failure** with their once-effective antiretroviral medications. This means that the drugs are no longer working to suppress viral replication, which will likely lead to increased destruction of CD4+ T cells and other immune cells.

Blood tests are now available to look at the genetic profile of a sample of HIV from a patient to determine whether the virus is developing resistance to one or more drugs in that patient's antiretroviral regimen. Comparison of the test results with patterns of HIV mutations known, from in vitro laboratory studies, to confer drug resistance allows physicians and patients to consider changing that regimen.

3

Antiretrovirals: The Big Picture

Medicines don't work if you don't take them.
—C. Everett Koop, former U.S. surgeon general

Once scientists gained some insights into the life cycle of HIV and the various ways in which HIV causes immunosuppression in the body, the focus shifted to combating this wily adversary. Although the first AIDS drug was approved by the U.S. Food and Drug Administration (FDA) less than four years after the discovery of HIV, it was 12 years before effective combinations of antiretroviral drugs—so-called cocktails of three or more HIV/AIDS drugs—became available. (Recall that *anti*retrovirals—literally, "against" retroviruses—are drugs that fight infections caused by retroviruses, the family of viruses to which HIV belongs. The terms *antiretrovirals* and *HIV/AIDS drugs* are used interchangeably.)

The widespread use of potent combination antiretroviral therapy resulted in dramatic clinical and survival benefits for HIV-infected patients. Overall, precipitous declines in HIV-related illnesses and delayed progression to AIDS and death have been observed since 1996.[27] In addition, in industrialized countries where patients have access to antiretroviral medicines, the quality of life for those living with HIV infection or AIDS has improved greatly since the beginning of the epidemic.

Today there are several different HIV/AIDS drug combinations with long-lasting effectiveness. At this time and for the foreseeable future, however, no single drug or combination of drugs is a cure

Figure 3.1 This lab technician is preparing a polymerase chain reaction (PCR) test, one of the tests that measures viral load. *(© Colin Cuthbert / Photo Researchers, Inc)*

for HIV infection or AIDS. No one drug or drug regimen can eradicate HIV from an infected individual, and no one drug or drug regimen can suppress HIV replication and infection of susceptible cells forever.

The effectiveness of an antiretroviral drug regimen for a patient is determined by comparing results of a diagnostic test, called the **viral load** test, before and after beginning or changing therapy. The test amplifies the viral RNA in a blood sample from an HIV-infected individual to reflect the amount of circulating virus in the body. The viral load test, which measures the number of copies of HIV RNA molecules per milliliter (mL) of blood, is performed to assess the patient's degree of infection,

and with sequential test results, the rate of HIV replication can be calculated. Viral load is therefore measured routinely, even before a patient begins antiretroviral therapy. (A discussion of when to initiate antiretroviral therapy is presented in Chapter 8.) Findings from recent studies that examined the feasibility of intentionally interrupting HIV/AIDS treatment ("drug holidays" for patients) have shown that HIV rebounds very soon after the antiretroviral drugs are stopped.[28,29,30] When the inhibitory action of the drugs is removed, the virus seems to come back with a vengeance and CD4+ T cell counts drop to dangerous levels. Thus, expert medical advice dictates that HIV-infected patients take antiretroviral therapy for life. The need for lifelong antiretroviral therapy to control HIV replication is a significant challenge for patients and the health care and social services professionals who treat them.

HIV-treating clinicians and their patients must weigh several variables when choosing the "best" combination of antiretrovirals: drug potency, tolerability, risk of long-term toxicity (adverse effects), convenience, and the individual patient's medical history and current life situation. Consideration of the risk-to-benefit ratio of a therapeutic agent is a basic principle of medicine. According to Drs. Alan S. Nies and S.P. Spielberg, contributing authors in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, "The utility of a regimen can be defined as the benefit it produces plus the dangers of not treating the disease minus the sum of the adverse effects of therapy."

ANTIRETROVIRALS TODAY

There are four broad classes of antiretroviral drugs in use today:

- reverse transcriptase inhibitors
- vucleoside or nucleotide reverse transcriptase inhibitors
- non-nucleoside reverse transcriptase inhibitors
- protease inhibitors
- integrase inhibitors
- entry inhibitors

The reverse transcriptase inhibitor class of antiretrovirals consists of two subclasses, which are defined by their specific interaction with the HIV reverse transcriptase enzyme. Currently, there are no FDA-approved HIV integrase inhibitors. Drug discovery efforts for new antiretrovirals continue to be strong as there is an ongoing need for treatments that are effective in HIV-infected individuals whose antiretroviral regimen no longer adequately suppresses HIV. Unfortunately, for a variety of reasons including intolerability and drug resistance to numerous successive antiretroviral regimens, some patients have exhausted all therapeutic options.

Investigational antiretroviral drugs in the newer therapeutic classes (e.g., integrase inhibitors) are usually initially evaluated in patients who are experiencing virologic failure with their current antiretroviral regimen. As HIV-infected individuals are living longer due to advances in clinical medicine and potent antiretroviral medications, there is a growing need for new antiretrovirals and other anti-HIV strategies.

SIDE EFFECTS

All antiretroviral drugs are associated with short-term side effects (occurring within days or weeks of starting a new drug) and possibly long-term complications (e.g., heart disease, diabetes). Treatment-related adverse effects and poor tolerability can interfere with the effectiveness of antiretroviral drugs as patients may decide to stop taking their regimen as prescribed or discontinue their regimen altogether. Numerous studies indicate that side effects negatively impact patients' daily activities and quality of life and account for the lion's share of antiretroviral drug discontinuations.

In addition to the physical discomfort or sickness they cause, side effects also have a psychological impact on patients. Specific toxicities can be disfiguring, disabling, and/or stigmatizing (e.g., excessive weight loss or gain, diarrhea, **jaundice**).

Figure 3.2 People with HIV and AIDS often need to take a complex combination of drug therapies to manage their disease. *(© AP Images)*

TAKING MEDICINES AS PRESCRIBED

HIV-infected individuals, like many patients with a chronic illness requiring lifelong therapy, face a huge challenge when they begin antiretroviral therapy. They must prepare themselves to take all the drugs in their antiretroviral regimen on time as prescribed for the rest of their lives. Health care and social services professionals work with patients to help them stick to their regimen because there are consequences associated with forgetting to take antiretroviral drugs, taking the medications erratically or incorrectly, and/or skipping doses. Some antiretroviral drugs are more difficult to swallow, so to speak, than others. For example, some cannot be taken with food because it may interfere with the absorption of the drug, which ultimately affects the drug's ability to maximally suppress HIV. Quite a few antiretrovirals have numerous interactions with

other medications (non-HIV medicines), some of which can have serious or life-threatening outcomes.

The consequences of not adhering to the dosing requirements of antiretroviral drugs include virologic and immunologic failure—HIV replication increases and CD4+ T cell counts decline. Skipping numerous doses routinely provides the perfect environment for drug-resistant HIV strains to emerge. Conversely, adhering to the dose and schedule (once a day or twice a day) of all drugs in an antiretroviral regimen significantly increases the likelihood of long-term virologic suppression.

Although potent antiretroviral regimens are more "patient friendly" in the twenty-first century (e.g., fewer pills per dose or per day and co-formulated pills), antiretroviral adherence remains an important and challenging clinical issue.

HIV/AIDS DRUGS IN THE DEVELOPING WORLD

An estimated 39.5 million adults and children worldwide were living with HIV at the end of 2006. Of these, 24.7 million, or 63 percent, live in sub-Saharan Africa. Of the estimated 2.9 million deaths from AIDS globally, 2.1 million, or 72 percent, occurred in people living in sub-Saharan Africa. Clearly, the need for HIV/AIDS treatments in sub-Saharan Africa is great; however, access there to antiretroviral therapy is limited for most people with the disease.

In sub-Saharan Africa, the median annual income is $384 (in U.S. dollars) and the generic co-formulated antiretroviral treatment known as GPO-VIR (three drugs in one pill: stavudine, lamivudine, and nevirapine) costs a few hundred dollars per year per patient—more than half of the median household income. By comparison, the annual cost for antiretroviral drugs is estimated to be about $20,000 in the U.S., where the median annual income is $42,409.

Human rights activists, advocates for the poor, and public health officials are making inroads in getting essential HIV/AIDS medicines to sub-Saharan African and other developing countries. In 2001, the World Trade Organization, the only international body that governs the rules of trade between nations,

CO-FORMULATED PILLS

For more than 10 years, HIV-treating clinicians and their patients have been able to combine three or more antiretrovirals into a single potent regimen that could successfully suppress HIV replication. Only in the past few years, however, has the pharmaceutical industry been able to deliver two or three antiretroviral drugs manufactured in a single pill. These co-formulated pills contain fixed doses of the individual drugs. The availability of these co-formulations has been a boon to patients: It reduces the number of pills to be taken per day, which makes it easier to take their daily medicine as prescribed.

Table 3.1 FDA-APPROVED CO-FORMULATED ANTIRETROVIRAL PILLS*

Combination *(generic names and abbreviation)*	**Trade name**	**Dosing**
Efavirenz (EFV)/emtricitabine (FTC)/ tenofovir (TDF)	Atripla	1 pill, once daily
Emtricitabine (FTC)/tenofovir (TDF)	Truvada	1 pill, once daily
Zidovudine (AZT)/lamivudine (3TC)	Combivir	1 pill, twice daily
Abacavir (ABC)/lamivudine (3TC)	Epzicom	1 pill, once daily
Zidovudine (AZT)/lamivudine (3TC)/ abacavir (ABC)	Trizivir	1 pill, twice daily
Lopinavir (LPV)/ritonavir (RTV)	Kaletra	2 pills, twice daily or 4 pills, once daily**

* Only efavirenz/emtricitabine/tenofovir (Atripla) is approved for use alone in the treatment of HIV-1 infection; all of these drugs must be used with other antiretroviral agents.

** Once-daily dosing for treatment-naïve patients only.

Source: U.S. Department of Health and Human Services. "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents" Available online. URL: http://AIDSinfo.nih.gov/guidelines/. Posted December 1, 2007.

adopted an Agreement on Trade-Related Aspects of Intellectual Property Rights to allow the production of generic antiretroviral drugs and other drugs such as antimicrobials for opportunistic infections for HIV/AIDS patients. Prior to this agreement, the pharmaceutical industry cried foul when governments in India and Brazil produced lower-cost generic versions of FDA-approved brand name antiretrovirals. Although the argument by pharmaceutical manufacturers to uphold international patent protection laws was valid, the 142 member states of the World Trade Organization agreed that the global HIV/AIDS crisis and the human toll outweighed the concern for continuing the long-standing economic incentive for bringing new products to the market. The 2001 agreement and subsequent reaffirmations by other organizations, such as the 2006 resolution of the general assembly of the United Nations, have been successful in making lower-cost generic versions of antiretroviral drugs available and in promoting bulk procurement of and price negotiations relating to medicines, prevention products, and diagnostic tests for HIV/AIDS and related infections and diseases.

Access to antiretroviral drugs in developing countries is limited by more than affordability. International aid organizations cite the lack of adequate health care infrastructure, including too few health care workers, and unpredictable drug availability from the pharmaceutical industry and relief efforts. Nevertheless, industrialized nation donors have stated their commitment to funding expanded access to HIV/AIDS treatment in developing countries. Organizations involved in this effort include:

- Doctors Without Borders
- U.S. Agency for International Development (USAID)
- World Health Organization's (WHO) 3 x 5 Initiative
- The World Bank Global HIV/AIDS Program
- The Global Health Fund
- Family Health International
- Bill & Melinda Gates Foundation

4

Inhibitors of the HIV Reverse Transcriptase Enzyme

Recent advances in therapy have obscured the difficult and often demoralizing character of the early years of therapies for HIV.

—Kent A. Sepkowtiz, M.D., infectious disease specialist, Memorial Sloan-Kettering Cancer Center, New York, 2001

The first drugs that were deemed acceptable for use in AIDS patients targeted a viral enzyme essential to the virus's survival—reverse transcriptase. Theoretically, these drugs could stop HIV in its tracks by disabling the enzyme responsible for the chemical reaction that produces viral DNA molecules (a necessary first step for the propagation of new virions). That was the theory. In reality, although reverse transcriptase inhibitors do disrupt the reverse transcription process, they do not do enough damage by themselves at doses safe to use in humans. The reasons for this involve basic principles of **pharmacology**, such as the way in which these drugs are distributed in the body—specifically, how readily they cross membranes and enter cells, and how they are metabolized (broken down) in the body and within cells.

As discussed in Chapter 2, to replicate itself, HIV uses a host cell's protein-making machinery to convert its genetic material (single-stranded HIV RNA) into double-stranded viral DNA. This reverse transcription step in the HIV life cycle can be terminated with potent but toxic drugs that also affect uninfected cells undergoing cell division. Two types of drugs that act on the HIV reverse transcriptase enzyme—each in a different way—have been found to be effective in selectively targeting this enzyme. These drugs are known as the nucleoside analog reverse transcriptase inhibitors and the non-nucleoside reverse transcriptase inhibitors.

Luck might not be the right word, but what else explains why reverse transcriptase is such an error-prone enzyme? It turns out that reverse transcriptase does not always copy the RNA sequence into DNA exactly as it should. This is why HIV has such a high mutation rate and why there is so much diversity of HIV types worldwide.

AZT: THE FIRST AIDS DRUG

Amazingly, the virus identified as causing AIDS still did not have an agreed-upon name in 1985, when a drug was found to inhibit its infectivity *in vitro*. AZT, or azidothymidine (now called zidovudine or ZDV), was approved by the FDA in 1987 after demonstration of reduced mortality in AIDS patients who were given four to six daily doses.[31] This first AIDS drug was used as a single-drug regimen (monotherapy) for a number of years before additional antiretrovirals became available. Doctors, patients, patient advocates, and activists knew that AZT was not a cure, but it did delay the rapid physical deterioration that AIDS patients were experiencing in the early years of the epidemic.

Just as new reverse transcriptase inhibitors were being tested and becoming available, scientists reported that drug-resistant HIV had been recovered from AZT-treated AIDS patients.[32] Although it should not have been surprising, it was

Figure 4.1 AZT was approved by the FDA in 1987 as the first treatment drug for AIDS. *(© RAGUET / Photo Researchers, Inc.)*

a psychological letdown for patients, AIDS-treating clinicians, and others concerned about the disease. The silver lining was that documentation of drug resistance with antiretroviral therapy stimulated researchers, particularly those in the pharmaceutical industry, to think about long-term therapeutic strategies for HIV/AIDS patients. It also turned out that several biochemical and pharmacologic properties of AZT make this drug especially well suited for preventing HIV transmission from mother to fetus or newborn.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

The nucleoside analog reverse transcriptase inhibitors are so named because they are chemical look-alikes of nucleoside

molecules found in all cells. Nucleosides are made up of either the ribose or deoxyribose sugar molecule chemically bonded to a nitrogen-containing base. DNA is a chain of nucleoside molecules bonded to a phosphate atom. These nucleoside analogs inhibit reverse transcription by terminating the synthesis of a viral DNA chain in the host cell's cytoplasm. Once HIV's reverse transcriptase enzyme adds a nucleoside analog—instead of a cellular nucleoside molecule—to a DNA chain in progress, the reaction stops.

U.S. FOOD AND DRUG ADMINISTRATION (FDA) APPROVAL PROCESS FOR DRUGS

The FDA is the federal government agency responsible for ensuring the safety and effectiveness of drugs. New drugs that are discovered and tested by pharmaceutical companies, government or private biomedical research organizations, or universities or academic medical centers must undergo formal evaluation by the FDA. The review process lasts about seven years, on average. According to the FDA's Web site, "Most drugs that undergo preclinical (*in vitro* and animal) testing never even make it to human testing and review by the FDA." It takes approximately 10 to 15 years, from drug discovery through testing and FDA review, before a new drug is approved for use as a prescription medicine. The steps in the process are as follows:

- ***In vitro* and animal testing.**
- **Proposal for human testing in clinical trials.**
- **Phase I clinical trials, to determine the drug's metabolism in the body and its most frequent side effects (typically involves 20 to 100 healthy individuals or "subjects").**
- **Phase II clinical trials, to obtain preliminary data on whether the drug works in individuals with the disease**

AZT and seven other **nucleoside reverse transcriptase inhibitors** have been approved by the FDA to treat HIV/AIDS. The typical antiretroviral regimen consists of two nucleoside reverse transcriptase inhibitors plus either a non-nucleoside reverse transcriptase inhibitor or an HIV protease inhibitor. Currently, there are five nucleoside reverse transcriptase inhibitors in clinical testing (all being sponsored by drug manufacturers new to the HIV/AIDS drug development arena) and about 20 in preclinical (*in vitro* and animal) testing.

or condition targeted by the drug (typically involves 30 to 500 individuals).

- **Phase III clinical trials, to gather a larger set of data (typically involves several hundred to about 3,000 individuals).**
- **Formal request by the "drug sponsor" for the FDA to consider a drug for marketing approval (the drug sponsor, usually a pharmaceutical company even if the drug was originally discovered in a university laboratory, files a new drug application).**
- **FDA scientists review the application to determine whether the studies the drug sponsor describes show that the drug is safe and effective for its proposed use.**

Sources:

U.S. Food and Drug Administration. "The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective. Available online. URL: http://www.fda.gov/fdac/special/testtubetopatient/drugreview.html. Accessed May 17, 2006.

http://www.phrma.org/files/Approving%20New%20Medicines.pdf

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

The **non-nucleoside reverse transcriptase inhibitors (NNRTIs)** are very different from their cousins, the nucleoside analogs. Non-nucleoside reverse transcriptase inhibitors actually bind to the HIV reverse transcriptase enzyme like a substrate to interfere with the reverse transcription step of

FAST-TRACK DRUG REVIEW PROCESS

The U.S. Food and Drug Administration (FDA) takes a lot of flak for the lengthy process it uses to review the safety and effectiveness of a new drug. Pharmaceutical companies and other drug manufacturers frequently complain about the hurdles that must be cleared in order to get a new drug approved and on the market. It typically takes six to seven years to identify a worthy drug candidate suitable for testing in humans, and another seven years to conduct clinical trials in humans. If no obvious safety issues arise and effectiveness is demonstrated in those trials, the FDA will review all the data over an average of one and one-half years.

The AIDS epidemic stepped up pressure on the FDA to hasten the drug testing and review process. In the 1980s, AIDS activists fought hard to bring attention to the impact of new-drug delays. Media coverage of demonstrations and protests allowed AIDS activists to communicate their message that the government needs to balance the risks of side effects or borderline effectiveness of new drugs with the clear risk of death for AIDS patients if no drugs are available. Activists shouted, "No more deaths," during a demonstration at FDA headquarters, and staged numerous other highly confrontational protests, including dousing public health scientists and HIV/AIDS researchers with red paint to symbolize the blood and death of AIDS victims.

the HIV life cycle. Only three non-nucleoside reverse transcriptase inhibitors are FDA-approved: efavirenz, nevirapine, and delavirdine. Although these are potent antiretrovirals at doses that are safe in humans, HIV is capable of developing resistance to all drugs in this subclass even when it is exposed to only one. Such cross-resistance limits the therapeutic options for patients.

The FDA responded by modifying its review and approval process for drugs aimed at HIV/AIDS, some cancers, and other life-threatening illnesses, recognizing that physicians and patients were willing to accept greater risks from products for such conditions. The FDA basically agreed that "zero risk" was unrealistic and that the goal was to balance risks and meet patients' needs. An accelerated drug review and approval process ("fast track") was put in place, and a high-priority category was created for all new drug applications for HIV/AIDS medicines. This radical change allowed AZT, the first AIDS drug sent to the FDA for review, to be approved within two years of the discovery of its *in vitro* anti-HIV activity. FDA approval of AZT was granted despite the side effects and toxicity observed during clinical trials.

Other reforms followed, including a parallel track mechanism to expand the availability of experimental drugs to individuals with AIDS or HIV-related diseases who did not have other satisfactory therapeutic options and could not participate in controlled clinical trials. The parallel track policy applies only to AIDS and HIV-related diseases.

Sources:

Brunton, Laurence L., J.S. Lazo, and K.L. Parker (eds). *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 11th ed. New York: McGraw-Hill, 2006.

Federal Register. Vol. 53. No. 204. October 21, 1988.

Federal Register. Vol. 63. No. 222. November 18, 1998.

Table 4.1 FDA-Approved Nucleoside Reverse Transcriptase Inhibitors (NRTI)

Combination *(generic names and abbreviation)*	**Trade name**	**Approval date**
abacavir (ABC)	Ziagen	December 1998
azidothymidine (AZT) or zidovudine (ZDV)	Retrovir	March 1987
didanosine or dideoxyinosine (ddI)	Videx, Videx EC	October 1991
emtricitabine (FTC)	Emtriva	July 2003
lamivudine (3TC)	Epivir	November 1995
stavudine (d4T)	Zerit, Zerit EC	June 1994
tenofovir disoproxil fumarate (TDF)	Viread	October 2001
zalcitabine (ddC)	Hivid	June 1992
Co-Formulated Pills		
abacavir and lamivudine (ABC/3TC)	Epzicom	June 1992
lamivudine and zidovudine (3TC/ZDV, COM)	Combivir	June 1992
lamivudine, zidovudine and abacavir (3TC/ZDV/ABC)	Trizivir	August 2004
tenofovir disoproxil fumarate and emtricitabine (TDF/FTC)	Truvada	August 2004

Source: U.S. Food and Drug Administration. "Drugs Used in the Treatment of HIV Infection." Available online. URL: http://www.fda.gov/oashi/aids/virals.html. Accessed May 17, 2007.

Of the three currently available non-nucleoside reverse transcriptase inhibitors, efavirenz has been shown to be the most potent. Efavirenz is recommended as a "preferred" NNRTI in antiretroviral regimens for patients beginning HIV/AIDS therapy. Efavirenz, however, is not appropriate for

pregnant women or women of reproductive age because of this drug's potential for causing birth defects. Efavirenz co-formulated with the nucleoside analogs tenofovir and emtricitabine is an all-in-one pill that has the added bonus of a convenient dosing schedule (once a day). Nevirapine, an alternative to efavirenz, carries a risk of serious, possibly life-threatening, rash and liver damage, particularly among patients with high CD4+ T cell counts. Delavirdine is the least effective of the NNRTI drugs and is not recommended for use in any initial therapeutic regimen.

At this time, there are at least five NNRTI drug candidates in clinical testing, one of which is in late testing (phase III clinical trial). Findings from more than 1,000 treatment-experienced patients participating in one of two **placebo**-controlled phase III trials evaluating the NNRTI etravirine (TMC125) are encouraging.[33,34] (A placebo is a dummy medication or treatment that has no effect, such as a sugar pill. Placebos used in clinical trials as controls are imitations of the medicine under evaluation; they can be tablets or capsules with inactive ingredients.) In the phase III trials, after six months of treatment (etravirine or placebo plus the protease inhibitor darunavir plus low dose of the protease inhibitor ritonavir plus two or

Table 4.2 **FDA-Approved Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

Combination *(generic names and abbreviation)*	**Trade name**	**Approval date**
delaviridine (DLV)	Rescriptor	April 1997
efavirenz (EFV)	Sustiva	September 1998
nevirapine (NVP)	Viramune	June 1996

Source: U.S. Food and Drug Administration. "Drugs Used in the Treatment of HIV Infection." Available online. URL: http://www.fda.gov/oashi/aids/virals.html. Accessed May 17, 2007.

more NTRIs), patients who received etravirine had greater virologic suppression than did those who received placebo. The patients in these studies had evidence of resistance to NNRTI and therefore these study results are especially noteworthy. As is true for all antiretroviral classes, continued development of new NNRTI is critical because of the need for additional therapeutic options for patients with extensive treatment history.

5

Inhibitors of the HIV Protease Enzyme

The HIV protease enzyme, one of the three viral enzymes packed into each HIV viral particle, **catalyzes** the cleavage reaction in which the newly manufactured, large, nonfunctional viral proteins in a host cell are snipped into smaller active proteins. It may not sound glamorous, but the job is an essential step in the HIV life cycle. The cleavage of the large polyproteins occurs as newly assembled HIV viral particles are budding from an infected cell. If newly released virions contain uncleaved polyproteins (such virions are said to be immature), then they will be incapable of infecting susceptible cells. Hence, drugs that inhibit the cleavage of these proteins can save innumerable cells from becoming infected by HIV.

The HIV protease inhibitors are largely responsible for taking antiretroviral therapy to the next level, for changing expectations, and raising hopes. Potent combination-antiretroviral treatment, which emerged as the standard of care in 1996, is credited with changing HIV/AIDS from an aggressive fatal disease to one that is largely manageable. One landmark study documented the precipitous decline in illnesses and mortality among HIV/AIDS patients from 1994 to 1997 using data from a large U.S. database of HIV-infected individuals.[27] Rigorous statistical analyses showed that the decline was specifically associated with the introduction and widespread use of protease inhibitor-containing antiretroviral therapy. Subsequent studies have consistently reported the same finding.

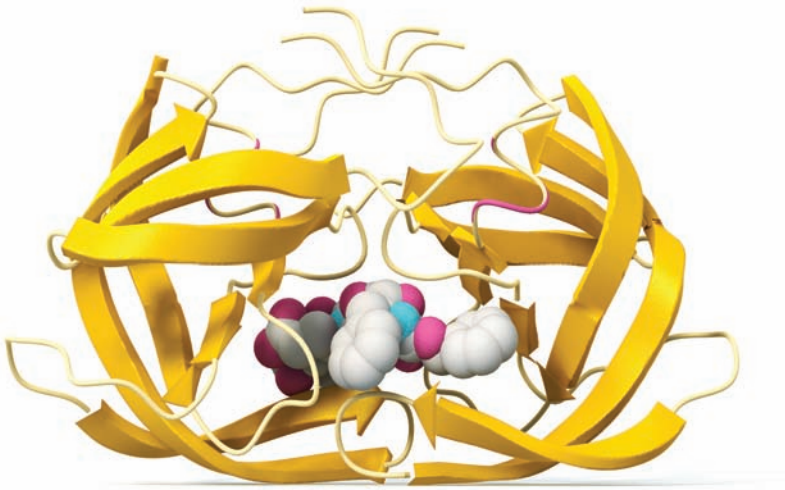


Figure 5.1 This computer model shows how protease inhibitor drugs bind to the HIV protease enzyme *(yellow)*. Protease inhibitors help prevent the process of viral replication and can slow the progression of HIV/AIDS, especially when they are used in combination with other drugs. *(© Phantatomix / Photo Researchers, Inc.)*

BOOSTING POWER

Individual HIV protease inhibitors may need to be "boosted" with a second protease inhibitor, which is co-administered at a lower dose than normally would be used to suppress HIV replication. The boosting protease inhibitor is usually ritonavir, but others are being evaluated. This boosting is a way to pharmacologically enhance the primary protease inhibitor, which is given at its regular therapeutic dose. It appears that boosting with ritonavir is needed for all protease inhibitors, although such boosting may not provide equal effectiveness among the different protease inhibitors.

So how is ritonavir able to boost the suppressive effect of another protease inhibitor? The pharmacological enhancement it provides is an example of a beneficial drug-drug interaction (the interaction between two co-administered drugs). The

enhanced, or boosted, concentration of the primary protease inhibitor in the blood occurs because ritonavir is a strong inhibitor of a key drug-metabolizing enzyme in the body. Like food and beverages, drugs are metabolized, or broken down, in our bodies by enzymes. Almost all tissues of the body contain these enzymes, called the cytochrome P450 "superfamily" of enzymes. The vast majority of medicines are metabolized by the cytochrome P450 enzymes, the highest levels of which are located in the liver and intestines.

All of the HIV protease inhibitors are metabolized by CYP3A4, the most abundant of the cytochrome P450 enzymes. Ritonavir's potent inhibition of CYP3A4 causes a significant slow-down in the metabolism of the co-administered protease inhibitor. This means that the primary protease inhibitor stays in the blood for a longer period than it would otherwise, which means that the drug has a longer time in which to exert its anti-HIV effect.

PROTEASE INHIBITOR METABOLISM

Inhibiting the metabolism of HIV protease inhibitors with subtherapeutic doses of ritonavir leads to a desirable boosting effect of the primary protease inhibitor. That is not the norm, however: The co-administration of drugs rarely results in a beneficial therapeutic effect. More commonly, there are problems with the co-administered drugs, particularly those that use the same drug-metabolizing pathway. The cytochrome P450 enzyme pathway used by the HIV protease inhibitors is also used by many other drugs. As a result, the protease inhibitors may interact with other drugs, sometimes leading to dangerous medical situations. An antacid, for example, can increase blood concentrations of the protease inhibitor to toxic levels. This is an example of an adverse drug-drug interaction. Some drug interactions are life-threatening, such as the use of the cardiovascular drug bepridil with the HIV protease inhibitors amprenavir, fosamprenavir, atazanavir, ritonavir, or tipranavir: The concentration of bepridil in the

blood is significantly increased when co-administered with any one of these protease inhibitors and can lead to cardiac arrhythmias.

HIV protease inhibitor drug metabolism can also be affected by the presence of certain foods, beverages, and natural products such as herbal supplements or remedies in the bloodstream. The herb Saint-John's-wort, most commonly used as an antidepressant, is an inducer of the cytochrome P450 system and therefore speeds up the metabolism of co-administered protease inhibitors. Co-administration of Saint-John's-wort with any one of the FDA-approved HIV protease inhibitors results in decreased blood levels of the protease inhibitor, which in turn results in decreased effectiveness (decreased ability to suppress HIV replication). Thus, patients taking protease inhibitor-containing regimens should not use Saint-John's-wort. Rest assured, the fine print in the "complete prescribing information" for all of the protease inhibitors includes a warning about the concomitant use of Saint-John's-wort.

Taking a glass of grapefruit juice with one of two protease inhibitors (saquinavir or indinavir) affects the blood levels of these drugs in different ways. Although grapefruit juice decreases the amount of the cytochrome P450 CYP3A4 enzyme in the small intestines and therefore increases the absorption of saquinavir into the blood through the gut wall, it decreases the concentration of indinavir in the blood by 26 percent (compared with no intake of any food or beverage). Indinavir is the only protease inhibitor whose metabolism is affected by food; indinavir blood concentrations are reduced by 75 percent when this drug is taken with a high-fat meal.

CLINICAL USE

In the United States, 10 protease inhibitors have been approved to treat HIV-infected patients. Of these, three protease inhibitors boosted with ritonavir are recommended as a component in initial antiretroviral regimens for untreated patients. Most clinicians and researchers agree that it is a good

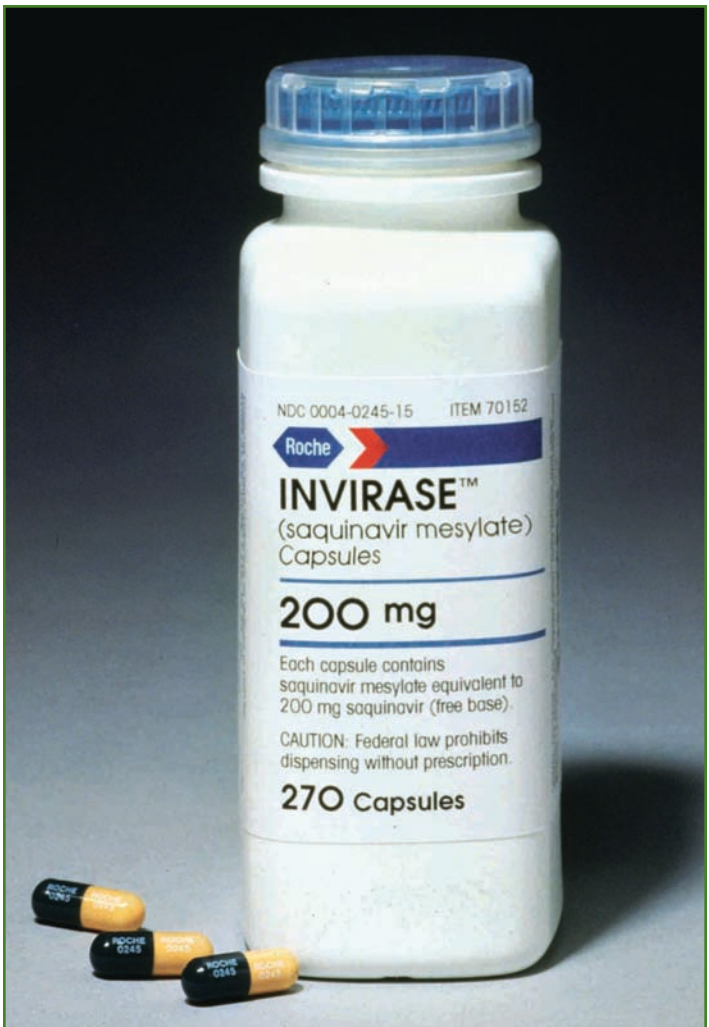


Figure 5.2 Invirase (saquinavir) was the first protease inhibitor to be approved by the FDA. *(© AP Images)*

treatment strategy to start antiretroviral therapy with a drug combination that can provide the greatest and most durable HIV suppression. This strategy is based on the knowledge that drug-resistant HIV strains will eventually emerge and on clinical trial data showing that the first antiretroviral regimen

Table 5.1 FDA Approved HIV Protease Inhibitors (PI)

Combination *(generic names and abbreviation)*	**Trade name**	**Approval date**
amprenavir (APV)	Agenerase	April 1999
atazanavir (ATV)	Reyataz	June 2003
darunavir (DRV)	Prezista	June 2006
fosamprenavir calcium (F-APV)	Lexiva	October 2003
indinavir (IDV)	Crixivan	March 1996
nelfinavir mesylate (NFV)	Viracept	March 1997
ritonavir (RTV)	Norvir	March 1996
saquinavir (SQV)	Invirase	December 1995
tipranavir (TPV)	Aptivus	June 2005
Co-Formulated Pills		
lopinavir and ritonavir (LPV/r)	Kaletra	September 2000

Source: U.S. Food and Drug Administration. "Drugs Used in the Treatment of HIV Infection." Available online. URL: http://www.fda.gov/oashi/aids/virals.html. Accessed May 17, 2007.

provides the longest-lasting benefits: longer suppression of HIV replication (low viral load, possibly for years), preservation of immune system function (normal CD4+ T cell counts), and symptom- or disease-free status (no serious infections requiring hospitalization).

SIDE EFFECTS

Like other classes of antiretrovirals, the HIV protease inhibitors are mostly well tolerated, but a number of short-term side effects may occur. Headache and abdominal discomfort with or without diarrhea are the most common side effects. In addition, accumulated clinical experience with protease inhibitor-containing antiretroviral regimens reveals that over time,

KILLER ADVERSE DRUG REACTIONS

Some side effects, or adverse effects, of medicinal drugs can be fatal. Adverse drug reactions are one of the top 10 causes of death in hospitalized patients in the United States—as many as 100,000 deaths per year! Even aspirin at low doses, recommended to prevent heart attacks and stroke, can kill: Fatal bleeding can occur in patients who have an undetected clotting disorder and take aspirin regularly.

Source: Lazarou, J., B.H. Pomeranz, P.N. Corey. "Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies," *Journal of the American Medical Association* 279, 15 (April 15, 1998): 1200-1205.

many treated patients develop metabolic alterations, such as impairments in glucose and insulin metabolism and changes in lipid metabolism (cholesterol and triglycerides).[35] In general medicine, these metabolic changes are associated with serious medical conditions such as hypertension, coronary heart disease, and stroke. Changes may also be seen in the distribution of body fat of treated patients—for example, some develop a round protruding stomach ("protease paunch"). Studies are still assessing the cardiac risk associated with taking antiretroviral drugs by comparing those taking them with untreated HIV-infected individuals and the general population. Also, it is controversial whether cardiac risk is limited to those on protease inhibitor-containing regimens. As always, taking medicine involves weighing risks: benefits versus adverse effects.

6

Inhibitors of the HIV Integrase Enzyme

HIV integrase can be considered the last frontier in HIV/AIDS drug therapy. HIV integrase is the last of the three essential viral enzymes to be targeted by antiretroviral drugs. Development of the HIV integrase inhibitor class of drugs has lagged behind that of the other two classes of HIV enzyme inhibitor drugs (reverse transcriptase inhibitors and protease inhibitors) primarily because of incomplete knowledge about the structure of the integrase enzyme and because of technical difficulties in the laboratory.

As of this writing, all HIV integrase inhibitors are in the investigational testing phase of development and none have been approved by the FDA for the treatment of HIV/AIDS. Nevertheless, at least two experimental drugs are in the late stages of development and appear to be on their way to winning FDA approval.

INTEGRATION STEP OF HIV LIFE CYCLE

In order for HIV to successfully produce new viruses or replicate within a susceptible host cell, the genetic material of HIV, RNA, must first be converted into DNA. You may recall from Chapter 2 that the reverse transcriptase enzyme catalyzes the reaction that converts or transcribes HIV RNA into HIV DNA. After this reverse transcription step, the viral DNA must be inserted into the host cell's DNA, a step in the HIV life cycle known as integration. This integration reaction is catalyzed by the HIV integrase enzyme.

Although "integrating" a viral DNA molecule into cellular DNA may sound simple, it actually involves a rather complicated

set of sequential enzyme reactions. In the first reaction, which takes place in the cytoplasm of the host cell, the integrase enzyme activates one end of each viral DNA strand, making it reactive.

The HIV integrase enzyme, combined with the reactive viral DNA, is immediately processed into a structure called the pre-integration complex and transported into the host cell's nucleus. Once inside the nucleus, a second reaction, called strand transfer, is catalyzed. In this reaction, the reactive ends of the viral DNA attack the host cell DNA. During the attack, viral DNA is inserted and joined (i.e., integrated) into the host cell DNA through stable chemical bonds that are formed between the two DNA molecules. Once integration is complete, the host cell is officially considered infected. After the strand transfer reaction, the new product (viral DNA plus host cell DNA) has some gaps, which are repaired by host cell DNA repair enzymes. When the host cell replicates (during normal cell division), the integrated viral DNA is transcribed along with the host cell DNA into RNA. In this way, the genetic information that was coded in the viral RNA of the HIV virus is transcribed and translated into viral proteins. Not all viral DNA is inserted into the host cell DNA. Instead, some of it forms circular viral DNA. The purpose of this circular viral DNA is not understood.

HIV INTEGRASE

Graphic illustrations of the HIV virion are not highly accurate. It turns out that there are 40 to 100 HIV integrase molecules packaged within each HIV virus particle.

The HIV integrase molecule has a central area, called the central core domain, that contains the enzyme's **active site** (or catalytic site). This is where the chemical reaction takes place. HIV integrase inhibitors work by blocking the active site, preventing the viral and host cell DNA molecules from binding to integrase, a process necessary for the chemical reaction that joins the two molecules. Thus, HIV integrase inhibitors

prevent the integration of the viral DNA into the host cell DNA, effectively preventing HIV from propagating itself.

INTEGRASE INHIBITORS IN THE PIPELINE

Although the first HIV integrase inhibitor was described more than 10 years ago,[36] the first potentially clinically useful integrase inhibitors were not discovered until 2000.[37]

As of July 2007, no HIV integrase inhibitors have received FDA approval. Four candidate compounds, however, are in clinical testing for safety and effectiveness. (See Table 6.1.) These investigational HIV integrase inhibitors are being evaluated in HIV/AIDS patients experiencing virologic failure with their current antiretroviral regimen who will likely benefit from an antiretroviral with a different mechanism of action.

The drugs currently in clinical trials block the reaction that occurs in the host cell nucleus (strand transfer reaction); none inhibit the first enzymatic reaction catalyzed by integrase (in which an end of the viral DNA strand is made reactive). Like

Table 6.1 FDA-Approved Nucleoside Reverse Transcriptase Inhibitors (NRTI)

Drug Name	Manufacturer *(Pharmaceutical Company)*	Status
MK-0518 (raltegravir or Isentress)	Merck & Co.	Phase III
GS-9137 (eltigravir)	Gilead Sciences Inc.	Phase III
364735 (GSK364735, S364735)	GlaxoSmithKline and Shionogi & Co. Inc.	Phase I

Sources:
http://www.retroconference.org/2007/Abstracts/28885.htm
http://clinicaltrials.gov/ct/show/NCT00443703?order=3 Accessed July 26, 2007.
http://clinicaltrials.gov/ct/show/NCT00298350?order=2 Accessed July 26, 2007.

WHY SO MANY NAMES FOR A DRUG?

Every drug, at one time or another, has at least four names:

- Chemical name based on the compound's chemical composition and structure.
- Developmental or experimental name.
- Generic (nonproprietary) name that remains the drug's official name throughout its lifetime.
- Trade (proprietary) name chosen by the pharmaceutical manufacturer and approved by the FDA and U.S. Patent and Trademark Office.

The chemical name of an investigational drug compound is assigned by rules established for the naming of chemical compounds by the International Union of Pure and Applied Chemistry. Because chemical names can be cumbersome, drug candidates are also identified by a combination of letters and numbers assigned by the company developing the drug. The letters typically stand for the drug company that discovered the compound or began to develop it. For example, "MK" in the integrase inhibitor MK-0518 is an abbreviation for Merck & Company, the drug developer.

As an experimental drug nears the end of development, it is given a generic name; in the case of MK-0518, that name is raltegravir. The generic name of a drug is assigned by the U.S. Adopted Names Council, and is approved by the World Health Organization. If and when a drug nears the approval stage, a drug is branded (given a brand name); in the case of MK-0518, that name is Isentress.

Sources:

Durkin, Tracy, and Julie Shirk. "The drug name game," *Modern Drug Discovery* 5, 8 (August 2002): 39–42.

Boring, Dan. "More names," *Modern Drug Discovery* 3, 8 (October 2000): 35–36.

the HIV reverse transcriptase inhibitors and protease inhibitors, all of the HIV integrase inhibitors are formulated for oral administration (tablets, capsules, or liquid suspensions).

The investigational HIV integrase furthest along in clinical development is the Merck compound MK-0518 (raltegravir; Isentress). Two ongoing international phase III clinical trials are being conducted to evaluate the safety and effectiveness of MK-0518 in a total of 699 HIV-infected patients, 462 of whom are actually receiving the test drug.[38,39] The study population consists of HIV-infected patients experiencing virologic failure with their current antiretroviral regimen (HIV RNA >1000 copies/mL) and have evidence of HIV resistant to at least one nucleoside and one non-nucleoside reverse transcriptase inhibitor and one protease inhibitor. Interim results after 16 weeks of treatment show that MK-0518, used in combination with reverse transcriptase inhibitors and protease inhibitors and/or an HIV entry inhibitor (see Chapter 7), had significantly greater virologic suppression than placebo combined with the same drugs. In addition, study patients receiving the MK-0518 combination had significantly greater increases in CD4+ T cell counts. The regimen containing MK-0518 was well tolerated—few patients discontinued taking the drug because of side effects.

In September 2007, the Antiviral Drugs Advisory Committee (a panel of clinical and research experts that advises the FDA) unanimously supported accelerated approval of raltegravir for patients experiencing virologic failure with approved antiretrovrial therapy. The recommendation from the committee was based on the latest available clinical trial data, which showed that the benefits of the drug outweigh its currently identified side effects. It is expected that the FDA will make a final decision regarding approval of raltegravir before the end of 2007. If approved, this drug would be the first commercially available HIV integrase inhibitor, which will mark another historic milestone in the HIV/AIDS treatment field.

7

Inhibitors of Viral Entry

Like all viruses, HIV is an intracellular parasite and therefore cannot replicate without a host cell. HIV needs a cell's protein-making machinery to churn out new viral proteins and new viral RNA for the production of progeny viruses. What if HIV is unable to gain entry into a cell? Bingo. Then HIV can not infect the cell and produce a fleet of progeny virions, and the cycle of chronic HIV infection is stopped. HIV entry, the first step in the HIV life cycle, is therefore a logical target for therapeutic intervention.

DISSECTING VIRAL ENTRY

How exactly does HIV gain entry into a target cell? Viral entry is actually a multistep process, a series of sequential, complex interactions between two viral envelope proteins and two host cell-surface proteins. These molecular interactions involve HIV attachment (binding) first to the CD4 receptor on a susceptible cell and then to a co-receptor (either CCR5 or CXCR4), and finally fusion between the HIV envelope and the cell membrane, culminating in the release of viral genetic material and viral proteins into the host cell's cytoplasm.

Unraveling the process of HIV entry into susceptible cells led to the identification of new targets for drug development and a new class of antiretroviral agents called entry inhibitors.[40,41] The specific targets for this therapeutic class are extracellular, unlike the HIV enzyme targets of other antiretrovirals. The fact that the targets are extracellular means that delivery to the site of action is

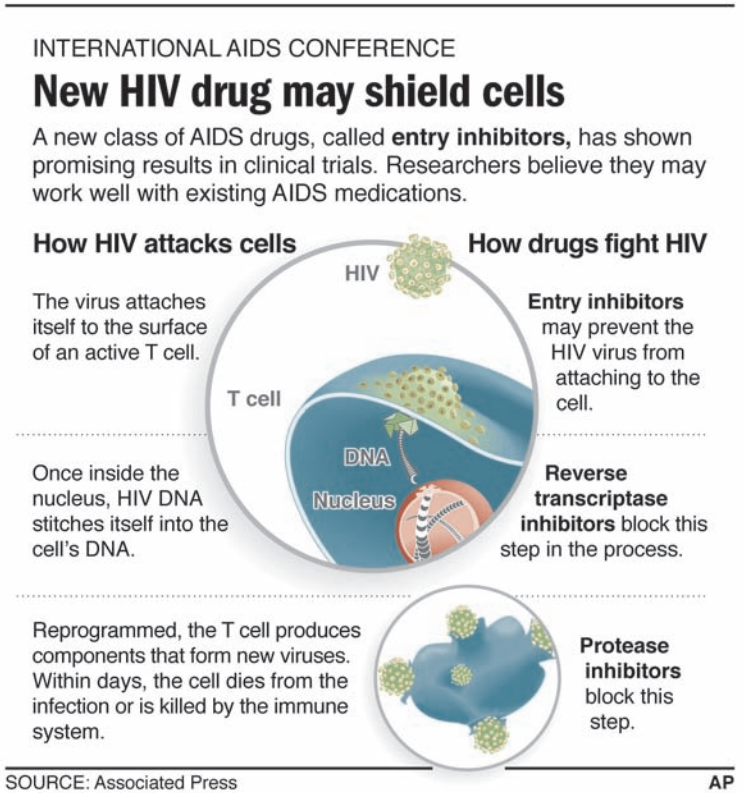


Figure 7.1 *(© AP Images)*

not complicated by cellular metabolism or transport across cell membranes. Reverse transcriptase, integrase, and protease inhibitors all act intracellularly.

Steps One and Two: Binding

HIV's ability to infect a cell is based on the presence of two cell-surface receptor molecules, the CD4 receptor and a co-receptor—either CC chemokine receptor 5 (CCR5) or CXC chemokine receptor 4 (CXCR4). Select white blood cells express both a CD4 receptor and a chemokine receptor on

their surface: CCR5 is predominantly expressed on monocytes, macrophages, dendritic cells, and CD4+ T cells, and CXCR4 is expressed on activated T cells.

HIV entry starts with the binding of the HIV gp120 envelope protein (gp is short for "glycoprotein") to the CD4 receptor on a host cell membrane. This binding activates HIV gp120—that is, it produces a change in the 3-dimensional structure of the gp120 molecule. This conformational change reveals a binding site on gp120 that will allow it to bind to another receptor on the cell membrane, the CCR5 or CXCR4 co-receptor.

WHAT'S A CHEMOKINE?

A chemokine (pronounced KEE-mo-kine) is a type of cytokine. Cytokines are small soluble molecules that act as chemical messengers between immune system cells. First identified in 1987, chemokines are now known to be produced in response to harmful stimuli such as bacterial and viral infections. On binding to a receptor on an immune cell surface, chemokines, with their chemoattractant properties, induce chemokine receptor-bearing cells to migrate toward the source of the chemokine. (Think chemotaxis on the molecular scale.)

Chemokines are divided into two groups, the CC and CXC chemokines, which act on immune cells that possess either CC or CXC receptors. An immune cell will have only one of these chemokine receptors on its surface. The "Cs" in CC and CXC stand for the amino acid cysteine and the "X" stands for any amino acid other than cysteine. When a chemokine binds to its receptor, a cascade of signaling events is triggered. For example, the CC chemokine RANTES (for regulated-upon-activation, normal T-cell expressed and secreted) is produced by activated CD4+ T cells and macrophages during inflammation and preferentially attracts certain immune cells such as monocytes and T cells to the site of inflammation.

Step Three: Fusion

HIV gp120 binding to the CD4 and chemokine receptors sets in motion the molecular rearrangement and shape change of HIV gp41, triggering the insertion of the HIV gp41 envelope protein into the cell membrane. The viral envelope and cellular membrane are pulled together, which allows them to fuse. (The HIV envelope and cell membrane are both made up of a lipid bilayer.) The "guts" of the viral particle are then released into the cytoplasm of the host cell.

HIV ENTRY INHIBITORS

Now that it is understood that viral entry into a host cell involves three sequential steps, it is easy to see how the HIV entry inhibitor drug class can have different targets. Based on their different mechanisms of action, entry inhibitors are divided into the following subclasses:

- Attachment inhibitors
  - CD4 receptor inhibitors
  - chemokine receptor inhibitors (CCR5 inhibitors and CXCR4 inhibitors)
- Fusion inhibitors

Only two entry inhibitors have been FDA approved: a fusion inhibitor (enfuvirtide, in 2003) and a CCR5 receptor inhibitor (in 2007). About 10 entry inhibitors are currently being evaluated in clinical trials and more than 20 additional entry inhibitors are in preclinical development.

HIV ATTACHMENT INHIBITORS

Attachment inhibitors prevent HIV gp120 from attaching to the CD4 receptor or a chemokine co-receptor (either CXCR4 or CCR5) on the surface of a susceptible host cell.

The first attachment inhibitor, a CCR5 receptor inhibitor called maraviroc, was approved by the FDA for use in adults in

August 2007. Maraviroc is intended for adults in whom other antiretrovirals have failed to adequately suppress HIV; the drug has not been tested in HIV-infected individuals who have never received any type of antiretroviral therapy. Maraviroc blocks HIV from using the CCR5 co-receptor on susceptible immune cells and therefore only patients with HIV strains that have an affinity for the CCR5 co-receptor can benefit from taking maraviroc. (Some patients harbor only HIV that has an affinity for the CXCR4 co-receptor and some patients harbor strains with an affinity for both co-receptors.)

Intense research efforts on the attachment inhibitors continue, with a number of drug candidates in various stages of development. Several are in clinical trials in HIV-infected patients and almost 50 are in preclinical testing.

Table 7.1 Attachment Inhibitors in Clinical Trials

Drug Name	Manufacturer *(Pharmaceutical Company)*	Status	Entry Inhibitor Subclass
TNX-355	Tanox-Biogen	Phase II	CD4 receptor binding
PRO 542 (CD4-IgG2)	Progenics Pharmaceuticals, Inc	Phase II	CD4 receptor binding
SCH-D (vicriviroc)	Schering-Plough	Phase III	CCR5 inhibitor
INCB9471	Incyte Corp	Phase II	CCR5 inhibitor
PRO 140	Progenics Pharmaceuticals, Inc	Phase II	CCR5 inhibitor
AMD11070 (aka AMD070)	AnorMed Inc	Phase II	CXCR4 inhibitor

Sources:
http://clinicaltrials.gov/ct/show/NCT00089700?order=1 Accessed April 18, 2007
http://clinicaltrials.gov/ct/show/NCT00055185?order=2 Accessed April 18, 2007
http://clinicaltrials.gov/ct/show/NCT00474370?order=1 Accessed July 26, 2007
http://clinicaltrials.gov/ct/show/NCT00393120?order=1 Accessed April 18, 2007
http://clinicaltrials.gov/ct/show/NCT00110591?order=1 Accessed April 21, 2007
http://clinicaltrials.gov/ct/show/NCT00089466?order=1 Accessed April 18, 2007

SPEAKING OF ANTIBODIES . . .

Antibodies: Proteins produced by the body's immune system to seek out and fight disease-causing microorganisms, other foreign substances that enter the body, and abnormal cells. Also called immunoglobulins. Each antibody is specific for a particular fragment of a microorganism or foreign substance (called an antigen).

Antigen: Any substance, such as a protein fragment, that can stimulate the production of antibodies. The body's immune system is programmed to produce antibodies in response to the presence of a foreign antigen, such as protein fragments on the surface of viruses, bacteria, and other microbes.

Monoclonal Antibodies: Antibodies produced from a single parent B cell (an immune cell) and therefore identical (clones). Since monoclonal antibodies have the same structure, including the same antigen-binding site, they all recognize and bind to the same antigen.

Humanized Antibodies: Monoclonal antibodies that are genetically engineered from mouse and human sources. Humanized monoclonal antibodies consist of antigen binding proteins derived from mouse monoclonal antibodies and grafted onto the framework of human immunoglobulin molecules. These recombinant antibodies do not stimulate a heightened immune response in humans like mouse monoclonal antibodies, and as a result they can be used for the treatment of humans with far less risk of anaphylaxis.

Source: Janeway, C.A., P. Travers, M. Walport, and M. Schlomchik. *Immunobiology: The Immune System in Health and Disease,* 5th ed. New York: Garland Science, 2001.

CD4 receptor inhibitors act by binding either to HIV gp120 or the CD4 receptor. TNX-355, a humanized **monoclonal antibody**, binds to a site on the CD4 receptor that may prevent the shape change in gp120 necessary for subsequent co-receptor

binding. PRO 542 is a **fusion protein** consisting of a fragment of the CD4 receptor molecule and a humanized monoclonal antibody that binds to HIV gp120, thereby preventing the virus from binding to the CD4 receptor.

The CCR5 inhibitors in clinical trials today can be divided into two groups based on their structure. The first group, called small-molecule inhibitors, consists of drugs thought to act by altering the shape of the co-receptor so that HIV gp120 cannot bind to it. The second group, called monoclonal antibodies and represented by PRO 140, consists of drugs believed to bind to sites on the CCR5 co-receptor, thereby blocking the binding of HIV gp120. CXCR4 receptor inhibitors currently being tested act similarly, binding directly to the CXCR4 co-receptor and preventing the binding of HIV gp120. Because CCR5 and CXCR4 inhibitors act on separate receptors, they only possess inhibitory activity against virus that has a preference for that co-receptor.

CD4 receptor inhibitors and CCR5 and CXCR4 inhibitors hold promise for HIV-infected patients who need to switch therapy because of virologic failure with other antiretroviral drugs. Because their mechanism of action is different from that of the other antiretroviral agents, the chances are good that HIV-infected individuals will reap some benefit from using these new agents. The small-molecule CCR5 inhibitors (maraviroc, SCH-D, and INCB9471) and AMD11070 are being manufactured as oral medications; all other attachment inhibitors must be injected since they are large proteins. Maraviroc is available in tablet form for twice daily dosing.

Maraviroc is the first CCR5 co-receptor inhibitor approved for use for HIV/AIDS. Recent results from two phase III trials in approximately 1,000 highly treatment-experienced patients infected with CCR5-tropic HIV revealed that patients receiving maraviroc (300 mg once or twice daily) together with other antiretroviral drugs (including a protease inhibitor) were twice as likely to achieve virologic suppression to undetectable levels compared with the best available standard therapy.[42,43]

FUSION INHIBITORS

The first FDA-approved drug in the entry inhibitor class was the fusion inhibitor T-20, or enfuvirtide. T-20, developed by Trimeris Pharmaceuticals as Fuzeon, received accelerated marketing approval from the FDA in March 2003. It is a large synthetic peptide (36 amino acids in length). Because it cannot be made into pill form, T-20 is administered by subcutaneous

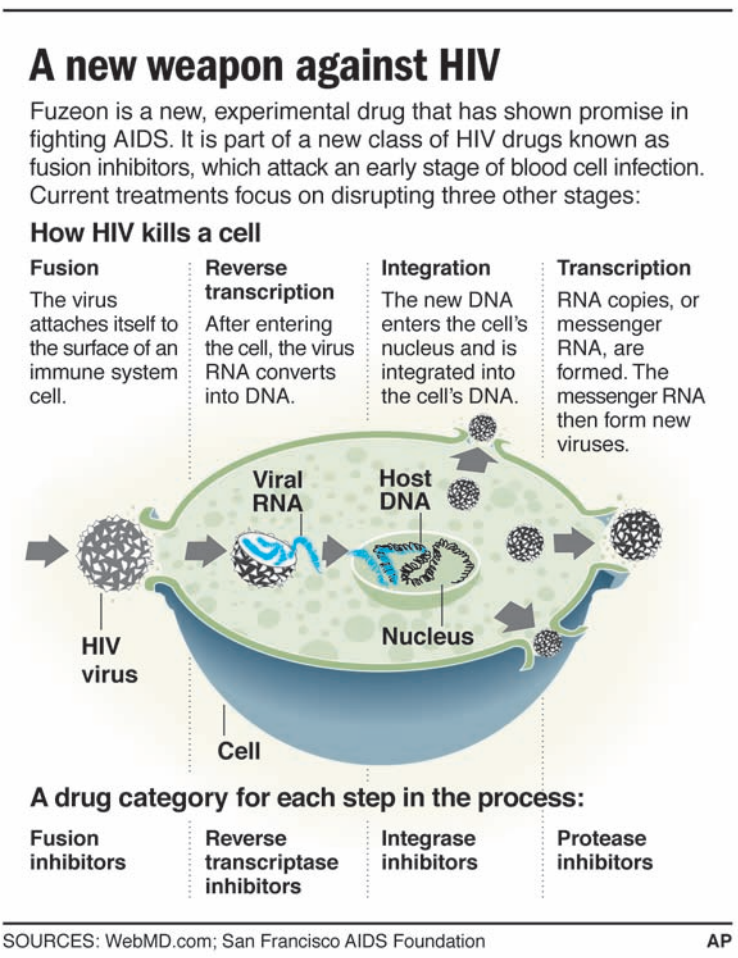


Figure 7.2 *(© AP Images)*

(under the skin) injection, with each 90-mg dose given twice daily. This is one reason why T-20 is not used as a component in antiretroviral regimens for patients beginning therapy. T-20 is used to treat antiretroviral-experienced HIV-infected patients who have evidence of virologic failure with their initial therapy and have limited therapeutic options because of drug resistance, side effects, drug interactions, or other medical conditions. [44]

T-20 works by binding to a region within the HIV gp41 molecule involved in the fusion of the viral envelope and cell membrane. T-20 binding prevents the normal shape change in HIV gp41 that occurs when the virus and host cell are pulled together during fusion.

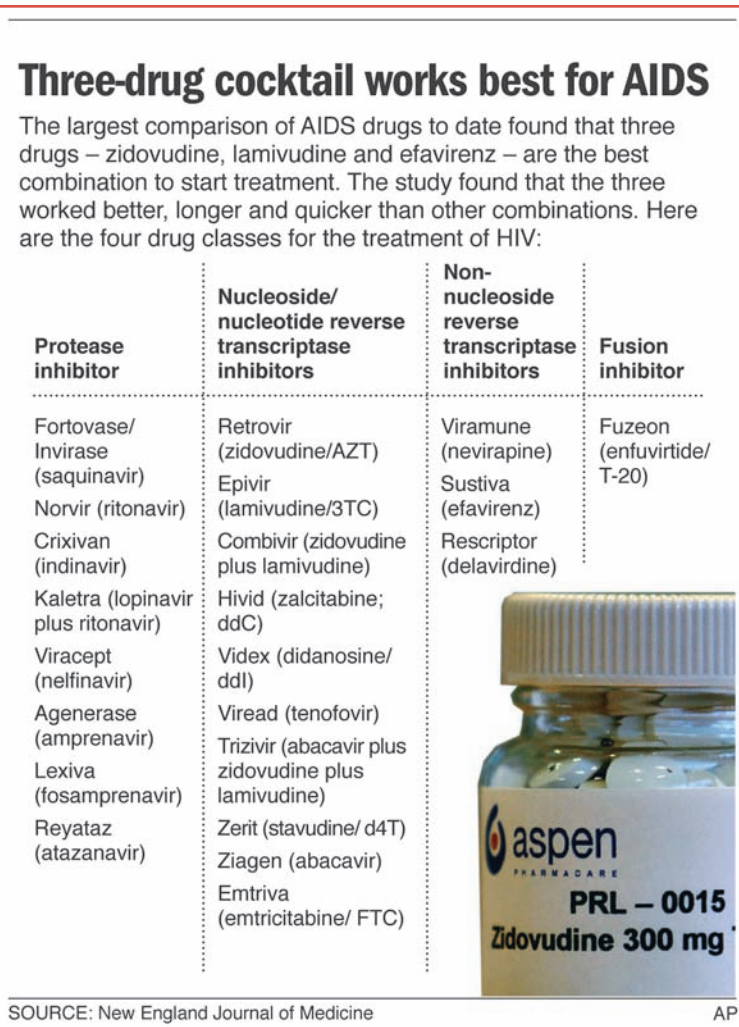
Second-generation fusion inhibitors are being developed, and two compounds in preclinical testing appear to be more potent than T-20 and possess antiviral activity against T-20-resistant HIV.

8

HIV/AIDS Treatment Guidelines

Treatment guidelines are written recommendations compiled by experts to help the medical community provide the best possible patient care. Several sets of HIV/AIDS treatment guidelines exist, all of which are designed to ensure that health care professionals and their patients are well informed about the rationale for use, the benefits, and the adverse effects of antiretroviral drugs before beginning lifelong antiretroviral therapy.[45,46,47,48] Based on more than 10 years of use, it is now well established that combination antiretroviral therapy improves the quality of life of patients with HIV infection (extending the symptom-free or disease-free period) and prolongs life, dramatically slowing progression to AIDS and death. Long-term chronic use of the drugs used to treat HIV/AIDS, however, may result in a range of long-term complications that develop five or more years after beginning therapy; these complications include metabolic abnormalities leading to hypertension, cardiovascular disease, and stroke.

Numerous issues need to be considered when prescribing antiretrovirals to the various HIV-infected patient populations: adult men and women, adolescents, children, pregnant women, newborns, and infants with HIV disease or AIDS. In the case of pregnant women, the guidelines provide information—based on a woman's specific disease characteristics and HIV/AIDS treatment experience



Three-drug cocktail works best for AIDS

The largest comparison of AIDS drugs to date found that three drugs – zidovudine, lamivudine and efavirenz – are the best combination to start treatment. The study found that the three worked better, longer and quicker than other combinations. Here are the four drug classes for the treatment of HIV:

Protease inhibitor	Nucleoside/ nucleotide reverse transcriptase inhibitors	Non-nucleoside reverse transcriptase inhibitors	Fusion inhibitor
Fortovase/ Invirase (saquinavir)	Retrovir (zidovudine/AZT)	Viramune (nevirapine)	Fuzeon (enfuvirtide/ T-20)
Norvir (ritonavir)	Epivir (lamivudine/3TC)	Sustiva (efavirenz)	
Crixivan (indinavir)	Combivir (zidovudine plus lamivudine)	Rescriptor (delavirdine)	
Kaletra (lopinavir plus ritonavir)	Hivid (zalcitabine; ddC)		
Viracept (nelfinavir)	Videx (didanosine/ ddI)		
Agenerase (amprenavir)	Viread (tenofovir)		
Lexiva (fosamprenavir)	Trizivir (abacavir plus zidovudine plus lamivudine)		
Reyataz (atazanavir)	Zerit (stavudine/ d4T)		
	Ziagen (abacavir)		
	Emtriva (emtricitabine/ FTC)		

SOURCE: New England Journal of Medicine AP

Figure 8.1 *(© AP Images)*

prior to the pregnancy—regarding the use of antiretrovirals to prevent transmission of HIV to the fetus or newborn. Panels of experts in HIV treatment, both in the United States and internationally, participate in crafting and drafting the treatment guidelines.

Table 8.1 Organizations That Develop HIV/AIDS Treatment Guidelines

Organization	Web site
US Department of Health and Human Services (US DHHS)	http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx
British HIV Association (BHIVA)	http://www.bhiva.org/
European AIDS Clinical Society	http://www.eacs.ws/guide/
International AIDS Society – USA	http://www.iasusa.org/pub/#guidelines
World Health Organization (WHO)	http://www.who.int/hiv/pub/guidelines/en/

In the U.S., the most widely used set of HIV/AIDS treatment guidelines for adults and adolescents is published by the U.S. Department of Health and Human Services (DHHS). The guidelines point out the advantages and disadvantages of the various treatment options and classify options as "preferred," "alternative," or "special circumstances only." Patients who are allergic to a component in a preferred antiretroviral drug obviously cannot take that medication. A patient's medical history, current physical and mental health status, and current medications for other conditions can limit which antiretroviral drugs are appropriate. Recommendations are also made for other issues that affect therapeutic decision-making, such as:

- timing of laboratory tests (CD4+ cell counts, HIV viral load)
- criteria for determining whether or when to begin HIV/AIDS drug therapy
- criteria for determining whether or when to change an antiretroviral regimen
- how to help patients adhere to dosing and other requirements of their prescribed treatment regimen

- how to manage the side effects associated with antiretrovirals (symptom relief may be provided by over-the-counter medications, but drug interactions need to be considered in such instances)

TREATMENT STRATEGIES

Experts have been hotly debating when to initiate antiretroviral therapy in patients who have been infected with HIV longer than six months (so-called chronic HIV infection). In 1996, when combining three or more antiretrovirals into a single regimen became *the* standard of care for virtually all HIV-infected patients, many expert clinicians proclaimed that it was best to "hit hard, hit early" in order to keep HIV replication as low as possible and to preserve the integrity and function of the immune system. Proponents of a delayed treatment strategy cited the potential long-term toxic side effects of the drugs and argued that because potent antiretroviral regimens may reverse immune system deterioration, it would be safe to start therapy later, when CD4+ T cell counts begin to fall. After more than 10 years of clinical experience with potent antiretroviral regimens, the debate continues. Today, those pushing

A TALE OF CONTRASTS

HIV/AIDS patients in wealthy countries can rely on established health care systems for treatment. Wealthy countries treat most HIV-infected pregnant women and their newborns, which has resulted in a low—less than 2 percent—mother-to-child transmission rate and few new pediatric HIV patients. By comparison, only 11 percent of HIV-positive women in low- and middle-income countries receive HIV treatment during childbirth, resulting in a large HIV/AIDS pediatric population. Of the 780,000 HIV-infected or at-risk children in these regions, only 15 percent were treated in 2006.

for earlier treatment acknowledge that the need for *lifelong* antiretroviral therapy could result in HIV-infected individuals running out of therapeutic options.

While virologic suppression *can* be long-lasting with a single potent antiretroviral regimen, so long as the patient adheres to the dosing requirements and does not miss any doses, all evidence to date indicates that a change in one or more drugs in the regimen is needed within three to six years in highly motivated patients with perfect or near-perfect medication adherence. A change in therapy may be needed for reasons other than treatment failure: Patients may develop allergic reactions to an ingredient in one of the drugs or they may develop a condition requiring a medication that will result in a dangerous drug–drug interaction with one of the antiretroviral drugs. In reality, patients often stop taking their drugs when they do not feel well (because of a cold, the flu, or any number of transient illnesses not related to HIV infection). Sometimes patients develop a symptom that they know is a side effect of one of their antiretroviral medications and they stop taking that particular pill for a while. Not surprisingly, patients simply tire of taking all their pills all the time and they take a break even though their doctor and counselors have warned them about the likelihood of treatment failure if they do not take all their pills on time as prescribed. The unknown long-term side effects of some of the newer antiretroviral drugs is an added argument for delaying the initiation of treatment until the patient's clinical status, immune system function, and/or viral load suggest that it is necessary to begin antiretroviral therapy. Health care professionals are advised to spend time with their HIV-infected patients who do not have symptoms regarding the decision to start therapy. It is a lifelong commitment and, therefore, careful review of the advantages and disadvantages with patients is part of the art of practicing good medicine.

TREATMENT OBJECTIVES

The goals of antiretroviral therapy, regardless of the patient population (adults, adolescents, children, infants, pregnant women), are suppressing HIV replication, maintaining immune system function, and delaying development of drug-resistant HIV strains. There may, however, be special considerations with some populations and some HIV risk groups, such as:

- Pediatric patients may have been exposed to HIV/AIDS therapy during gestation (testing for drug-resistant virus may be appropriate).
- Drug absorption, distribution, and metabolism differ in children compared with adults (medication dosing is therefore different).
- Adherence to dosing schedules can be especially challenging for the young, patients with unstable housing and employment situations, injection drug users, and individuals with substance abuse problems, mental illness, or serious concurrent medical conditions (e.g., impaired kidney function, cancer, chronic hepatitis).

INITIAL ANTIRETROVIRAL THERAPY

In the United States, the initial therapeutic program for HIV infection is likely to be based on the DHHS lists of preferred treatment options. Preferred drug options are expected to yield long-term drug effectiveness with acceptable side effects and require minimal effort to use. Alternative treatment options typically have a reduced level or duration of effectiveness, more objectionable side effects, or are more difficult to use. Nonetheless, an alternative program may be the only suitable option if, for example, the viral strain is resistant to the preferred therapy. In addition to alternative and preferred options, other

drugs may be considered under special circumstances—usually when better options have been exhausted. Finally, some treatment regimens are not recommended at any time because they lack sufficient viral activity or have unacceptable side effects, adherence hurdles, high risk of resistance development, medication interactions, or lack of benefit when compared with standard regimens.

For patients beginning lifelong antiretroviral therapy, the recommendation is a regimen consisting of one potent non-nucleoside reverse transcriptase inhibitor (NNRTI) or one potent protease inhibitor (PI) plus two nucleoside reverse transcriptase inhibitors (NRTI).

Antiretroviral regimens are, however, individualized to the patient's situation, taking into account issues such as drug interactions, drug toxicity, drug resistance, pregnancy, concomitant medical conditions, and perinatal issues. The regimen may change over time as resistant strains develop, immune function declines, or HIV disease progresses. Selection of an initial regimen must, therefore, reserve options for future therapy.

For children beginning lifelong antiretroviral therapy, the recommendation is a regimen consisting of one potent non-nucleoside reverse transcriptase inhibitor (NNRTI) or one potent protease inhibitor (PI) plus two nucleoside reverse transcriptase inhibitors (NRTI).

TREATING PREGNANT WOMEN AND NEWBORNS

Treating HIV in pregnant women or new mothers is similar to treating HIV in other adults, but with the added consideration of the developing fetus or newborn. The same factors affecting decisions regarding therapy (e.g., disease status and testing for drug resistance) are considered along with the potential for HIV transmission and the effects of therapy on the fetus and newborn. The treatment options available to pregnant women include some, but not all, of those available to other adults;

Table 8.2 **DHHS HIV/AIDS Treatment Guidelines for Adults and Adolescents: Preferred Components of Initial Antiretroviral Regimens**

PREFERRED NNRTI	
Drug	**Comments**
efavirenz (Sustiva)	• Considered best NNRTI option • Should not be used by women who are pregnant or have significant chance of becoming pregnant
PREFERRED PI OPTIONS	
atazanavir (Reyetaz) + ritonavir (Norvir)	• Once-daily dosing • Jaundice as side effect • Cannot be used with antacids, H2 antagonists, or proton pump inhibitors
Lopinavir/ritonavir: Kaletra (co-formulation)	• Two pills, twice-daily dosing • Side effects: diarrhea, elevated blood lipids, especially triglycerides • Efficacy during late-stage pregnancy is uncertain
fosamprenavir (Lexiva) + ritonavir (Norvir)	• Twice-daily dosing • Efficacy similar to lopinavir/ritonavir
PREFERRED NRTI OPTIONS (CO-FORMULATED PILLS)*	
emtricitabine (FTC)/tenofovir (TDF): Truvada	• One tablet, once-daily dosing • Kidney function must be monitored due to potential renal impairment associated with TDF
zidovudine (AZT)/lamivudine (3TC): Combivir	• One tablet, twice daily dosing • Increased risk of bone marrow suppression
NNRTI/NRTI/NRTI CO-FORMULATED PILL	
efavirenz (EFV)/emtricitabine (FTC)/tenofovir (TDF): Atripla	• One pill, once daily

* Lamivudine can be substituted for emtricitabine and vice-versa as individual pills, not co-formulations.

Table 8.3 DHHS HIV/AIDS Treatment Guidelines for Children: Preferred Components of Initial Antiretroviral Regimens

PREFERRED NNRTI OPTIONS	
Drug	**Comments**
efavirenz (Sustiva)	• For children age 3 or older • Available as capsules, tablets • Should not be used by girls who are pregnant or by sexually active girls who have a chance of becoming pregnant
nevirapine (Viramune)	• Available in a liquid formulation • For children younger than 3 who cannot swallow pills • Should not be initiated in girls with >250 CD4+ T cells/μL or boys with >400 CD4+ T cells/μL
PREFERRED PI	
lopinavir/ritonavir (Kaletra) (co-formulation)	• Available as co-formulated tablet or liquid suspension • Should be taken with food
PREFERRED NRTI OPTIONS	
zidovudine (Retrovir) + lamivudine (Epivir) OR didanosine (Videx) OR emtricitabine (Emtriva)	• Didanosine: Should not to be given on an empty stomach; limits use in infants • Emtricitabine: Dosed once daily; available as an oral formulation
didanosine (Videx) + lamivudine (Epivir) OR emtricitabine (Emtriva)	• Should not to be given on an empty stomach; limits use in infants • Emtricitabine: Dosed once daily; available as an oral formulation

it may be necessary to avoid drugs that are associated with adverse effects to the fetus or that may be ingested by the newborn through breast milk. An additional concern is whether it is prudent to interrupt an established antiretroviral regimen in a pregnant woman, a treatment decision that could cause drug resistance to develop.

THE RYAN WHITE CARE ACT

Ryan White (December 6, 1971–April 8, 1990) was an inspirational boy who battled not only the disease, but also the stigma of AIDS in the early years. He was 13 when he was diagnosed with AIDS in 1984. Ryan had become infected with HIV when he received a blood transfusion for his hemophilia. Fear that the virus could be spread from casual contact led his community to expel Ryan from his school. His case became the focal point for AIDS activists, and he received much support from celebrities (including Michael Jackson, Elton John, and Kareem Abdul-Jabbar). In 1990, the same year that Ryan died of AIDS-related pneumonia, Congress enacted the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act. This federal program provides medical, psychological, and social services to people living with HIV/AIDS.

Source: U.S. Department of Health and Human Services. "The Ryan White HIV/AIDS Program." Available online. URL: http://hab.hrsa.gov/history.htm. Accessed May 17, 2007.

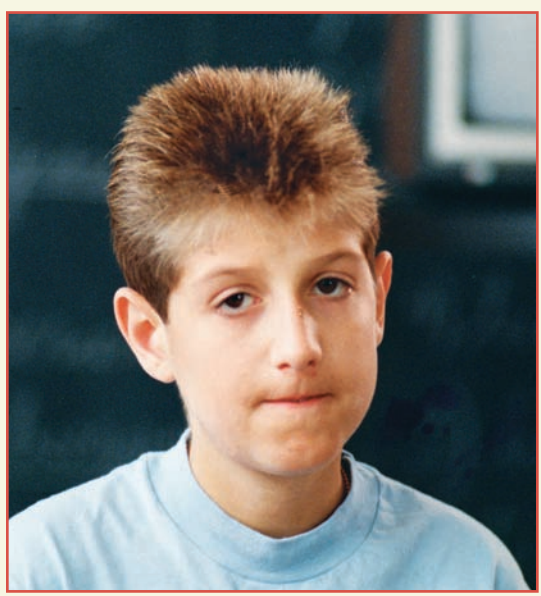


Figure 8.2 *Ryan White. (© AP Images)*

HOW CAN PERINATAL TRANSMISSION BE PREVENTED?

Perinatal transmission, the transmission of HIV from the mother to her fetus or newborn may occur during gestation, during childbirth, or when breastfeeding. In the developing fetus, transmission often occurs late in gestation with the

ELIZABETH GLASER PEDIATRIC AIDS FOUNDATION

Elizabeth Glaser, wife of actor/director Paul Michael Glaser, contracted HIV through contaminated blood she received during the birth of their daughter Ariel in 1981. Elizabeth developed a complication during this pregnancy called placenta previa, and she began hemorrhaging immediately after Ariel was delivered. Remember, 1981 was the year that the first AIDS cases were described, although no one realized yet that the bizarre aggressive infections in previously healthy men was the result of immunodeficiency, which in turn was due to a virus. Ariel became infected with HIV through breastfeeding, and a brother, Jake, born three years later, was infected during gestation. It was not until Ariel developed unexplained illnesses in 1985, when she was 4, that Elizabeth, Ariel, and Jake were diagnosed with AIDS. No antiretroviral therapy was available at that time (AZT, now called zidovudine or ZDV, was not approved for use in adults until 1987). After Ariel died in 1988, her mother co-founded the Elizabeth Glaser Pediatric AIDS Foundation. She wanted to ensure that Jake and other pediatric AIDS patients would have access to treatment and to raise public awareness of pediatric AIDS, the need for pediatric drugs, and research on perinatal HIV transmission. Elizabeth Glaser died in 1994, leaving a remarkable legacy in the area of pediatric AIDS. Jake Glaser is still healthy as this book goes to publication.

Source: http://www.pedaids.org/AboutUs/FoundationHistory.aspx

ZIDOVUDINE (ZDV) TO PREVENT PERINATAL TRANSMISSION

- **Drug-sensitive HIV strains transmit perinatally**
- **Drug readily transfers from mother to fetus via the placenta**
- **ZDV is metabolized to its active form within the placenta, maximizing protection**
- **ZDV lowers genital HIV RNA levels, reducing risk of transmission during childbirth**
- **ZDV readily enters the newborn's central nervous system, reducing HIV in the brain**

virus likely passing through the placenta. During labor and childbirth, the virus may pass through blood or other body fluids, particularly with vaginal delivery.

HIV-infected pregnant women can reduce the risk of transmitting the virus to their fetus or newborn. The mother's viral load should be reduced as much as possible using antiretroviral agents that do not pose a risk to the developing fetus. Use of the nucleoside reverse transcriptase inhibitor zidovudine during pregnancy, even if the viral load is extremely low, helps to protect the developing fetus.

HIV may be transmitted in breast milk to the newborn through frequent exposure of the mouth and gastrointestinal tract. Use of formula feeding (rather than breastfeeding) is believed to reduce the transmission risk.

Cesarean section decreases the transmission risk when viral load is $\geq$1000 copies/mL (or the viral load is unknown) in women who are not receiving antiretroviral therapy or are receiving zidovudine only. Because of the risk of transmission, invasive procedures such as amniocentesis or use of fetal scalp electrodes are avoided during gestation and delivery. The

TREATMENT FAILURE

Virologic failure:

- **>400 HIV RNA copies/mL after 24 weeks, >50 copies/mL after 48 weeks, or >400 copies/mL after prior viral suppression**

Immunologic failure:

- **CD4+ T cell increase of fewer than 25-50 cells/μL in first year of therapy, or decline in CD4+ T cell count to below baseline**

Clinical progression:

- **Occurrence of HIV-related illness after >3 months on therapy**
- **In children, ≥6 months of clinical symptoms (neurodevelopmental deterioration, substandard growth rate, severe or repeated illness or other infections)**

risk of HIV transmission also declines if the pregnant woman discontinues use of illicit drugs, alcohol, and tobacco and uses safe sexual practices to avoid contracting other HIV strains or sexually transmitted diseases.

Zidovudine has unique characteristics that make it particularly suited to the task of limiting perinatal HIV transmission. To reduce the risk of such transmission, the drug is typically administered to a woman during pregnancy and childbirth and is given to the newborn for six weeks after birth. Zidovudine has not caused any significant changes in maternal immune function, disease progression to AIDS, or death rate and has not been associated with growth or developmental adverse effects in the newborns or children born to HIV-infected mothers, although long-term assessments are still under way.

WHEN THE DRUGS ARE NOT WORKING

Initial antiretroviral regimens will eventually fail to suppress HIV in the long run. Treatment failure may manifest as a lack of sustained viral suppression, poor immunologic response, or disease progression to AIDS. Underlying causes of failure may include high viral load, low baseline CD4+ T cell counts (signifying that the immune system has been seriously, possibly irreversibly overwhelmed before therapy was ever initiated), co-infections, suboptimal potency of the antiretroviral regimen, toxic or adverse effects of the drug regimen (causing patient to skip doses), suboptimal drug concentration (due to drug interactions or age-related changes in development), or development of drug-resistant viral strains. Patients should be monitored on an on-going basis for changes in status; for example, dosing requirements may need adjustment as the young patient grows and develops or as other medications are used.

9

Ongoing HIV/AIDS Drug Discovery Efforts

The race for safe and effective HIV/AIDS medicines has morphed from a marathon into a steeplechase event. Looking back over the history of the epidemic, it is inspiring that clinicians, researchers, pharmaceutical manufacturers, public health officials, patients, and patient advocates responded to the sense of urgency and collaborated to help bring viable drug products to the market so quickly. A multidisciplinary approach was necessary since the disease intersected the fields of virology, molecular biology, **immunology**, general or internal medicine, and numerous medical specialties (e.g., infectious diseases, ophthalmology, gastroenterology). Patients, health educators, social services professionals, and patient advocates communicated the need for medicinal chemists, pharmacologists, and pharmaceutical manufacturers to consider the number of pills in a dose (total daily pill count), the size of pills, and the dosing frequency (how many doses a day). Voilà, today there are more than 20 antiretroviral drugs, several of which are once-daily medications. (The dosage of the first AIDS drug, AZT, in 1987 was five or six times a day!) Co-formulated pills that combine two or more antiretrovirals in a single pill are now available.

HIV-infected patients are living longer healthier lives because of effective antiretroviral drugs; however, that does not mean it is not a

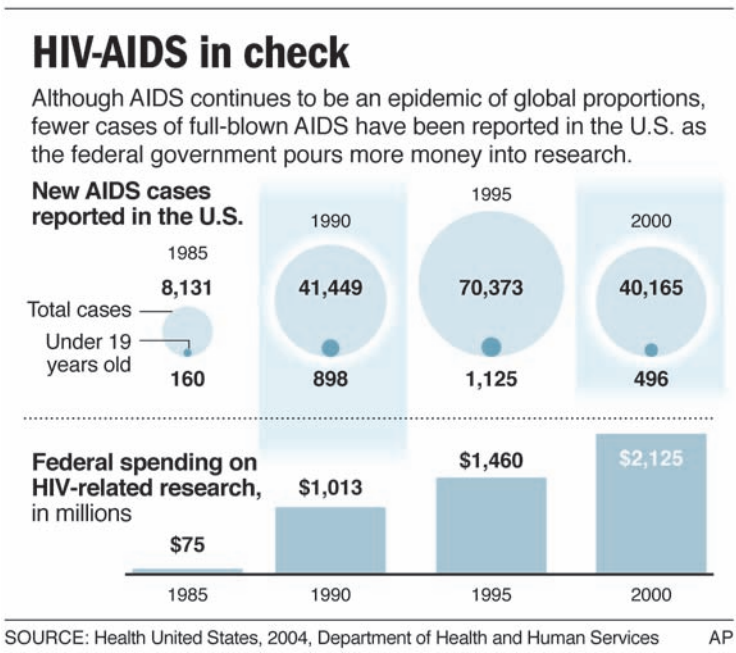


Figure 9.1 *(© AP Images)*

challenge to keep HIV replication controlled and the immune system intact and functional.

Drug discovery efforts to identify new and better antiretroviral drugs remain quite intense. Novel mechanisms to attack HIV are being explored as more molecular details of the virus and of the virus-host cell interaction are revealed. Scientists today are faced with designing drugs or manipulating molecules to inhibit numerous HIV strains—those that are sensitive to all antiretrovirals ("wild-type virus") and the myriad variants with mutations that confer resistance to one or more existing antiretrovirals. The therapeutic targets under investigation today include the major antiretroviral drug classes—reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, entry inhibitors—as well as seemingly obscure targets.

NOVEL MECHANISMS TO FIGHT HIV

Creative and inquisitive minds plus scientific genius will likely yield better or more diverse ways to treat HIV/AIDS. New drugs that act by mechanisms different from those of existing treatments are in various stages of testing. (Preventing HIV/AIDS is a whole other research arena and includes the search for preventive vaccines.)

Sizable troves of novel antiretroviral drugs are in the preclinical stage (*in vitro* or animal testing) of drug development or are in early clinical trials:

- HIV virion infectivity factor (Vif) inhibitors: Small molecules that inhibit the activity of the small HIV regulatory protein Vif. *In vitro* studies have shown that all cells susceptible to HIV infection (e.g., CD4+ T cells) possess enzymes with potent antiretroviral activity: A family of cytidine deaminases, including APOBEC3G. The HIV Vif protein counteracts the effect of APOBEC3G. Early studies defining the interaction between the Vif protein and APOBEC3G appear likely to yield several drug candidates that will interfere with Vif-APOBEC3G binding, allowing the cellular enzyme to exert its natural antiretroviral effect.
- Mifepristone: An inhibitor of a small accessory HIV protein (Viral protein R, or Vpr) that is involved in regulating the rate of HIV replication. *In vitro* studies show that mifepristone inhibits the "on switch" (HIV LTR) and also inhibits reactivation of HIV that is integrated into the cellular DNA of inactivated cells.
- PA-457 (bevirimat): The first drug in a new class of antiretrovirals called HIV maturation inhibitors. Bevirimat, an oral medication, is being evaluated in HIV-infected patients with drug-resistant HIV strains, and is currently in phase II clinical trials. Maturation is a late stage in the HIV replication cycle. Maturation inhibitors

prevent the cleavage of a structural viral protein (called HIV p24). Blocking the conversion of this protein's precursor to a mature viral protein results in the release of noninfectious virions from an infected cell. Without the mature form of this protein, any HIV virus particles released from an infected cell are incapable of infecting susceptible host cells.

- Positive transcription elongation factor (P-TEFb) inhibitors: Small molecules that prevent the completion of transcription of viral DNA. The host cell possesses negative and positive elongation factors; the positive elongation factors permit the elongation of DNA transcription products ("full length transcripts"). It is now known that HIV co-opts these positive elongation factors to ensure that viral DNA is completely transcribed. In *in vitro* studies, P-TEFb inhibitors have been shown to bind to one of HIV's regulatory factors that promote and recruit the cell's positive transcription elongation factors. It's an early step in identifying a drug target.
- Valproic acid: A drug that has been used for years as an antiseizure medicine and is now being studied for its ability to stimulate the release of HIV from dormant (latent) T cells. By stimulating latently infected cells to spew out HIV, the re-emerged virus is vulnerable to attack by other antiretrovirals. Currently, valproic acid is in phase II clinical trials to evaluate its effect in combination with other active antiretroviral therapy on reducing the size of HIV latent reservoirs in infected CD4+ T cells.

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Glossary

active site—The area of an enzyme where a chemical reaction takes place, setting off a chemical reaction. Also called catalytic site.

anaphylaxis—Severe hypersensitivity reaction to an allergen, including a component in a drug.

antibiotics—Drugs used to treat bacterial infections.

antibodies—Also called immunoglobulin. Proteins produced by the body's immune system that recognize and fight disease-causing microorganisms, other foreign substances that enter the body, and abnormal cells. Each antibody is specific for a particular fragment of a microorganism or foreign substance.

antifungals—Drugs used to inhibit the growth of disease-causing fungi (including yeast and molds).

antigen—Any substance, such as a protein fragment, that can stimulate the production of antibodies by the body's immune system.

antimicrobial—A drug used to kill a microbe; this general class of drugs is further broken down to the specific type of microbe for which the drug is intended (e.g., antiviral, antifungal, antibiotic, antiparasitic).

antiretrovirals—Drugs or biologic agents that act against a retrovirus.

antiviral—A drug used to fight viral infections.

B cells—Also called B lymphocytes. One of two major types of lymphocytes in the immune system; B cells can differentiate into mature cells that produce antibodies.

bacterium—A microorganism that can be beneficial or harmful to the plant or animal it infects.

CD4 receptor—Receptor on the surface of select immune system cells (most notably T lymphocytes or T cells) that HIV uses to gain access to the interior of those cells. The normal function of this receptor is activation of the immune system whereby protein fragments of invading microbes or abnormal cells are "presented" to immune cells that will participate in destruction and removal of the invader.

CD4+ T cells—A type of immune system cell.

catalyzes—Increases the rate of a chemical reaction.

chemotaxis—A biological phenomenon in which cells are attracted to or repelled from a chemical stimulus, such as a chemical concentration gradient.

chemotherapy—The use of drugs to treat an illness (term derived from "chemicals" plus "treatment"). Common usage of the word by those not in the medical field refers to cancer chemotherapy with the connotation of intense and toxic drugs.

cytoplasm—The contents of a cell, excluding the nucleus, within the confines of the cell membrane.

DNA—See *deoxyribonucleic acid.*

dendritic cells—Specialized phagocytic (debris-eating) cells of the immune system that circulate in the epidermis and lymphatic vessels, and migrate to lymph nodes when necessary. Dendritic cells engulf and digest pathogens, and display a protein fragment of the pathogen (an antigen) on the cell surface for recognition by T lymphocytes.

deoxyribonucleic acid (DNA)—The primary genetic material of all organisms; a helical ladder-like chain of sugar molecules (deoxyribose), nitrogen-containing molecules (nitrogenous base), and phosphate atoms.

dermatologic—Relating to the skin.

drug resistance—Decreased sensitivity over time of an organism, such as a bacterium or virus, to a drug. Disease-causing microorganisms adapt to prolonged or intermittent exposure to a drug by developing mutations that enable it to escape the deleterious effects of the drug.

envelope—The membrane-like structure that surrounds a virus's internal components (genetic material and enzymes).

enzymes—Protein molecules that facilitate a chemical reaction without being changed.

epidemiologists—Scientists who study of factors that influence the emergence, distribution, and frequency (number of new cases or existing prevalence) of a disease or a condition in a population or geographic area. Epidemiologists are sometimes referred to as disease detectives or disease-tracking researchers.

fusion protein—A protein made from two or more proteins using genetic engineering techniques.

genes—Heritable units in chromosomes that provide the instructions for making proteins necessary for life, which serve either a structural or regulatory function.

Glossary

genome—The complete set of an organism's genes or genetic material, composed of DNA (deoxyribonucleic acid) in humans and RNA (ribonucleic acid) in HIV.

immunology—The study of the structure and function of immune systems and the immune response of individual species.

infectious diseases—Contagious or communicable infections associated with illnesses.

integrase—A viral enzyme that catalyzes the integration (insertion) of viral DNA into the DNA of the host cell.

integration—The step in the life cycle of a retrovirus in which the viral DNA is inserted into the host cell DNA (in a chromosome). A cell is considered infected when this integration phase is complete.

jaundice—A condition characterized by a yellowing of the skin, mucous membranes, and sclera of the eye due to altered secretion of bile by the liver.

Kaposi's sarcoma—A cancer of the blood vessel walls.

lymph—The fluid that bathes the body's tissues and circulates in lymphatic vessels.

lymphadenopathy—A condition characterized by persistently swollen lymph nodes, generally accompanied by lethargy, malaise, and sometimes fever.

lymphoma—Cancer of lymphoid tissue (e.g., lymph nodes, bone marrow, lymphatic vessels).

macrophages—Specialized phagocytic (debris-eating) cells of the immune system that are distributed throughout the body's tissues.

microbes—Also called microorganisms. Bacteria, virus, fungi, parasite, are microbes.

microglia—Phagocytic monocyte-derived cells that, upon migration from the peripheral blood into the central nervous system, differentiate into resident cells of the brain.

microorganisms—Also called microbes. Bacteria, virus, fungi, parasite are microorganisms.

monoclonal antibody—An antibodiy produced from a single parent B cell (an immune cell); monoclonal antibodies are identical (clones) and therefore recognize the same specific antigen.

monocytes—Phagocytic cells of the immune system; they are the immature circulating precursor of macrophages.

nucleoside reverse transcriptase inhibitors (NRTIs)—An antiretroviral drug that is a chemical analog (look-alike) of a cellular nucleoside and acts against HIV by inhibiting the reverse transcriptase enzyme.

non-nucleoside reverse transcriptase inhibitors (NNRTIs)—An antiretroviral drug that binds to HIV's reverse transcriptase enzyme and thereby prevents the enzyme from its normal activity of transcribing HIV RNA into DNA.

opportunistic infections—Infections that occur only in individuals with compromised immune systems, such as those with HIV infections, transplant patients, and cancer patients receiving radiation therapy and/or chemotherapy.

pathogens—Disease-causing microbes.

perinatal transmission—The passage of a substance (nutrients, body fluids or a component in body fluids such as antibodies, infectious agents such as a virus) from mother to developing fetus or newborn.

phagocytic—Cells that engulf and break down microbes marked for destruction, foreign substances or particles, and dead or dying cells; literally "debris eating."

phylogenetic—Genetics from an evolutionary perspective. Molecular biologists study the genome or specific DNA sequences of different HIV or SIV strains to determine relatedness and to pinpoint when mutations may have emerged.

Pneumocystis carinii—A protozoal parasite that can cause pneumonia in humans.

pharmacology—The study of drug action, including chemical or biologic origin, effects and uses; the study of how and why drugs work (or don't work) in the body.

placebo—A dummy medication or treatment that has no effect, such as a sugar pill or sham surgery. Placebos used in clinical trials as controls are imitations of the medicine(s) under evaluation; they can be tablets or capsules with inactive ingredients.

protease—An enzyme that catalyzes or facilitates the breakdown of a protein.

protease inhibitor—A drug that blocks the action of the enzyme protease, which is needed for viral replication. Many digestive enzymes in humans are proteases. Bacteria, fungi, and viruses also have proteases.

Glossary

receptor—A molecule on the surface of cells that acts as a receiving dock for specific molecules on the surface of other cells to trigger a set of cellular events. Cellular receptors can be exploited by a microbe to allow it access to the cell.

retrovirus—A family of RNA viruses that includes HIV; retroviruses use a backward. ("retro") process, called reverse transcription (RNA into DNA), to make proteins necessary for the virus to replicate itself.

reverse transcriptase—The enzyme responsible for carrying out reverse transcription.

reverse transcription—The process used by retroviruses whereby ribonucleic acid, or RNA, is converted into deoxyribonucleic acid, or DNA, as a step in the production of proteins.

T lymphocytes—White blood cells of the immune system, which originate in the thymus; also called T cell.

vaccines—Preparations of killed or attenuated (weakened) microorganisms or a preparation of immune cells or products (e.g., antibodies) that stimulates or boosts an immune response to fight or control an infection or other condition (e.g., cancer). Generally, vaccines are used prophylactically to *prevent* an infection, disease, or cancer; however, therapeutic vaccines used to *treat* infections, diseases, or cancers also exist.

viral load—The amount of virus in the body. A diagnostic test, called a viral load test, measures the concentration of HIV in a blood sample to determine the amount of circulating HIV.

virion—A single virus particle that exists outside a host cell (i.e., in blood plasma, lymph, and extracellular space); also referred to as cell-free virus or cell-free viral particle.

virologic failure—The loss of ability or inability of an antiretroviral drug or biologic product to suppress viral replication to a predefined cutoff value (e.g., 50 plasma HIV RNA copies/mL or less).

virology—The study of viruses.

wasting syndrome—An HIV-related condition characterized by profound involuntary weight loss (more than 10 percent of body weight), chronic diarrhea, weakness, lethargy, and fever for more than 30 days.

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Further Reading

Web Sites

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Doctors Without Borders
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Elizabeth Glaser Pediatric AIDS Foundation
http://www.pedaids.org

Family Health International
http://www.fhi.org/en/HIVAIDS/index.htm

Global Fund to Fight AIDS, Tuberculosis, and Malaria
http://www.theglobalfund.org/en/about/how/

HIV/AIDS Clinical Trials
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www.niaid.nih.gov/publications/aids.htm

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The AIDS Memorial Quilt
http://www.aidsquilt.org

National Institute of Allergy and Infectious Diseases
http://www3.niaid.nih.gov/

National Institutes of Health Office of Science Education
http://science.education.nih.gov

The Pharmaceutical Research and Manufacturers of America
http://www.phrma.org

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http://www.kidshealth.org/teen/infections/stds/std_hiv.html

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http://www.usaid.gov/our_work/global_health/aids/

U.S. Department of Health and Human Services—Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents
http://aidsinfo.nih.gov/guidelines

U.S. Food and Drug Administration—Drugs Used in the Treatment of HIV Infection
http://www.fda.gov/oashi/aids/virals.html

U.S. National Institutes of Health
http://www.nih.gov/

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