Diseases and Disorders

AIDS

by Sudipta Bardhan-Quallen

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On cover: On World AIDS day, December 1, 2003, people in the Philippine Islands light candles to commemorate victims of AIDS.

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"The Most Difficult Puzzles Ever Devised"

CHARLES BEST, ONE of the pioneers in the search for a cure for diabetes, once explained what it is about medical research that intrigued him so. "It's not just the gratification of knowing one is helping people," he confided, "although that probably is a more heroic and selfless motivation. Those feelings may enter in, but truly, what I find best is the feeling of going toe to toe with nature, of trying to solve the most difficult puzzles ever devised. The answers are there somewhere, those keys that will solve the puzzle and make the patient well. But how will those keys be found?"

Since the dawn of civilization, nothing has so puzzled people—and often frightened them, as well—as the onset of illness in a body or mind that had seemed healthy before. A seizure, the inability of a heart to pump, the sudden deterioration of muscle tone in a small child—being unable to reverse such conditions or even to understand why they occur was unspeakably frustrating to healers. Even before there were names for such conditions, even before they were understood at all, each was a reminder of how complex the human body was, and how vulnerable.

While our grappling with understanding diseases has been frustrating at times, it has also provided some of humankind's most heroic accomplishments. Alexander Fleming's accidental discovery in 1928 of a mold that could be turned into penicillin

has resulted in the saving of untold millions of lives. The isolation of the enzyme insulin has reversed what was once a death sentence for anyone with diabetes. There have been great strides in combating conditions for which there is not yet a cure, too. Medicines can help AIDS patients live longer, diagnostic tools such as mammography and ultrasounds can help doctors find tumors while they are treatable, and laser surgery techniques have made the most intricate, minute operations routine.

This "toe-to-toe" competition with diseases and disorders is even more remarkable when seen in a historical continuum. An astonishing amount of progress has been made in a very short time. Just two hundred years ago, the existence of germs as a cause of some diseases was unknown. In fact, it was less than 150 years ago that a British surgeon named Joseph Lister had difficulty persuading his fellow doctors that washing their hands before delivering a baby might increase the chances of a healthy delivery (especially if they had just attended to a diseased patient)!

Each book in Lucent's Diseases and Disorders series explores a disease or disorder and the knowledge that has been accumulated (or discarded) by doctors through the years. Each book also examines the tools used for pinpointing a diagnosis, as well as the various means that are used to treat or cure a disease. Finally, new ideas are presented—techniques or medicines that may be on the horizon.

Frustration and disappointment are still part of medicine, for not every disease or condition can be cured or prevented. But the limitations of knowledge are being pushed outward constantly; the "most difficult puzzles ever devised" are finding challengers every day.

Everybody's Problem

LONG BEFORE THE disease called AIDS was known by that name, an epidemic had begun. This deadly scourge that has ravaged the world began in the 1950s with isolated cases detected in Europe and Africa. The main symptoms were strange infections that should not have been life threatening but nonetheless proved fatal. For example, Dr. Margrethe Rask became ill with a breathing disorder in Zaire in 1976; though it was clear she was dying, neither she nor any other doctor could determine the reason. After Rask's death in December 1977, an autopsy revealed that she had been slowly suffocated by the growth of millions of microorganisms called *Pneumocystis carinii* in her lungs. Pneumonia caused by this microbe was rare, and as far as doctors knew, no one died of such infections.

By the 1970s, dozens of these unexplained cases were appearing in major cities in Europe and Africa, puzzling doctors who treated the dying patients. By 1979, it had spread to the United States and the rest of the world. Within a few short years, people were dying by the thousands. Doctors concluded that a new disease was to blame for the previously inexplicable deaths, but this conclusion did not offer any hope for treatment.

In 1982, the mysterious disease was finally given a name—acquired immune deficiency syndrome, or AIDS. In the span of a few years, AIDS went from an unknown disease to a household name, taking a tremendous human toll in the process—and that was just the beginning.

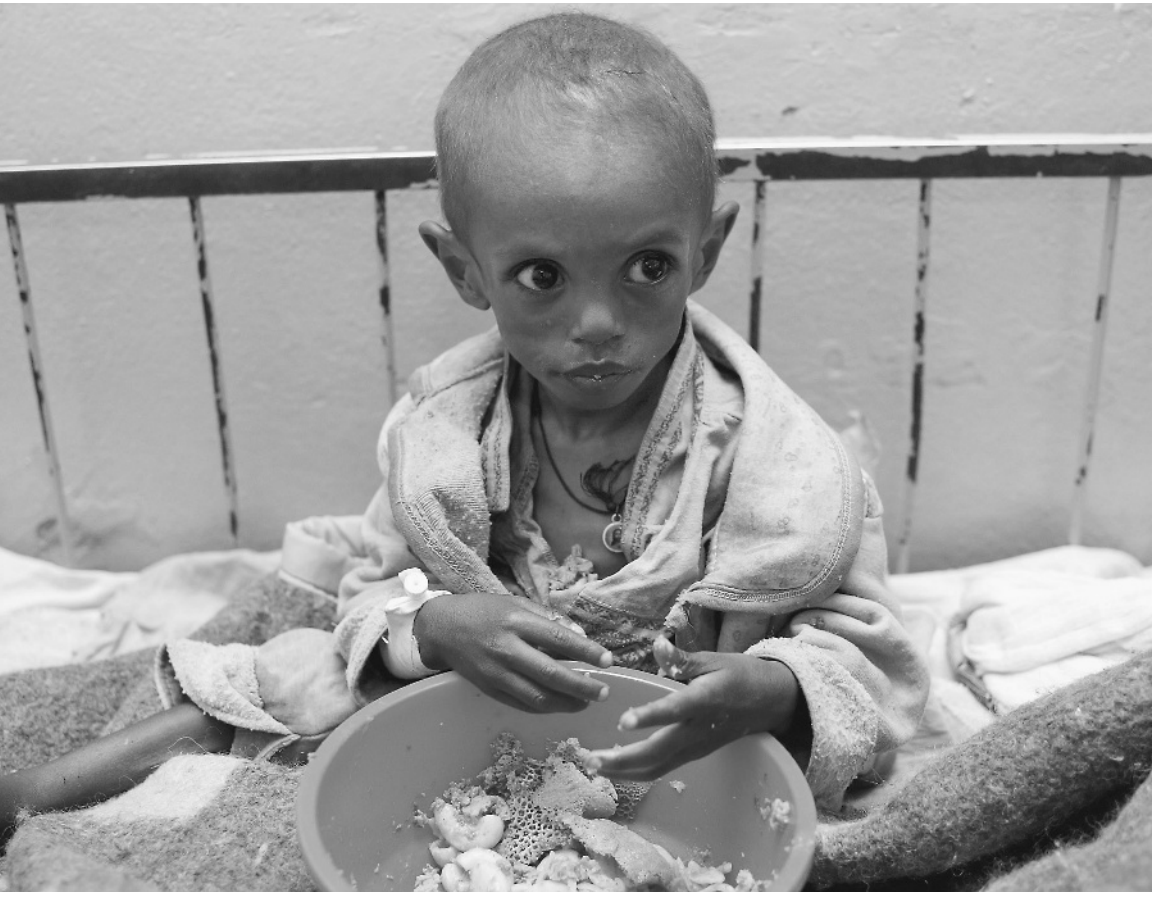
The Face of Suffering

Throughout the 1980s, AIDS spread virtually unchecked, in part because the earliest victims, primarily homosexual men and intravenous drug users, lived on the margins of society. Some people were quick to characterize AIDS as a punitive disease visited upon those who were, in their opinions, immoral or depraved. For example, American televangelist Reverend Jerry Falwell said with reference to homosexuality, "AIDS is a lethal judgment of God on America for endorsing this vulgar, perverted and reprobate lifestyle."[1] A number of organizations in the United States vigorously opposed government funding of AIDS research on the assumption that the disease was a problem of so-called deviants. Those who engaged in heterosexual relations and did not take drugs intravenously, the thinking went, had little to fear from AIDS.

At a 1983 AIDS vigil in New York City's Central Park, people hold numbered signs, each representing a victim of the worldwide AIDS epidemic.

Over time, however, AIDS did not stay confined to groups that could be dismissed as outside the mainstream. In fact, the virus that causes AIDS, human immunodeficiency virus (HIV), was shown to infect victims without regard to gender, age, race, sexual orientation, or social status. By 2004, worldwide heterosexual contact—not homosexual sex or intravenous drug use—became responsible for 90 percent of all adolescent and adult HIV infections. Women became a significant portion of those with HIV infections, as did babies born to infected mothers. In little more than

This malnourished Ethiopian boy was born infected with AIDS. Infected babies born to infected mothers make up a significant percentage of AIDS cases around the world.



two decades the HIV/AIDS epidemic spanned the globe and affected people regardless of varying cultures and lifestyles.

A Growing Problem

The near-universal vulnerability to infection and the lack of any cure meant that AIDS would become a major killer. Indeed, AIDS has become the fourth-leading cause of death around the world, claiming more lives than cancer, malaria, tuberculosis, or diabetes. Experts estimate that every day, sixteen thousand people globally are infected with HIV, and that 42 million people are living with HIV or AIDS. It is now clear that AIDS cannot be considered someone else's problem.

With the huge increase in HIV cases, efforts to prevent transmission of the virus have become a concern for everyone. Said Dr. Sharon Hillier of the University of Pittsburgh School of Medicine, "The issue of HIV prevention is not a gay issue or a women's issue—it's a human issue."[2] Making people aware of the disease and of how they could reduce their risk of contracting AIDS became a priority for the U.S. government. In fact, in 1988, the U.S. government spent $17 million to mail Surgeon General C. Everett Koop's pamphlet, *Understanding AIDS,* to 107 million households in the country. Efforts of this sort are ongoing. As of 2004, millions of dollars are spent each year for HIV education around the world.

A Glimmer of Hope

In addition to HIV education and prevention, many resources are being devoted to research into treating the disease as well as into making treatments available globally. The most significant advance in HIV/AIDS treatment since the disease was identified is simply that doctors now have treatments to offer. In 1982, the year AIDS was given its name, doctors could offer AIDS patients no medical treatments. The best they could do was battle the infections that arose due to the destroyed immune system—a battle that doctors and their patients always eventually lost. Though there is still no cure for HIV infection, patients today have hope in the form of a variety of drugs that better protect the immune system from being ravaged by HIV.

These treatments have begun to change HIV infection from a terminal to a chronic illness—that is, one that can be controlled and that does not necessarily kill its victim. However, the drugs do not work for every patient; moreover, they are not equally available throughout the world. Because of the limitations in the effectiveness of current treatments, scientists continue to push forward to search for new HIV therapies, including vaccines and gene therapy. Many scientists feel that a cure for AIDS is possible by 2025, but, in the words of leading AIDS researcher Dr. David Ho, director of the Aaron Diamond AIDS Research Center in New York City, "It will require an extraordinary effort of political will among our leaders to get it to the people who need it most."[3]

Chapter 1

The Origins of an Epidemic

IN MOST OF the world, AIDS was not recognized as a problem in its own right until around 1981—decades after the disease first arose in humans. Scientists now think that AIDS became evident in humans as early as the 1950s, in Europe and Africa, although proper diagnoses were not made at the time. Since AIDS escaped detection for so long, it is impossible to say how many people died of AIDS-related illnesses in the years before doctors became familiar enough with the disease to identify it in patients. In fact, before 1981, most people had never even heard of the disease—and no one understood how it killed.

Awareness of a looming epidemic was growing rapidly by the end of 1982. Over sixteen hundred cases of AIDS had been diagnosed in the United States; over six hundred Americans had died of the disease. Because of the increased awareness and the evident threat to public health, major initiatives were quickly taken to increase understanding of AIDS and to improve diagnostic techniques. Doctors at the federal government's Centers for Disease Control and Prevention (CDC) worked to track and understand the progression of the disease in individual patients. The goal was to recognize symptoms of AIDS, thereby helping with diagnosis. In addition, scientists worldwide sought to isolate the microorganism that causes AIDS and to develop an effective blood test for diagnosis.

The Beginning

In the United States, awareness of the AIDS epidemic can be traced back to a 553-word article, simply titled "*Pneumocystis* Pneumonia—Los Angeles." The article appeared in the June 5, 1981 issue of the

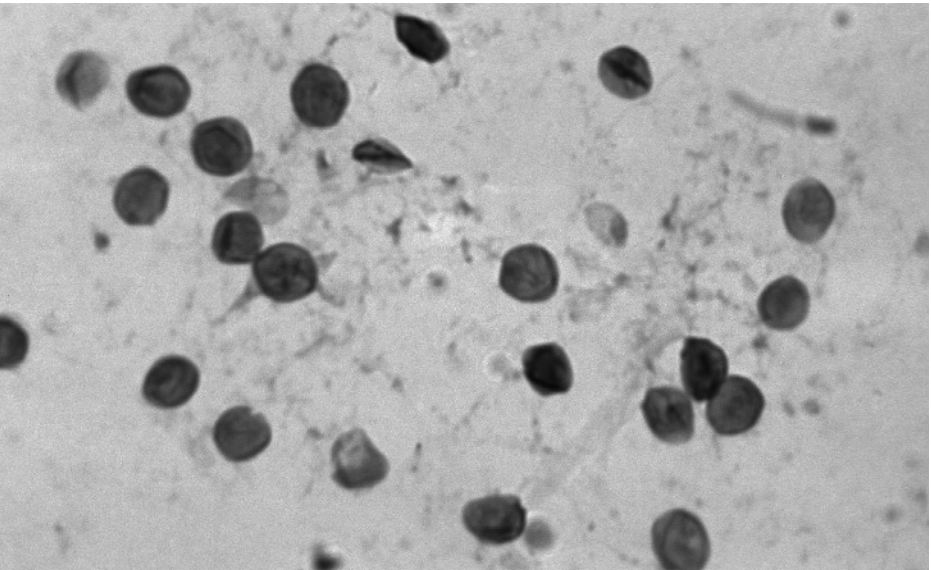
Morbidity and Mortality Weekly Report (MMWR), the CDC's weekly newsletter aimed at informing health care professionals of current medical concerns. The report did not mention a previously unknown virus; instead, authors Dr. Michael Gottlieb and Dr. Wayne Shandera wrote:

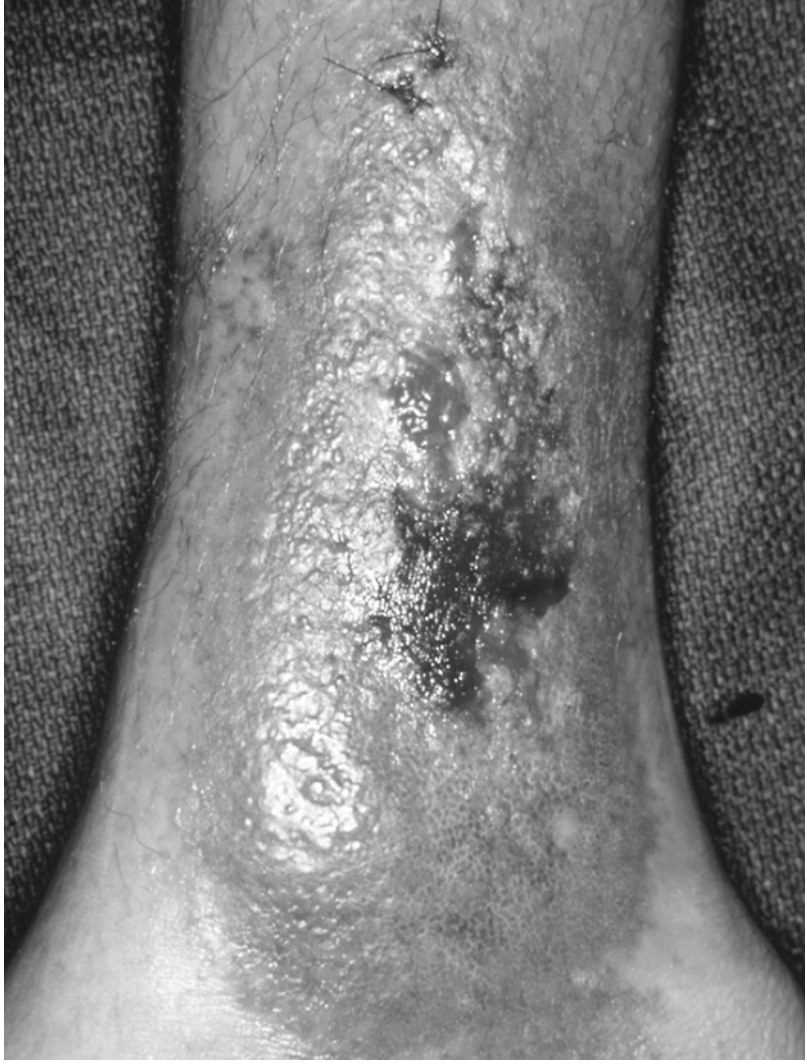
> In the period October 1980–May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia (PCP). . . . The fact that these patients were all homosexuals suggests an association between some aspect of a homosexual lifestyle or disease acquired though sexual contact and *Pneumocystis* pneumonia in this population.[4]

Gottlieb's and Shandera's patients were dying, apparently of PCP, even though PCP was a generally treatable disease that seldom proved fatal. The patients showed other strange symptoms as well: swollen lymph nodes, fevers, weight loss, oral yeast infections, and elevated levels of cytomegalovirus (CMV), a virus that normally causes no adverse symptoms but which in these patients seemed to overwhelm the body. In addition, these patients suffered from reductions in counts of T cells, which are vital for the immune system's proper function.

In the ensuing months, more cases of strange sicknesses among homosexual men were reported. In addition to cases of PCP, doc-

In 1981 several homosexual men died of a normally treatable form of pneumonia caused by the bacteria Pneumocystis carinii *(pictured). Doctors speculated that a new disease made them susceptible to the pneumonia.*





An increase in the number of homosexual men with the rare skin cancer Kaposi's sarcoma (pictured) provided further evidence that a new disease was spreading throughout the gay community.

tors saw young men in their twenties and thirties suffering from a rare skin cancer called Kaposi's sarcoma (KS). Many doctors conjectured that the unusual illnesses were linked in some way, and the CDC issued a warning to physicians: "Physicians should be alert for Kaposi's sarcoma, PC pneumonia, and other opportunistic infections associated with immunosuppression in homosexual men."[5] By the end of 1981, 422 cases of the syndrome, that is, a group of symptoms that collectively characterize a disease, were reported in the United States alone, with 156 people dead—and still, no one knew the cause.

Following the Trail

When the CDC began studying the syndrome, it became immediately clear that a hallmark was a loss of immune function that allowed the development of opportunistic infections—illnesses that would have never occurred had the immune system been functioning properly. More and more patients were diagnosed with the same strange maladies: yeast infections, toxoplasmosis (a rare parasitic disease that usually causes no negative symptoms in healthy people), infections from cryptococcosis (a fungus commonly found in bird droppings), CMV infections, as well as KS and PCP. A whole host of other rare illnesses were also soon added to the list. Doctors reported patients afflicted with the syndrome were showing signs of diseases as exotic as feline leukemia, a major cause of death in cats, and cryptosporidiosis, a parasitic disease usually seen only in sheep and goats. It appeared that these patients' immune systems were so compromised that microorganisms usually unable to infect humans at all were able to create life-threatening infections.

Another seemingly consistent feature was that the syndrome appeared to affect only homosexual men; in fact, it seemed that the more promiscuous the subject, the more likely he was to become infected. In a *New York Times* article, Dr. James Curran of the CDC stated that heterosexual men and women, regardless of sexual orientation, were apparently safe from the syndrome: "The best evidence against contagion is that no cases have been reported to date outside the homosexual community or in women."[6] With this assumption in mind, in January 1982, the syndrome was named gay-related immunodeficiency disease, or GRID.

Doctors at the CDC looked for connections between the victims of GRID, in an effort to establish the disease's mode of transmission. From interviewing victims, they were soon able to establish social and sexual connections between people who later developed symptoms of GRID. Of the first nineteen cases of GRID investigated, sexual links were confirmed between nine of them. The suspicion arose that whatever was causing GRID was transmitted sexually.

Cancer, a Virus, and GRID

Scientists already knew that certain infections could result in immune suppression; moreover, there were viruses that had been identified that did just that. Certain cancers had also been linked to viral infections, and these cancers sometimes interfered with proper immune function. For example, the human T cell leukemia virus (HTLV) had been shown in 1980 to be a cause of T cell leukemia in Japan and the Caribbean. Patients with T cell leukemia, like those with GRID, experienced severe drops in T cell counts.

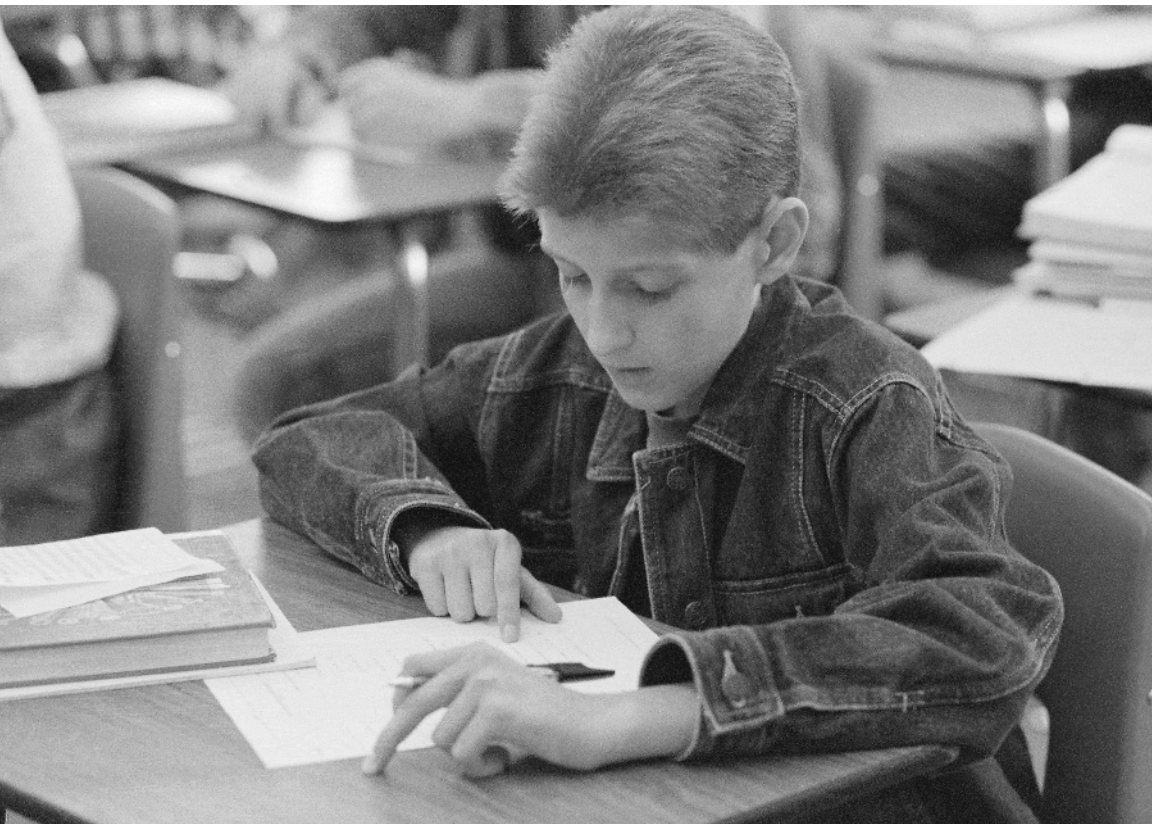
Some researchers at the CDC supported the notion that GRID also was caused by a virus. This had ominous implications: Viruses do not consider sexual orientation when they infect a host. If a virus was causing GRID, there was no reason to believe that the contagion would stay confined to the relatively small population of homosexuals. Scientists predicted that the epidemic would soon spread to people outside the gay community.

Drug Addicts, Hemophiliacs, and Children

The prediction turned out to be correct. As early as mid-1981, doctors had noticed symptoms in intravenous drug users that in hindsight were consistent with GRID. By early 1982, at least twenty-three heterosexuals, mostly intravenous drug users, were counted among GRID victims.

Many scientists felt that the infections seen in intravenous drug users suggested that GRID could be spread through the blood as well as through sexual contact, and that it was more likely to have a viral cause. Since intravenous drug users often shared needles, they were exposed to the blood of other drug users. This means of disease transmission was well known. The blood contact spread diseases such as hepatitis B, which was caused by a virus.

The theory that GRID was spread through blood contact got further corroboration when a number of people with hemophilia began showing symptoms. Hemophiliacs, who have a blood disorder that prevents proper clotting following injury, often require transfusions and injections of the components their own blood lacks. In



Teenager Ryan White and many other hemophiliacs contracted AIDS in the mid-1980s, confirming the theory that AIDS could spread through blood contact.

early 1982 in Miami, an elderly man with hemophilia was diagnosed with *Pneumocystis.* He was not an intravenous drug user, but because of the hemophilia, he received regular injections of a clotting agent. The clotting agent, isolated from the blood of non-hemophiliac blood donors, is called Factor VIII.

The man's doctor initially believed that *Pneumocystis carinii* microorganisms might have contaminated the patient's doses of Factor VIII. Bruce Evatt at the CDC, however, assured the physician that these bacteria were large enough that they would have been completely filtered out during the process of Factor VIII isolation. Only very small microbes, such as viruses, could pass through the filtering process.

The number of nonhomosexual GRID cases continued to rise. By mid-1982, two more hemophiliacs were confirmed to have GRID. Infected intravenous drug users were also becoming more common. Furthermore, there were reports of children of GRID-infected drug addicts showing GRID symptoms from birth. One account told of a seventeen-month-old baby who had oral yeast infections, *staphylococcus aureus* infections, and an infection of a bacterium called *Mycobacterium avian-intracellular,* which was usually only seen in birds. Another thirty-week-old infant was suffering from infections including PCP, cryptococcosis, and CMV—all hallmarks of GRID. Soon, doctors at the CDC were forced to conclude that GRID was not purely a homosexual disease. Furthermore, the fact that babies could be born with the disease made it clear that, although lifestyle was a risk factor, virtually anyone could contact GRID. As this fact became clear, scientists redoubled their efforts to find the cause of GRID.

A New Name and a New Fear

In light of the new information regarding who was at risk, the name "gay-related immunodeficiency disease" seemed inappropriate. Curran argued that a more neutral name should be given to the disease. He later recalled, "By now there had been reports of cases in injecting drug users, and in women who were sex partners of men with AIDS, so it was time to describe it more broadly."[7] After some discussion, a new name was proposed: "acquired immune deficiency syndrome," or AIDS. The new name implied a greater risk for the population at large, and more of the public began to take interest in the AIDS situation.

Much of the interest was sparked when a new source of fear concerning AIDS was identified: Blood banks could and had been providing infected blood to unsuspecting patients. The first known case of transfusion-related infection came in 1983, when a fifty-three-year-old man was diagnosed with AIDS. He was not a homosexual, an intravenous drug user, or a hemophiliac, but he had undergone open-heart surgery twenty-nine months before the diagnosis. During his surgery, doctors had given him blood transfusions.

When more transfusion recipients—thirty-nine of them by the end of 1983—began showing AIDS symptoms soon after they had received blood, the list of who was at high risk for contracting AIDS was greatly expanded. Dr. Harold Jaffe of the CDC described the situation: "When it began turning up in children and transfusion recipients, that was a turning point in terms of public perception. Up until then it was entirely a gay epidemic, and it was very easy for the average person to say 'So what?' Now everyone could relate."[8]

A patient receives a blood transfusion. Because the microorganism responsible for AIDS had not been identified in the early 1980s, blood banks unwittingly supplied tainted blood.

Infected Blood

It became more difficult to argue that AIDS was not in the blood. Yet even though the medical evidence suggested that AIDS could be transmitted through blood contact, there was still a great deal of resistance to that theory, especially from the blood banks, many of which sold blood for a profit. If blood banks admitted that their product might be infected, there would be serious financial repercussions for the entire industry.

The problem was having no way to test blood for a microorganism that had not yet been identified. As a stopgap measure, in 1983, the CDC proposed that blood products be tested for hepatitis B, citing the fact that an overwhelming number of people in the highest risk groups for AIDS—gay men, hemophiliacs, and intravenous drug addicts—had also at some point contracted hepatitis B. In fact, 88 percent of homosexual AIDS patients, 80 percent of hemophiliac AIDS patients, and virtually 100 percent of intravenous drug–addict AIDS patients tested positive for hepatitis B. Removing hepatitis B–positive blood from the supply could therefore be expected to reduce the risk of a recipient contracting AIDS.

The blood-banking industry, however, rejected the plan outright. Dr. Aaron Kellner, president of the New York Blood Center, stated that the cost of testing was prohibitive; he estimated the national cost to perform hepatitis B tests would be $100 million annually. He contended that the small number of AIDS cases that resulted from tainted blood was not enough to justify such an expensive course of action: "We must be careful not to overreact. The evidence [that the blood supply may be seriously tainted] is tenuous."[9]

The Virus Hunt

With the increase in the number of people perceived to be at risk for contracting AIDS, scientists both in the United States and elsewhere knew that answers to the fundamental problems of the epidemic—what causes AIDS and how doctors could diagnose the disease before a victim spreads it—had to be found, and quickly. Researchers at the National Institutes of Health (NIH) in Bethesda, Maryland, and at the Pasteur Institute in Paris followed seemingly unrelated trails in search of the virus that caused AIDS.

At NIH, Dr. Robert Gallo headed the team that was hunting for the AIDS virus. Gallo was an expert in retroviruses, a class of virus whose genes are stored, not as deoxyribonucleic acid (DNA), but as ribonucleic acid (RNA), another type of genetic material. He had identified the only two retroviruses scientists knew of, HTLV-1 in 1979 and HTLV-2 in 1982, both of which were involved in human T cell leukemia. Since that disease also greatly affected T cells, Gallo had long contended that AIDS was also caused by a retrovirus, similar to HTLV-1 and HTLV-2. Despite this promising theory, Gallo and his team had made very little progress in actually identifying the cause of AIDS. By early 1983, they had examined blood samples from thirty-three AIDS patients but had found HTLV-related genetic material in only two of them.

A Major Breakthrough

In the meantime, scientists at the Pasteur Institute had experienced greater success. Dr. Luc Montagnier was in charge of the AIDS research effort at the Pasteur Institute. Using a tissue sample from a French AIDS patient, Montagnier attempted to grow the AIDS virus in a laboratory culture of human T cells. Fifteen days later, the cell culture showed traces of a protein called reverse transcriptase that is used by retroviruses when they proliferate in host cells.

Montagnier was able to isolate the virus from the tissue sample and compare it to other previously identified retroviruses. He was sure that the AIDS patient's virus was different from anything seen before. In May 1983, Montagnier announced his discovery of the AIDS retrovirus, which he later named lymphadenopathy-associated virus (LAV). Montagnier, however, was not able to prove conclusively that LAV actually caused AIDS. Gallo's group, meanwhile, had finally isolated a retrovirus they called HTLV-3 in the blood of AIDS patients. In 1984, they were able to demonstrate a strong correlation between its presence and the onset of AIDS symptoms.

It was eventually shown that LAV and HTLV-3 were the same virus. Since both research teams had worked on the discovery and made important contributions, Gallo and Montagnier agreed to

Working independently, American doctor Robert Gallo (right) and French doctor Luc Montagnier both managed to isolate HIV, the virus that causes AIDS.

share credit for discovering the virus that causes AIDS. Rather than choose between the names LAV or HTLV-3, in early 1987, an international committee renamed the organism human immunodeficiency virus, or HIV.

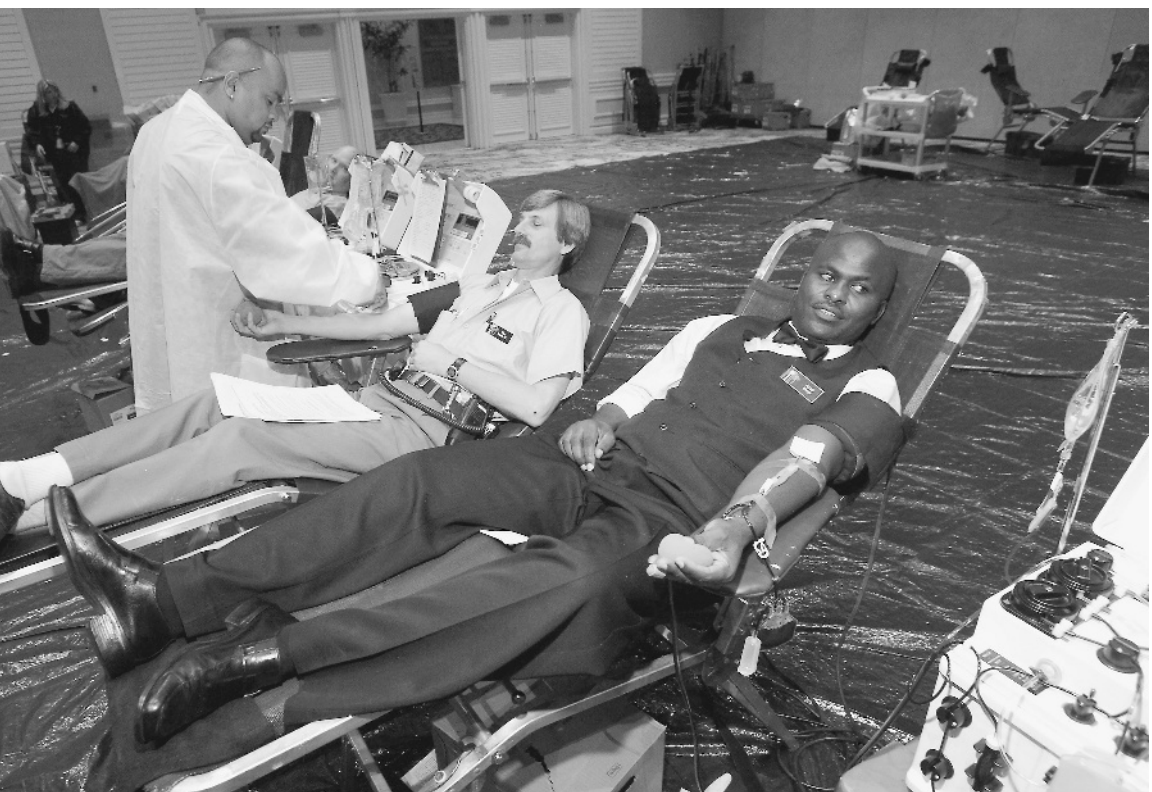
Test Results

By the time the AIDS virus was renamed HIV, a number of scientists had developed tests to screen for its presence in blood samples. These tests were slightly different from each other, and none detected the virus itself; rather, they detected the presence of antibodies to HIV, which the immune system creates in response to exposure to the virus.

The newly developed HIV tests were widely used to screen readily available blood bank samples as well as individuals concerned that they might have contracted HIV. In 1985, after the U.S. Food and Drug Administration (FDA) approved a blood-screening test for HIV, the American Red Cross reported that one in five hundred American blood donors was a carrier of HIV. Even more alarming, because millions of people had received blood tranfusions since the beginning of the AIDS epidemic until the time testing became routine, thousands of transfusion recipients were unknowingly carrying—and transmitting—the disease. The situation elsewhere was even more alarming. That same year, for example, random samples of blood from seventy-five hundred Parisians were screened for HIV antibodies. The study found that one in two hundred people was infected with HIV. Furthermore, an estimated fifty additional infections were occurring every week in hospitals through infected blood.

When the blood-banking industry finally agreed to a "look back" program in April 1986 to identify people who had previously received

Once HIV was identified, researchers were able to develop tests to screen donated blood for the presence of the virus.



AIDS-infected blood, the statistics were terrifying to the public. In the final weeks before blood banks began using the HIV test to screen samples, 150 infected donors gave blood that was transfused into 200 unsuspecting patients. In addition, studies revealed that the rate of HIV infection among homosexual men ranged between 10 percent in areas such as New Mexico to 70 percent in areas such as San Francisco or New York City. The CDC also estimated that 25 percent of the approximately 900,000 intravenous drug users were infected with HIV. Overall, the national estimates of Americans carrying HIV ranged from previous figures of 500,000 to 1 million people to approximately 2 million.

The concern felt by the American public grew with the new statistics, but CDC and Health and Human Services officials sought to allay fears by reiterating that the highest risk of contracting HIV was limited to the described risk groups: homosexual men, intravenous drug users, hemophiliacs, and transfusion recipients. Heterosexuals who did not use intravenous drugs, or did not have sex with people in the described risk groups, were still considered to be at low risk. According to Dr. Otis Bowen, secretary of Health and Human Services in 1987, "There is not an [AIDS] epidemic among heterosexuals, as some people think."[10] Bowen, however, was mistaken. HIV could be transmitted by any sexual intercourse. Heterosexual individuals who had unknowingly contracted HIV were, in fact, able to transmit the disease. In this way, AIDS was spreading silently through the mainstream.

Though the HIV test provided valuable information that would help prevent the spread of the disease, it did nothing to relieve the suffering of HIV patients; their symptoms continued, irrespective of confirmation from the blood test that they only carried the virus. In fact, the test was often detrimental to these patients' quality of life. As Gallo explained, "We'd see reminders in the faces of all the infected people that we'd done nothing for them. I'd say: 'We have a blood test now.' That was a life-saving public health advance, but they'd say: 'What's a blood test to me—it only defines me as infected.'"[11] With the tools in place to identify patients with HIV, the next steps in the AIDS crisis were to gain an understanding of the disease and to find effective treatments, and perhaps even cures.

Chapter 2

Anatomy of an Infection

IN THE YEARS following the discovery of HIV, much has been learned about the disease called AIDS. Scientists have worked to sort out misconceptions and get the truth to the public. In the two decades since the initial diagnoses of AIDS, it has been well established how HIV is transmitted and what behaviors are considered high risk. Furthermore, doctors have become more aware of the specific physiological changes that occur during each stage of the disease, resulting in treatment plans that can target the virus at its most vulnerable points, thereby improving the quality of life of AIDS patients.

Panic

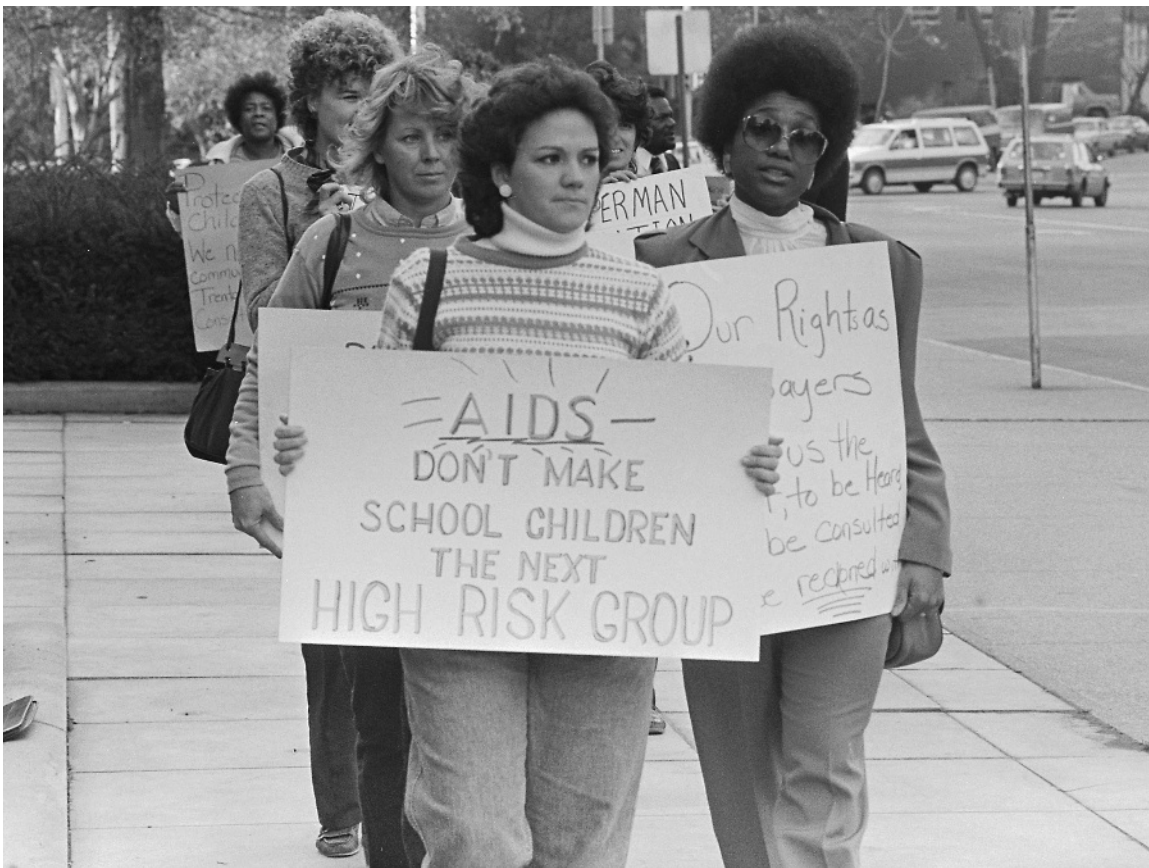
The HIV blood test had great implications for public health. The infection rate from blood transfusions dropped to nearly zero when the HIV test was used for screening purposes. Furthermore, the spread of the disease could be better controlled when doctors could identify and then counsel infected individuals on how to keep from spreading the disease. People who were informed that they carried the virus could also begin treatment before symptoms arose, resulting in increased longevity.

The public health benefits were almost forgotten, though, when HIV testing proved how extensively the virus had spread through the population. The American public practically panicked. People were confused about ways that HIV could and could not be transmitted, and conflicting reports from doctors made many sectors of the public somewhat distrustful of the medical profession. While

the CDC maintained that HIV could be transferred only through bodily fluids such as blood and semen, some doctors openly expressed the belief that the virus could be transmitted through contact as casual as "sharing a bologna sandwich,"[12] in the words of one observer. Another report stated that HIV could be excreted in tears. According to Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, "Somehow that sprang a fear that it [HIV] must be all over the place."[13]

Parents like Darlynn Spizzeri, a New York City mother, kept their children out of school because "we are afraid our children will catch the disease even if those so-called, quote-unquote experts say it is impossible."[14] There was talk about quarantining HIV-infected individuals, or at least making it illegal for them to engage in sexual activities.

Concerned parents protest against allowing children with AIDS to attend school. Misconceptions as to how AIDS is spread created an atmosphere of panic throughout the United States.



Scientists, who understood that many of the public's fears were based in misconceptions, now struggled to find ways to prove that the fears were mostly unfounded. Work began to raise consciousness about HIV and AIDS and to define the course of the disease more clearly.

HIV Transmission

Some of the most important information to be gained after HIV was discovered was a better understanding of the ways in which the virus could be transmitted. Despite many conjectures and myths that sprang up when the public first learned about AIDS, the CDC identified specific high-risk behaviors for contracting HIV and ascertained that the disease could not be spread through casual contact.

Further research confirmed that the virus could be found in bodily fluids as diverse as saliva, tears, blood, breast milk, semen, urine, and vaginal secretions. Many believed that this pervasive presence of HIV would prevent doctors from achieving control over the epidemic. In reality, though, as stated by Stephen Schultz, the assistant commissioner of the New York City health department in 1985, "AIDS is not an easy disease to come by. It is hard to get [from casual contact]."[15] This observation has held true through all the subsequent investigations.

There are several reasons that HIV is considered fairly difficult to contract outside the defined high-risk behaviors. The probability that a person will be infected with HIV upon exposure to the virus depends on what kind of bodily fluid is being exchanged, the concentration of virus in that fluid, how long the fluid has been out of an infected individual's body, and how the virus enters the body of the recipient. The high number of variables involved in a successful infection often puts the odds against getting HIV, especially when proper precautions are taken.

In an infected person, fluids such as blood, semen, vaginal secretions, and breast milk have relatively high concentrations of HIV; an exchange of these fluids carries with it a high risk of contracting HIV. However, fluids such as saliva, tears, and urine have low levels of HIV and pose a low risk of transmitting HIV. Saliva, in fact, is a particularly hostile environment for HIV: Because of the strong diges-

tive enzymes present, saliva will kill up to half of the viruses exposed to it within thirty minutes. In fact, because of this harsh environment, HIV is unlikely to be spread through activities such as kissing, unless there are open sores in the mouths of the people involved.

Since casual contact, such as shaking hands, hugging, or using the same seats, elevators, or bathrooms as infected people, does

not involve exposure to high-risk bodily fluids, the danger of becoming infected with HIV in this way is practically nil. According to Dr. Mirko Grmek, "There is absolutely no evidence that AIDS has ever been spread under normal living conditions—not in schools, not in crowded buses or trains, not in restaurants, not at the hairdressers', not in business meetings."[16]

Risky Behavior

As it turns out, the human skin is an excellent barrier against most microbes, including HIV. Because of this, simple contact with HIV-infected fluids will not result in infection. The fluid must enter the individual's body and get past the body's natural defenses for an infection to occur.

People who run the highest risks of contracting HIV are those who engage in unprotected sex with an infected person and intravenous drug users who share needles with HIV-positive individuals. Health care workers who come into contact with bodily fluids such as blood and semen also run a significant risk of contracting HIV, but this risk is usually reduced by routine precautions, such as the use of rubber gloves when handling biological specimens. Pregnant mothers who are HIV-positive and transmit

To minimize the risk of contracting HIV from bodily fluids, a police doctor wears rubber gloves while examining a heroin-stuffed condom retrieved from a body cavity of a drug dealer.

the virus to their children do so either in the womb or during birth through blood contact.

Since blood used for transfusions in the United States is now routinely screened for HIV, this is no longer considered high risk, although it is still theoretically possible to become infected through transfusion. Blood transfusions do remain a risk for transmitting HIV in other parts of the world, however, especially in underdeveloped areas where the blood supply is not screened as thoroughly. For example, in 2001, it was reported that tens of thousands of villagers in China's Henan Province contracted HIV through infected blood.

Preliminary Signs

As HIV transmission became better understood, further spread of the disease could be prevented. People were informed about high-risk behaviors and what precautions, such as using condoms during sexual intercourse and not sharing needles for intravenous drug use, should be taken to reduce the risk of contracting HIV. These precautionary measures did not, however, offer any solace to those already infected. To help these people, better understanding of the infection process itself had to be gained.

What researchers have learned is that after HIV enters the body of a new host, the virus particles seek out helper T cells in the bloodstream. When an HIV particle encounters a T cell, the virus attaches to proteins on the surface of the cell and then fuses its viral membrane to the cell membrane. Upon fusion, HIV injects its genetic material into the cell and begins the process of replication.

Early studies of AIDS were aimed at understanding the way the disease progresses in infected individuals and drew attention to some of the preliminary signs of HIV infection. It was found, for example, that many of the people who had AIDS recalled noticing flu-like symptoms long before they experienced the opportunistic infections that are the hallmarks of AIDS. Patients suffer from symptoms like fever, fatigue, diarrhea, rash, swelling of the lymph nodes, mild muscle aches, and headaches. These symptoms often go unnoticed as they are relatively mild and are often assumed to be indicative of less serious infections such as mononucleosis.

The initial infection is also associated with fluctuations in T cell levels, but those quickly return to normal.

Since the initial symptoms are fairly mild and the victim returns to feeling healthy, many people who subsequently test positive for HIV have a hard time accepting that they carry a life-threatening virus. Upon learning that he was HIV infected, Raul of East Los Angeles declared in 1996, "I've thought about it, but I just can't picture it happening to me. I think I'll probably die of something else."[17]

A Virus Factory

It is now well understood that the flu-like symptoms that are the hallmark of initial HIV infection are the results of the body's initial attempt to battle the virus. In this stage, referred to as the acute stage of infection, the virus rapidly infects specialized cells called helper T cells and multiplies quickly. Because HIV is able to integrate its own viral genetic material to that of the host cell, it can trick the host into producing viral proteins during the normal life cycle of the cell, turning the host into a living HIV factory. New HIV particles bud off the host cell and are released into the bloodstream.

Very high levels of HIV are present in the blood during acute infection. In fact, more than 10 billion new viral particles are produced each day of this phase. Because so much of the virus is produced, this is the most infectious stage of the disease; HIV-positive individuals are more likely to infect others during acute infection than they are later on.

The immune system fights the initial infection with killer T cells, whose numbers increase during this stage, and will eventually supplement the attack with antibodies produced by another type of immune cell, the B cell. This immune response aims to kill as many virus-infected cells as possible to contain the infection. In this case, these virus-infected cells are helper T cells, responsible for helping B cells produce antibodies. Unfortunately for the patient, the immune system is unable to clear HIV completely from the body.

The Virus Lies in Wait

At some point in its response to HIV infection, the body begins producing antibodies to the virus. Enough helper T cells survive the

initial onslaught of HIV to allow B cells to generate HIV-specific antibodies. This point is referred to as seroconversion, when a blood test can detect HIV-positive status.

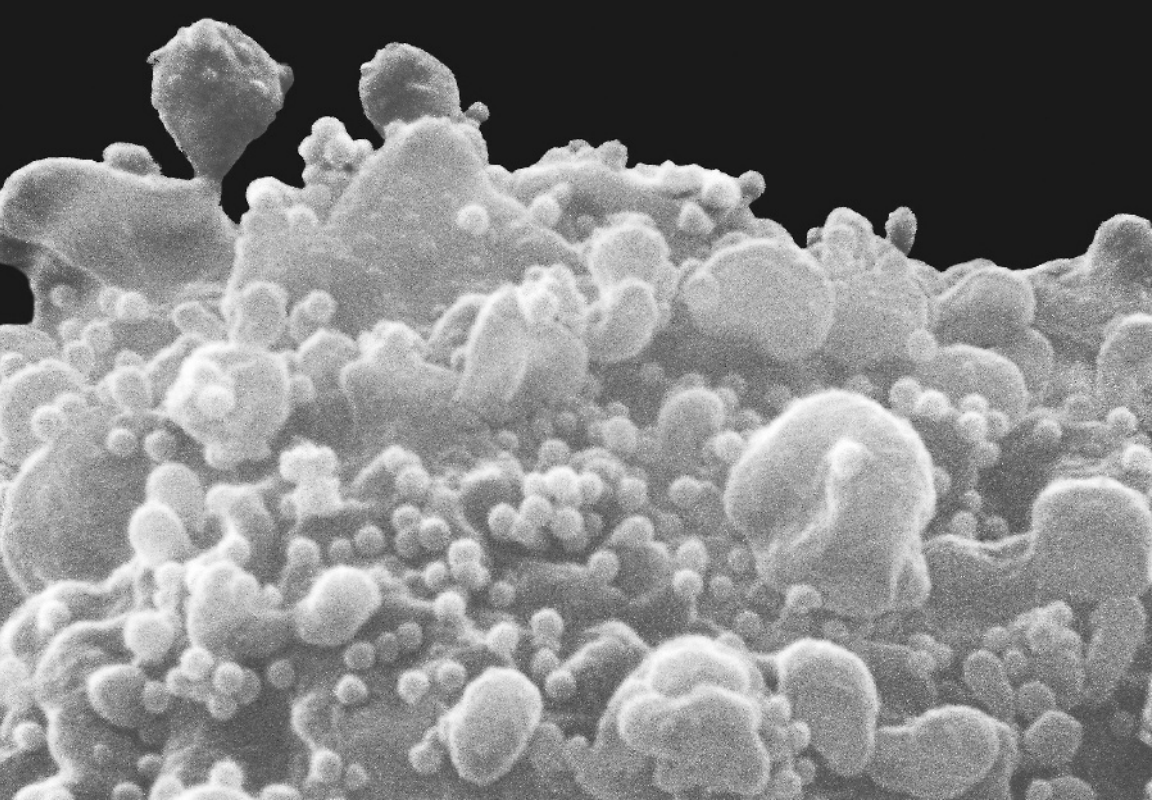
Overall, the body is able to control HIV in the early stages of the disease. Since the body mounts a strong immune response, the vast majority of HIV particles are cleared from the body almost as soon as they are produced. Eventually, the number of viral particles in

the blood declines, and new helper T cells are produced at a high enough rate to return their levels to normal. The patient enters a stage known as clinical latency, a time during which HIV does not cause harmful symptoms.

During clinical latency, reservoirs of HIV are found in lymphoid tissues, such as the lymph nodes. HIV also continues to hide in certain immune cells. Since the viral DNA is integrated into the DNA of these cells, permanent HIV reservoirs are created as long as those cells or their descendants live. This is extremely problematic for fighting the disease because, even though the viral particles in the bloodstream are destroyed by the immune system, the HIV that remains hidden is protected from the immune response. Drugs administered to HIV-positive patients cannot completely eliminate the virus in these reservoirs either. "We now know that these reservoirs are established very early in the course of infection,"[18] says Fauci.

Although there are far fewer viral particles detected by blood tests during clinical latency than in the acute stage, HIV is still transmissible. In fact, each year of the dormant phase of HIV infection, which can last on average between two and fifteen years, more and more virus emerges from the concealed reservoirs. The numbers of HIV particles produced each day are astronomical. "We've learned that 10 billion to 1 trillion HIV viruses are produced in one day in the human body,"[19] says Dr. David Ho. The viral load in the blood seems to remain constant because the body fights back daily, clearing the viral particles continuously. "It's like a person running on a treadmill,"[20] Ho explains. This constant level of viral concentration established during latency, which in the average patient ranges between ten thousand and one hundred thousand HIV particles per milliliter of blood, usually stays relatively constant.

This constant onslaught of virus, which must be continually cleared, gradually weakens the immune system. In other words, the treadmill effect slows, and the virus begins to win. As the immune system sustains damage, HIV-positive patients may experience mild, nonspecific symptoms, such as skin rashes, fatigue, slight weight loss, night sweats, or yeast infections in the mouth. These phenomena do not necessarily mean that AIDS is imminent, but



HIV particles (the smallest spheres) are visible in this micrograph image of the surface of an infected helper T cell. The virus infection will destroy this disease-fighting cell.

in an immune-compromised HIV-positive individual, the risks of developing even more serious symptoms increase.

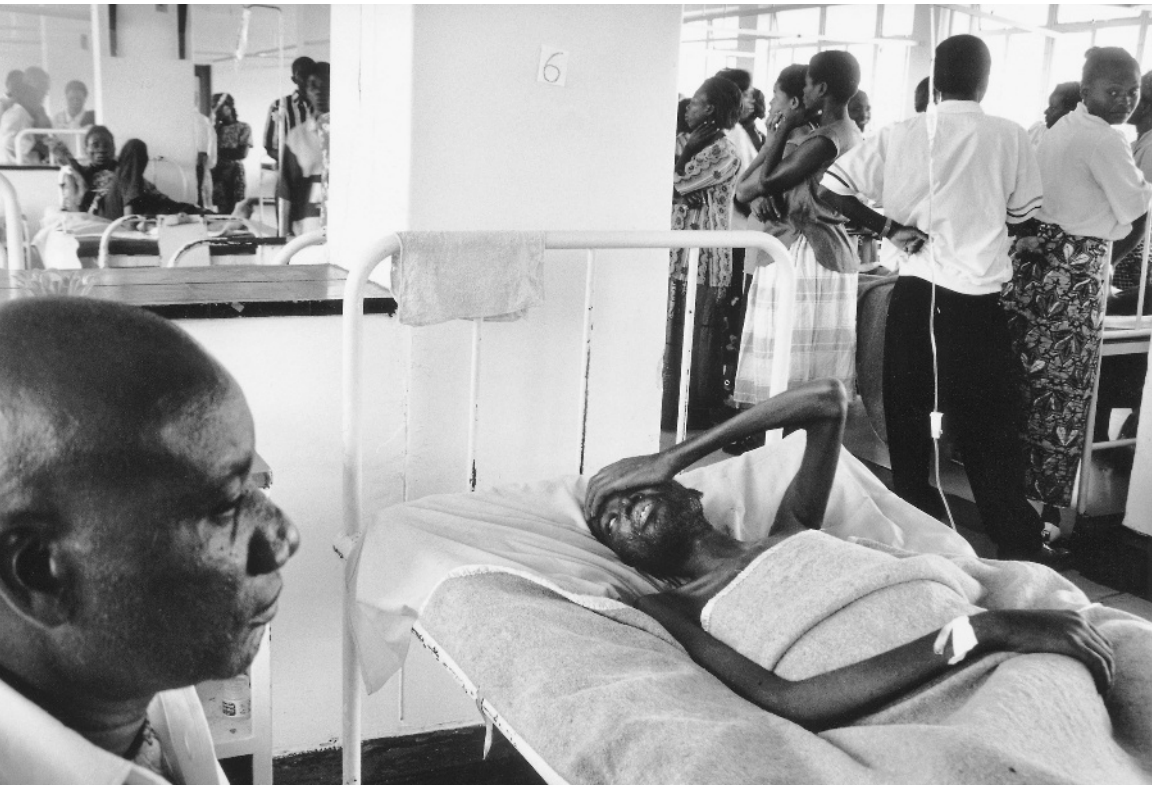
Onset of AIDS and Decline

No matter how strong an immune response the body mounts, most HIV-positive individuals can achieve only temporary control over the virus. The number of helper T cells that would normally aid in the production of antibodies to fight the infection gradually declines, weakening the immune response. This allows the virus to gain a stronger foothold in the body. The concentration of HIV in the blood increases, and subsequently more T cells are infected and killed. As the cycle continues, the infected individual suffers more infections and other health problems. Interestingly, there seems to be a correlation between the level of viral concentration during latency and the length of the dormant period: the higher the concentration of blood HIV in latency, the more rapidly the patient will progress to AIDS.

The point at which doctors say an HIV infection has turned into AIDS is defined by a patient meeting criteria set by the CDC. According to the CDC's current definition, a person is considered to have AIDS when he or she tests positive for HIV and has either a helper T cell count of less than two hundred cells per milliliter of blood (normal levels are between five hundred and eighteen hundred) or has at least one opportunistic infection. The most common opportunistic infections included in the CDC's definition of AIDS are some that had been diagnosed in the earliest AIDS patients: *Pneumocystis carinii* pneumonia (PCP); Kaposi's sarcoma (KS); cryptococcosis; yeast infections (Candidiasis) of the esophagus, trachea, bronchi, or lungs; cytomegalovirus disease (CMV); and toxoplasmosis of the brain.

Once AIDS develops, the patient can rarely survive more than two years without treatment from drugs designed to combat HIV. In the late stages of AIDS, the body is left without an immune system. Practically all the helper T cells are eliminated, rendering

A Zambian man sits at the bedside of a loved one in the final stages of AIDS. At this point, the disease has left the patient with virtually no immune system.



the immune system unable to produce antibodies against infections. The body can no longer mount an immune response, even to the mildest pathogens. Even when antibitotics and other drugs are administered, opportunistic infections run rampant. Eventually, the effects of the infections kill the patient.

Avenues for Treatment

With greater understanding of the way HIV infection affects the body and how it develops into AIDS, researchers have found potential avenues for treatment. For example, having identified HIV as a retrovirus, scientists have been able to use the particular characteristics of this type of virus against it. Although they have yet to find a drug that kills HIV, they have made strides in developing drugs that slow the virus's growth. With the advent and development of these and other drugs, doctors believe they are on the verge of converting AIDS from a terminal illness to a chronic, yet manageable, disease.

Chapter 3

New Weapons Against HIV

On April 23, 1984, Secretary of Health and Human Services Margaret Heckler announced that the virus that caused AIDS had been discovered and that scientists had perfected a process that enabled them to grow large quantities of the virus in order to study and characterize it. She also declared, "We . . . believe that the new process will enable us to develop a vaccine to prevent AIDS in the future. We hope to have such a vaccine ready for testing in approximately two years."[21] Her final prediction was that "there will be a . . . cure for AIDS before 1990."[22] Unfortunately, for the thousands of AIDS victims, families, and others who dealt with the human tragedy of the disease every day, Heckler's predictions were far too optimistic.

Two decades later, Heckler's words still echo as a constant reminder of how much more complicated HIV has proven to be than scientists first estimated. As of 2004, HIV vaccines were still in development, over 22 million people worldwide had died of AIDS, and there was no cure in sight.

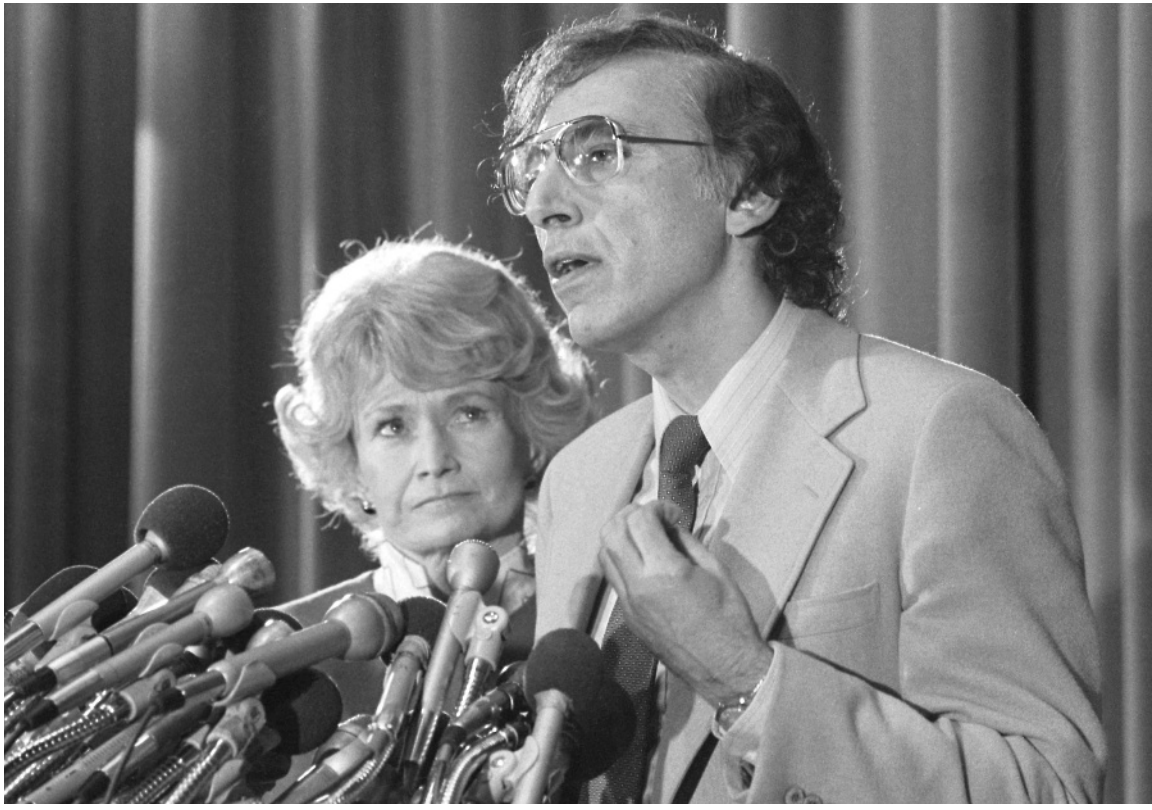
In the years following Heckler's announcement, it became increasingly clear that finding a cure would not be the straightforward task she had outlined. Nevertheless, research into treatments moved forward, and by 1987, the first AIDS drug, AZT, was approved for use by the FDA. This was soon joined by many other drugs; as of 2004, almost two dozen medications had been approved to treat HIV infection. Though none of these drugs cure HIV, they greatly increase patients' survival time and improve their quality of life.

Stopping the Cycle

In 1985, Dr. Hiroaki Mitsuya of the NIH demonstrated that the drug AZT was able to inhibit the replication of retroviruses, the family of viruses that HIV belongs to, at least in laboratory cultures. Mitsuya believed that AZT could also be effective in human AIDS patients.

AZT represents the first of a class of drugs known as nucleoside reverse transcriptase inhibitors (NRTIs). These drugs control HIV by interfering with the action of proteins essential to the virus's life cycle. Since HIV is a retrovirus, all of its genetic information is stored as a single strand of RNA. In order for HIV to function, it

In April 1984, Secretary of Health and Human Services Margaret Heckler, appearing here with Dr. Robert Gallo, announces the discovery of the virus that causes AIDS.



In the mid-1980s AIDS patients bearing the lesions of Kaposi's sarcoma took hope in AZT, a drug that in laboratory tests inhibited the replication of HIV.

has to convert its RNA into DNA. To accomplish this task, HIV uses chemical compounds, called nucleosides, found inside the cells it infects, as well as a protein called reverse transcriptase.

As part of its life cycle, a healthy cell normally makes DNA from nucleosides, which float freely inside the cell. Upon infection, HIV immediately begins to make the DNA it needs, using the cell's own nucleosides as the building blocks. Reverse transcriptase, using a

strand of the virus's RNA as a template, determines the order in which to assemble those nucleosides to form a strand of DNA. When viral DNA is produced, HIV proteins can be made, leading to the production of new HIV particles. The new viral particles bud off the infected T cell and are released into the bloodstream.

Early studies suggested that AZT did indeed benefit HIV-positive patients. The drug interferes with reverse transcriptase's ability to convert viral RNA to DNA. When AZT enters a cell, it is transformed into a chemical compound that closely resembles a nucleoside—closely enough to fool reverse transcriptase. When the protein mistakenly tries to use this false nucleoside, however, DNA synthesis is halted, meaning that viral replication cannot continue. As a result, HIV cannot infect additional cells. According to Dr. Samuel Broder, director of the National Cancer Institute, who tested AZT in laboratory cultures of HIV-infected cells and demonstrated the drug's apparent interference with viral replication, "Attacking the virus by this unique enzyme has given us a foundation stone on which we can build new therapies and combination therapies, hopefully ultimately developing a cure for HIV infection."[23]

Upswing

Despite the effectiveness of AZT, scientists said from early on that this drug was not the final answer to the HIV puzzle. Dr. Robert Windom of the Department of Health and Human Services urged in 1986 that people be cautious in their optimism: "This is not a cure. We don't want to overpromise to the thousands of people who have AIDS."[24] Still, AZT offers many benefits to those infected with HIV. Because it greatly reduces the virus's ability to self-replicate, the decline of the immune system is slowed. Opportunistic infections, as a result, are greatly reduced. In addition, when taken during pregnancy, AZT reduces the risk of HIV transmission from pregnant mother to fetus. Studies have also shown that the earlier AZT is taken, the more effective it is. According to Dr. Jerome Groopman of the New England Deaconess Hospital regarding a 1989 study, "This is the first clear proof that early intervention makes a difference. It's exciting, and it's a finding of real importance."[25]

Scientists saw AZT as the basis for developing even more effective drugs. In 1989, for example, Broder said, "AZT is analogous to saying the Wright brothers can fly. The Wright brothers did not design the 747 that you can fly to Europe. AZT has made it possible to see that something can work against the retrovirus that causes AIDS."[26] In the years since the successful trial of AZT, other NRTIs have been developed, including ddC, ddI, d4T, and 3TC. Though all the drugs work on the same principle, they each interfere with reverse transcriptase in a slightly different way.

Broken Promise

Continuing research on NRTIs and other treatments was and remains vital. For one thing, the toxic side effects of these drugs on healthy cells are undeniable. To a certain extent, the drug interferes with the normal cellular processes in healthy tissue as well, which leads to tissue damage. For example, even in the earliest trials, patients suffered significant reductions in their red and white blood cell counts from damage to bone marrow. In fact, so severe are side effects like nausea, anemia, diarrhea, liver damage, nerve damage, and bone marrow damage that many patients—between 40 percent and 80 percent of AZT users—are forced to discontinue treatment.

Moreover, NRTIs are only able to slow replication of HIV, not stop it completely. This means that the virus is able to linger, waiting for an opportunity to strike. That opportunity often presents itself due to HIV's notorious adaptability.

As happens in all living things, random mutations arise whenever HIV's genetic material is copied. Usually, the mutations do not have significant effects, but every once in a while, a mutation will occur that changes HIV's ability to survive under adverse conditions. In the case of NRTIs, HIV's reverse transcriptase changes to the point where it is no longer fooled into using the false nucleoside during DNA synthesis. This means viral replication is able to continue, and in each replication cycle, the beneficial mutation is passed on to more viral particles. Eventually, a single NRTI by itself ceases to limit HIV replication.

A New Class of Drug

The limitations of NRTIs forced scientists to scramble to find something else to fight HIV. By 1994, researchers at pharmaceutical companies had found another class of potentially beneficial compounds, called protease inhibitors. These compounds interfere with the action of a protein called protease, which, like reverse transcriptase, plays an important role in the life cycle of HIV.

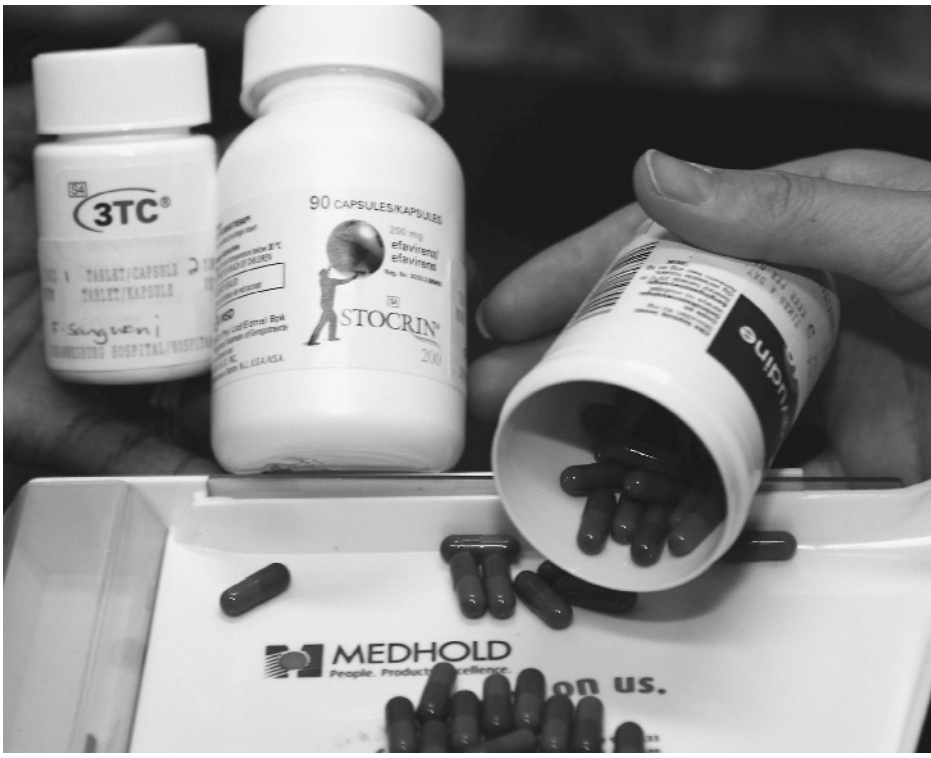
Protease inhibitors interfere with a later step in HIV's life cycle than NRTIs do, but the net effect is the same: The virus cannot replicate as efficiently. The first protease inhibitor, saquinavir, was approved for use by the FDA in December 1995. Since then, four other protease inhibitors have been approved: ritonavir, indinavir, nelfinavir, and amprenavir. Scientists initially thought that these drugs could do more than simply slow replication, as AZT and other NRTIs did, and stop HIV from replicating altogether. At first, the results looked promising. A 1996 study using ritonavir showed that over the seven months of the drug trial, the death rate due to AIDS was cut in half when ritonavir was administered. Unfortunately, the effects were temporary, just as they had proven to be for NRTIs. In fact, it often took less than a month for some resistance to these protease inhibitors to develop. The resistant HIV particles would then reproduce and continue to degrade the patient's immune system.

In addition, the side effects of protease inhibitors could be just as debilitating to patients as those of NRTIs. Nausea, abdominal pain, vomiting, and diarrhea are common; kidney toxicity, liver damage, pancreas problems, and headache can also be severe, sometimes even life threatening.

A Growing Arsenal

While protease inhibitors were being developed and tested, another class of drug also became available for use against HIV. Similar to NRTIs, these drugs also interfere with reverse transcriptase activity to prevent viral replication. Instead of mimicking nucleosides to fool reverse transcriptase, however, these drugs physically block reverse transcriptase. They are known as nonnucleoside reverse transcriptase inhibitors (NNRTIs).

The first NNRTI approved by the FDA in 1996 was called nevirapine. Once again, clinical trials showed that patients who took only nevirapine quickly developed drug resistance, and side effects similar to the other classes of anti-HIV drugs were also observed. Scientists, however, learned something new about anti-HIV drugs: When nevirapine was given to patients in combination with other anti-HIV medications, drug resistance took much longer to



Today doctors prescribe a cocktail of multiple drugs to AIDS patients. Research has shown that it takes much longer for HIV to mutate enough to develop resistance to all the drugs in the cocktail.

occur. One clinical trial, for example, showed that when nevirapine was combined with AZT and ddI, the treatment was significantly better at reducing HIV levels and increasing helper T cell counts than treatments using AZT and ddI only.

Cocktail Hour

The realization that a single drug cannot control HIV as well as a multidrug approach can has proven to be a major breakthrough in AIDS research. When doctors attack HIV simultaneously with combinations of NRTIs, NNRTIs, and protease inhibitors, the virus is unable to mutate fast enough to develop resistance to all the drugs at once. Says Dr. Dani Bolognesi, chief executive officer of the pharmaceutical manufacturer Trimeris Corporation, "HIV so

far has been able to resist anything. There are so many viral variants that the chance that one can overcome a specific inhibition is certainly there. We now combine a number of different inhibitors that operate under different mechanisms so the chance that HIV replicates and spawns a variant that is resistant to all are low."[27]

How patients respond to the cocktail therapies varies. Some patients on the new therapies have proven to be unable to tolerate the combination of powerful drugs; others get no benefit from the treatments. In a number of patients, however, the drug cocktail is so effective in eliminating HIV from the blood that doctors consider their patients in remission. According to Dr. Paul Volberding of San Francisco General Hospital, "We have seen patients whose viral load has gone below our ability to find it."[28]

Some successes with drug cocktail treatments are dramatic. For example, in July 1995, thirty-seven-year-old Dan Cusick was told that an AIDS-related illness would probably kill him by October. His doctors, however, prescribed a three-drug cocktail, and within weeks tests could no longer detect even trace amounts of HIV in

An AIDS patient hugs his nurse after learning that, following treatment, his body shows no trace of HIV.

Cusick's blood. Similarly, fifty-four-year-old John Rife's immune system was so weakened that opportunistic infections ranging from virulent pneumonia to AIDS-related cancers ravaged his body. Within a month of starting the drug cocktail, Rife's cancer was gone, and HIV levels in his blood were undetectable as well.

Starting Early

As effective as the drug cocktails have proven against HIV, some scientists hope for more—that combination therapy can completely eliminate HIV. One such scientist is the previously mentioned Ho. As early as 1994, Ho tested his theory that patients who were treated early on in HIV infection—during clinical latency—could benefit more from combination therapy than the patients who usually receive these treatments—those who had already developed AIDS. For his study Ho chose twelve men whose helper T cell count had dropped below five hundred cells per milliliter of blood, but was still higher than the count of two hundred that signifies the onset of full-blown AIDS. He then treated these patients with a combination of AZT, 3TC, and a protease inhibitor, either indinavir or ritonavir. Three of the participants had to withdraw from the trial early due to adverse reactions to the drugs. At the 11th International Conference on AIDS, however, Ho revealed that the nine men who remained on the therapy showed no evidence of HIV in their blood within three months of commencing treatment. As Ho explained to the conference attendees, his results prove that it is "time to hit HIV, early and hard."[29]

The Possibility of Eradication

The effectiveness of combination therapy, now referred to as highly active antiretroviral therapy (HAART), offers some hope that the Holy Grail of AIDS research, a cure, may be in sight. As studies were conducted that followed patients' progress as they underwent combination therapy, it became clear that HAART remains effective for years rather than months, as is the case when single drugs are administered. Many scientists, including Ho, propose that effective HAART could lead to the eradication of HIV from an infected individual's body. However, HIV's ability to remain

hidden in reservoirs continues to be problematic. As Ho explained in a 1997 interview:

> The available therapies have helped us eliminate over 99 percent of the virus in infected individuals. But we are learning about additional viral compartments. In our patients who have been treated very early and very hard, and have received this treatment two years now, we are still finding a residual pool of virus resting in certain CD4 cells, in a very quiescent way. This poses a new obstacle to deal with.[30]

Since even single copies of the virus can infect new cells to produce thousands of additional viral particles, anything less than 100 percent elimination cannot be considered a cure.

Adding to the challenge is that HAART often has severe side effects, making it impossible for many patients to continue taking the drugs indefinitely. In addition, scientists have not completely identified the effects of prolonged HAART on killer T cells. Although in the short term the treatment is clearly beneficial, evidence has surfaced about the toxicity of HAART on other immune system components. Finally, there is the possibility that, as toxic as HAART treatments are, they might need to be strengthened in order to keep working. One of Ho's collaborators, Dr. Linqui Zhang, noted, "It is sobering to realize that the so-called highly active antiretroviral therapy is actually not always active enough. As we strive to eradicate HIV-1 infection or induce a remission, we must focus on the possibility of further intensifying antiretroviral treatment, even though current therapies are already toxic, costly and complex."[31]

The Road Ahead

Researchers continue to strive for refinements to HAART. One such refinement is reducing the complexity of HAART regimens, making it easier for people to adhere to them. For example, in Zerit XR, which received FDA approval in 2002, a day's worth of therapy is contained in a single pill. Though Zerit XR must be combined with other anti-HIV drugs to be effective, many others are becoming available in once-daily or twice-daily formulations.

The success of HAART, however, has in some ways hurt efforts to prevent the spread of HIV. According to Dr. Jessie C. Gruman, executive director of the Center for the Advancement of Health, "Because HIV/AIDS is no longer an assured death sentence, new issues in disease management have arisen—cost and adherence. The success of new treatments presents an additional challenge, helping patients keep from returning to risky behaviors that could spread the disease anew."[32]

Living with HIV

Even with powerful HAART drugs, there is a considerable amount of variability among AIDS patients in the way the disease affects their quality of life. Some are so debilitated by the disease that holding a job or performing household chores becomes impossible,

This South African AIDS patient (right) responded so well to drug treatment that today she is able both to support herself and to volunteer as an HIV/AIDS campaigner.

whereas others may go for long periods of time where they function normally, only to succumb to a single severe opportunistic infection.

Still, many HIV-positive individuals find HAART invaluable. People, such as San Francisco hairdresser Puck, who had been given months to live, now look forward to much longer lives. Puck was once in search of a way to pay his final medical bills; after he began HAART treatment, however, his disease came under control and his thoughts turned from final expenses to saving for his retirement.

As the lives of people with AIDS have been extended by HAART, a new dilemma has emerged: where to find the funds to pay for the expensive treatments. In many cases, health insurance policies do not cover HAART, and patients have had to go deep into debt to pay for the medications they need. In 1990, Congress created the AIDS Drug Assistance Program (ADAP) to subsidize the cost of HIV and AIDS treatment. However, as the demand for treatment increases, people are turned away because of budget constraints. In 1996, ADAP had set aside $188.5 million; by 2002, the budget had increased to $878.6 million, and still, there are insufficient funds to help all who applied. There is, however, hope that economics will no longer be an issue for patients who seek HAART. Since 2000, the cost of HAART in the United States has dropped from ten thousand dollars per patient annually to approximately three hundred dollars. The challenge going forward will be to provide effective anti-HIV treatment to people around the world, especially in developing countries, where even today's relatively modest prices make AIDS drugs completely unaffordable.

Chapter 4

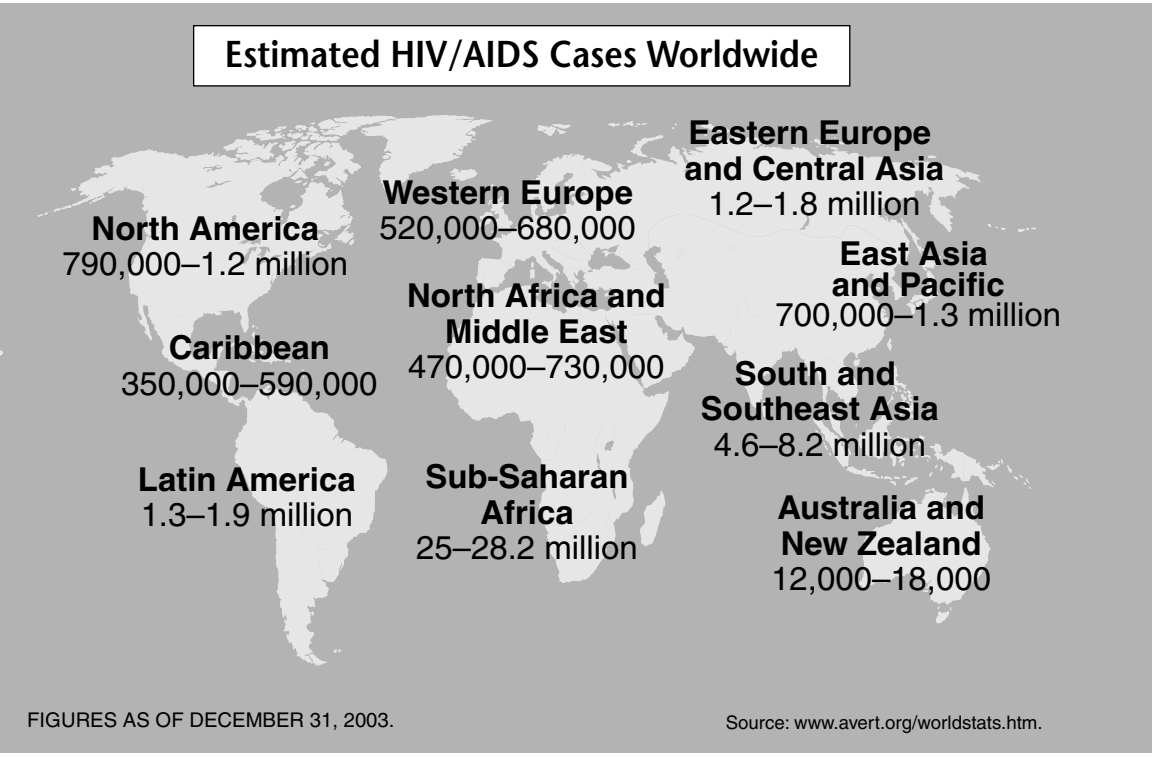
A Global Epidemic

THOUGH HAART HAS been successful in treating HIV infection, in reality, this therapy is available mainly to people in wealthier nations such as the United States and those in western Europe. In other places, such as Africa and Asia, where the epidemic is growing at an alarming rate, people simply cannot afford expensive HAART drugs, even at the reduced prices now being offered. Education and prevention efforts, which have slowed the spread of HIV in some parts of the world, have also been a challenge to implement in the developing world where cultural barriers, paired with the lack of access to educational materials, often thwart prevention efforts.

Bleak Prospects

According to a 2003 Joint United Nations Program on HIV/AIDS (UNAIDS) estimate, there are over 40 million people worldwide living with HIV or AIDS. Over 28 million of these cases are found in sub-Saharan Africa alone. In fact, all the HIV and AIDS cases in North America, Europe, and Central Asia combined account for fewer than 10 percent of the global total.

In places such as the United States and the nations of western Europe, the spread of HIV has often been reduced through public safety efforts and public education campaigns. For example, the blood supply in the United States is screened for HIV. This has reduced the rate of HIV transmission from blood transfusions to almost zero. Similarly, other preventive measures have curbed infection rates. As Americans were informed that the use of condoms during sexual activity reduced the risk of HIV transmission, a great majority of the population took the advice seriously. Likewise, public policy initiatives such as needle exchange



programs helped reduce the spread of HIV among intravenous drug users.

The problem, however, is that all too often in the developing world, similar measures are not used. Sex education in any form is rare in many parts of the developing world. Consequently, a great number of people there lack even a basic understanding of how HIV is spread. Misconceptions arise and proliferate, often with devastating results. For example, when some prostitutes in Kenya learned that, in Africa, HIV was transmitted mainly through heterosexual contact, they began to offer their clients unprotected anal intercourse, since they considered this to be homosexual contact and thus safe. In reality, anal sex is even more likely to result in HIV transmission, so the virus spread even more easily. Other unsafe practices, including needle sharing, are similarly unrecognized and therefore uncurbed in much of the developing world. As a result, HIV infection due to intravenous drug use is increasing in many parts of the world.

The African Epidemic

Among the regions hardest hit by AIDS is Africa. Seven African countries now report that 20 percent or more of their citizens are infected with HIV. In South Africa, experts estimate one in five adults is infected, while in Botswana and Zimbabwe the estimates are one in three and one in four, respectively. One of the reasons that sub-Saharan Africa is so devastated by HIV is that the public health systems in these countries are ill-equipped to treat any kind of epidemic, least of all one that produces so many victims requiring expensive and complicated long-term care. As a consequence, average annual health care spending per person in Africa is estimated by the World Bank to be thirty-four dollars, as compared to the twenty-five-hundred-dollar average spent in developed countries such as the United States. Given the lack of funds, it is highly unlikely that African countries can buy and distribute the HAART drugs necessary to prolong the lives of their HIV-infected population, even at the reduced prices that many pharmaceutical companies have promised.

Contributing to the AIDS crisis in Africa is a tendency among many African leaders to ignore the epidemic. Not a single African head of state or government attended the 11th International Conference on AIDS in Zambia in 1999. Even the president of Zambia, Frederick Chiluba, who officially hosted the event, failed to show up. This inattention came in spite of the fact that the same year, 1999, marked the first time that President Daniel Arap Moi of Kenya and President Robert Mugabe of Zimbabwe used the word *disaster* to describe the AIDS epidemic.

An initial failure to grasp some basic facts about AIDS exacerbated the problems in Africa. For example, South African president Thabo Mbeki for many years publicly questioned the link between HIV and AIDS and opposed efforts to develop a national plan to provide antiretroviral drugs to South Africans. It was not until 2003 that former American president Bill Clinton and others convinced Mbeki to change his position and support anti-HIV drug programs.

Partly as a consequence of their leaders being misinformed or in denial, the average person in Africa, especially in rural areas, does not know basic facts about HIV and AIDS; even many of those dying of AIDS do not understand what is killing them. The tragedy goes beyond the individuals struck down by AIDS: Because the epidemic has become so widespread, over 10 million African children have been orphaned by AIDS. Experts estimate this number could reach 30 million by 2010. Many of these orphans are themselves infected with HIV, and, left to fend for themselves, many face a bleak future.

In the past, South African president Thabo Mbeki (center) and other African leaders had ignored the AIDS epidemic, allocating few resources to help prevent the spread of the disease. This trend is beginning to change.

HIV in Asia

As compared to Africa, statistics seem to suggest that Asia has yet to feel the full effects of the AIDS epidemic. After all, only Cambodia, Thailand, and Myanmar have infection rates above 1 percent, and India boasts an infection rate of 0.7 percent. These statistics, however, are only part of the story. Given the large populations in Asian countries, even the low percentages translate into huge numbers of HIV-infected individuals. There are now an estimated 7 million people in Asia living with HIV.

Experts find the trend in HIV incidence in Asia at least as troubling as the actual numbers. As Dr. Peter Piot, executive director of UNAIDS, warned, "The epidemic in Asia threatens to become the largest in the world. . . . With more than half the world's population, the region must treat AIDS as an issue of regional urgency. The question is no longer whether Asia will have a major epidemic, but rather how massive it will be."[33] Though the Asian population at large remains relatively free of HIV, a large percentage of intravenous drug users and sex workers are now infected with the virus. In some areas, the HIV incidence in these groups is at least 20 percent and can be as high as a staggering 80 percent. Such high rates of infection mean that serious HIV outbreaks could happen at any time. According to UNAIDS, "Injecting drug use and sex work are so pervasive in some areas that even countries with currently low infection levels could see epidemics surge suddenly."[34]

As in Africa, most Asian countries have not adequately educated their citizens about HIV and AIDS. Although sexual intercourse is the major means of HIV transmission in Asia, many people do not know to take basic precautions such as using condoms during intercourse to prevent the spread of HIV. However, in the countries that have taken measures to educate the public, there has been notable success. In Thailand and Cambodia, where large government-sponsored programs to promote the use of condoms are in effect, HIV incidence is actually on the decline.

Potential Problem Areas

Though Africa is by far the region hardest hit by HIV, and Asia is considered by experts to be where the next massive AIDS outbreak

Dracula appears in an antidrug and AIDS awareness poster in Vietnam. Medical professionals fear that a massive epidemic will occur in Asia in the near future.

will strike, there are many other regions of the world at risk from HIV. As is the case with Asia, there is an overall low rate of HIV infection in Latin America, but experts feel that an epidemic may explode at any time. A 2003 study reported that though HIV is still concentrated in high-risk populations, such as prisoners, intravenous drug users, commercial sex workers, and homosexual men, the virus is slowly spreading to the general population. In some

places such as Honduras and southeastern Brazil, HIV is already present in the population at large.

The countries of the Caribbean do not account for a large number of worldwide HIV infections, but as a percentage of the population, HIV now infects over 2 percent of the adults in the region. Certain countries are far more beleaguered by the disease; Haiti, for example, reports HIV incidence levels of 5 percent to 6 percent. In general, the virus is poised to spread to the larger Caribbean population if effective prevention programs are not put into place.

In many of these areas where HIV is becoming increasingly problematic, social isolation and discrimination prevent adequate treatment or education. Homosexual men and commercial sex workers, for example, often are stigmatized and as a result tend to be overlooked by those offering HIV care or counseling. Developing nations face the dual challenge of overcoming social stigmas accompanying high-risk lifestyles as well as misconceptions surrounding HIV in order to keep the spread of the virus in check.

Women at Risk

Throughout the developing world, women are at the highest risk of contracting HIV. In part, this is due to social custom. Heterosexual contact is the primary mode of HIV transmission in these areas, and in what are often male-dominated cultures, women are often ignored if they demand that their partners use condoms during intercourse. In addition, some of the most reliable preventive measures can stigmatize those who use them. According to Karungari Kiragu of Johns Hopkins University, "If women demand condoms to be used, [it] means they must have been running around."[35]

The higher risk for women is especially pronounced in Africa. According to UNAIDS, African women are 1.2 times more likely to be infected with HIV than men; among women age fifteen to twenty-four, the ratio increases to 2.5 times more likely to be infected with HIV. Cultural traditions such as wife inheritance, whereby a brother-in-law marries his brother's widow, also place women at greater risk. Said Kiragu, "The problem is, if the new

husband has HIV, the woman may not know and may not have a choice [to refrain from sexual activity] anyway."[36]

Another reason that women are particularly at risk is that it is much easier to transmit the virus from a man to a woman than the other way around. The sensitive tissues of the vagina and cervix can easily be bruised and torn during intercourse; these small cuts and abrasions make it easier for HIV to enter the body. On the other hand, penile tissue does not sustain the same amount of damage and therefore does not as often present open cuts through which the virus can enter.

Even in areas where some types of HIV transmission have been stemmed, women remain at risk. For example, through well-funded and politically supported prevention programs, Thailand reduced the number of new HIV infections from 143,000 in 1991 to 29,000 in 2001. Women, however, are still disproportionately infected during heterosexual contact with their husbands, boyfriends, and, in the case of sex workers, clients. Many of these women are the partners of intravenous drug users who have contracted HIV through infected needles. Though this is a large problem, the Thai government has yet to prioritize prevention programs for drug users, and HIV continues to spread in the population of drug users and their sexual partners.

From Mother to Child

With the numbers of HIV-infected women on the rise, the problem of mother-to-child transmission (MTCT) of HIV is becoming more serious as well. In fact, MTCT is responsible for over 90 percent of the HIV infections in children under age fifteen.

HIV can be transmitted from an infected mother during pregnancy, during childbirth, or after birth through contaminated breast milk. The risk of transmission is approximately 15 percent to 30 percent, even if a mother does not breast-feed her infant. When infected mothers breast-feed, however, the risk of HIV transmission to their babies rises to 25 percent to 50 percent. Approximately six hundred thousand HIV-infected infants are born each year around the world, with over 90 percent of these infections taking place in sub-Saharan Africa.

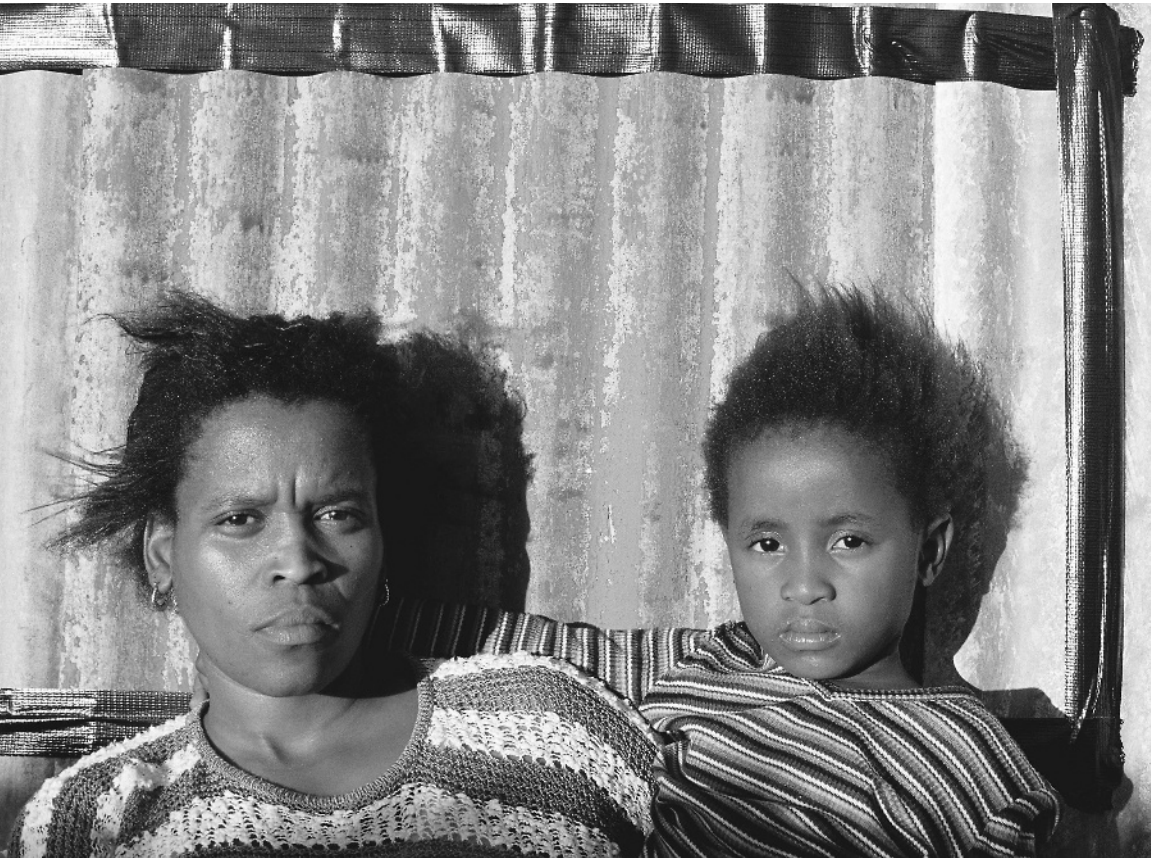
An African man comforts his sister, who is terminally ill with AIDS. Women in developing nations are more likely to develop AIDS than men.

There is hope, however, for curbing MTCT. In fact, through education, counseling, access to antiretroviral drugs, safe delivery practices, and the availability of breast-milk substitutes, MTCT has been virtually eliminated in the developed world. Taking antiretroviral drugs, including nevirapine and AZT, can reduce the risk for MTCT dramatically when administered during pregnancy, during labor, and soon after birth. In addition, the use of breast-milk substitutes eliminates the risk of MTCT through breast milk. Unfortunately for the women at greatest risk, that is, women in the developing world, drugs are not always available, and often

the women do not even know to seek treatment. In addition, many of them do not have access to clean water for mixing infants' formula, thus limiting their ability to avoid breast-feeding.

A number of groups, including the United Nations Inter-Agency Task Team on MTCT and several private foundations, have put programs into place to reduce MTCT. These programs currently include pilot projects in Botswana, Brazil, Burundi, Cambodia, Côte d'Ivoire, Honduras, Kenya, Rwanda, Thailand, Uganda, the United Republic of Tanzania, Zambia, and Zimbabwe. Along with counseling and education, drugs such as nevirapine are now being of-

This South African woman learned of her own HIV infection when her daughter (right) was born HIV-positive. Mother-to-child transmission of the disease has declined significantly in developed countries.



fered free of charge to developing countries. This is vital to the effort to stop the spread of HIV and could potentially save the lives of three hundred thousand children each year. Still, the most effective way to prevent MTCT remains to protect women from HIV infection in the first place.

Headway

In light of the wealth of new information about HIV's incidence and treatment, many developing countries have stepped up their efforts to address the AIDS crisis. India, for example, with at least 4 million reported cases of HIV infection, has instituted a number of national programs to stanch the spread of the disease. The National AIDS Control Organization (NACO) is actively upgrading the Indian blood-banking industry to prevent the spread of HIV through infected blood, as well as establishing countrywide HIV testing centers to give people an opportunity to learn their HIV status. NACO's goals also include the institution of public education programs about HIV and AIDS, aimed especially at young people and commercial sex workers, as well as financial assistance for HIV research within India.

The governments of South Africa and China, both of which spent years downplaying the risks of AIDS to their citizens, announced in 2003 that their governments would provide antiretroviral drugs to anyone who needed them. This represents a $680-million-a-year commitment by these countries to buy HIV drugs and to set up the health care infrastructure to administer them properly.

Help from Abroad

For the most part, however, since the countries that are most devastated by HIV are often also the poorest ones, government-funded national programs to combat HIV and AIDS can only go so far in dealing with the problem. Experts feel strongly that it will take a global approach with humanitarian efforts by wealthier nations and organizations to get a handle on the AIDS crisis.

To that end, a number of groups have endeavored to battle AIDS around the world. UNAIDS was founded in 1996 to pool resources from several agencies including the World Health Organization;

the UN Children's Fund; the UN Development Program; the UN Educational, Scientific, and Cultural Organization; the UN Fund for Population; and the World Bank. The projected overall UNAIDS 2004–2005 budget exceeds $522 million, with more than $200 million pledged by the United States. Said Piot, "I feel strongly that this year, we really are entering a new phase of the global response. . . . There is a growing political momentum never seen for any public health problem, and indeed rarely for any international issue."[37] Even with this increased global response, unfortunately for the victims of HIV and AIDS, UNAIDS projects that it will need at least $10 billion annually to fight AIDS in the developing world.

Private foundations have joined in the battle against AIDS in an effort to reduce that gap between the money pledged by various nations and the money that is actually needed. The Bill and Melinda Gates Foundation, for example, has committed over $500 million to curtail the spread of HIV and to treat HIV-positive individuals around the world, including a 2003 pledge of $200 million over five years to India. The Clinton Foundation, established by former American president Bill Clinton, has arranged for antiretroviral drugs to be made available at low cost or no cost in developing countries. For example, thanks to the Clinton Foundation's intervention, four Indian drugmakers will begin producing these drugs for only $140 per patient annually. A similar plan has been put into place in Africa and in the Caribbean through the efforts of the Clinton Foundation.

The Cost of Health

With all antiretroviral drugs or other HIV treatments, cost is always a concern. At the current spending rates, billions of dollars annually will be necessary to treat the global AIDS crisis. In 2003 alone, an estimated $4.7 billion was spent by governments, global organizations, private foundations, and individuals on AIDS treatment and prevention. There is, however, no end in sight. Unless prevention and education programs soon become much more successful, the total cost of the AIDS crisis has the potential to become destructive to the economies of the nations hardest hit. Said Jose

UNAIDS director Peter Piot speaks to journalists in Cape Town, South Africa, on June 5, 2001, the twentieth anniversary of the first reported case of AIDS.

M. Gatell, cochair of the 14th International AIDS Conference, "Access to life-saving medicines is not a gift or a commodity but a basic human right, in fact one of the most basic human rights."[38] In light of this, scientists have realized that an HIV vaccine is essential to ensure that AIDS will no longer be a threat.

Chapter 5

The Dream of a Vaccine

DESPITE ALL THE research that has gone into developing treatments for HIV and AIDS, many experts believe that prevention of HIV infection in the first place remains the best hope for halting the epidemic. To that end, experts believe that an HIV vaccine is required since, historically, only vaccines have been able to eradicate a given disease. As Sam Avrett, the associate scientific director of the International AIDS Vaccine Initiative (IAVI), explained:

> Vaccine research is critical because a vaccine is one of the best foreseeable ways to control the AIDS epidemic, both in the U.S. and around the world. Anyone who has worked in HIV prevention knows that, while behavioral change and condoms and clean needles go a long way toward preventing HIV, staying uninfected is hard. . . . Although behavior change can do a lot, it is just not realistic to expect individual behavior change, by itself, to control this epidemic.[39]

Some experts hope that not only might HIV vaccines prevent infection, but that because they boost the immune system, many of the vaccines in development might also be therapeutic. In other words, even in HIV-positive individuals, vaccination could have a positive effect by keeping an HIV infection from developing into AIDS.

The financial commitment of governments and private foundations is one measure of the importance policy makers place on vaccine research. In the United States alone, some $456.3 million is earmarked for HIV vaccine research in 2004. Experts believe that

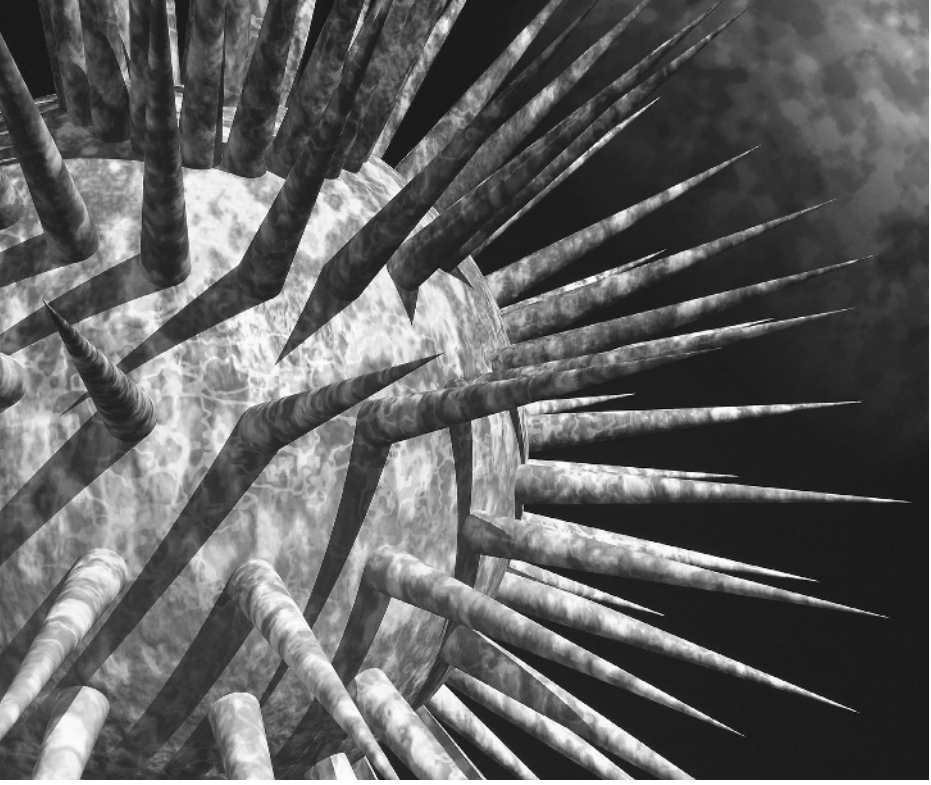
the amount of money spent will continue to increase disproportionately to other components of HIV research because of the great value of effective HIV vaccines. Vaccine development, however, has not been a straightforward endeavor; after decades of research, although a number of different approaches have been identified, there has been no definitive success.

Starting Point

In the 1980s, when scientists first began to search for a vaccine to prevent HIV infection, they approached the problem as they had for other diseases such as polio: first cripple the virus, and then use the crippled virus to train the body's immune system to deal with the real infection. With polio, the crippled virus was inactive, and the vaccination was safe—that is, there was no chance that the vaccination would cause the disease it was supposed to prevent. For the most part, scientists felt that it would be fairly easy to develop an HIV vaccine. As Gallo recalled in 2001, "I thought it would be exceedingly difficult to get new therapy against HIV; [I] thought [it would be easier] to get a vaccine."[40] Gallo now admits that he and many others were wrong. In the case of HIV, the virus has proven far too complicated for the traditional approach to work; it mutates so rapidly and produces so many viral variants that vaccinating a patient against one strain will not necessarily confer immunity against all forms of HIV. It requires a deeper understanding of HIV at a molecular level for a successful vaccine to be developed.

With further research, many molecular details of HIV have been revealed and understood. Scientists have discovered the structure of the virus and the way that HIV latches on to helper T cells. The virus's ability to mutate and the extent of the mutations are better understood. With the new information, slow progress has been made toward vaccine development.

By the early 1990s, scientists had begun to see initial successes in animal subjects. For example, in 1990, three groups of scientists at Immuno AG in Vienna, Genentech in south San Francisco, and the Pasteur Institute in Paris were able to use HIV vaccines to protect chimpanzees from infection. Building on these initial triumphs, vaccines for humans were soon ready to be tested.



Pictured is a computer-generated image of a virus. Like all viruses, HIV's outer protein coat is studded with protein spikes, allowing it to bind to host cells before infecting them.

Early Disappointments

In 1992, human clinical trials of AIDSVAX, a vaccine developed by a California company called VaxGen, began. Specific for strains of HIV common in North America, AIDSVAX was made of synthetic proteins that are copies of a protein found on the surface of HIV. This surface protein, called gp120, facilitates the binding of HIV to helper T cells. AIDSVAX essentially tricked the immune system into mounting an immune response against the synthetic gp120 proteins, even though there was no accompanying HIV infection. Since only gp120 viral proteins are introduced, patients could not get AIDS from the vaccine. Rather, the hope was that the vaccine recipient would get a head start in developing HIV-specific antibodies, and presumably, real HIV particles would be destroyed in the bloodstream before infection could occur.

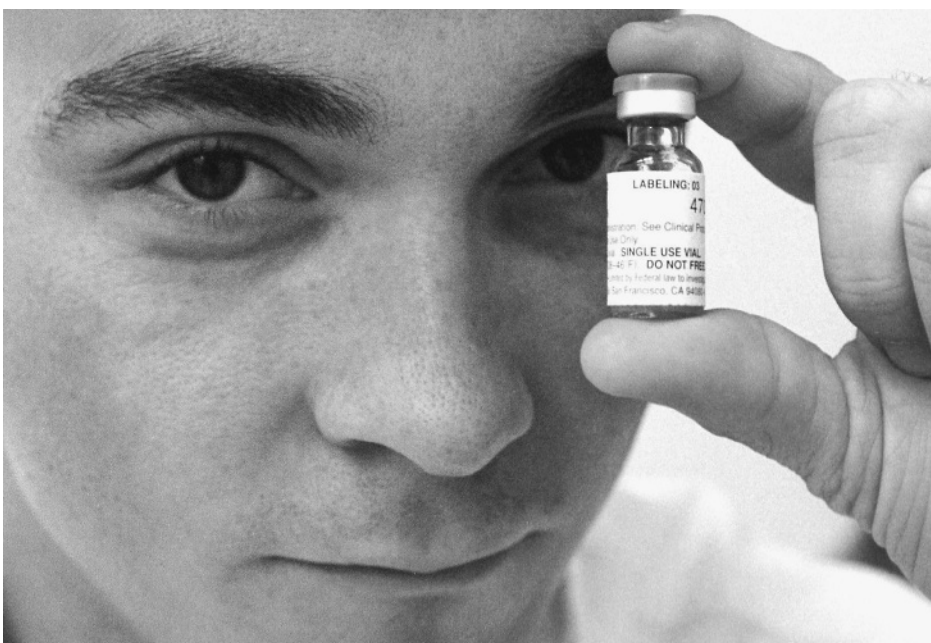
After it was proven safe in the first two phases of clinical trials, AIDSVAX became the first AIDS vaccine to enter the final phase of testing. Two large-scale trials were put into place to test the vac-

cine's ability to prevent HIV infection. The first involved fifty-four hundred volunteers from the United States, Canada, Puerto Rico, and the Netherlands, and the second involved twenty-five hundred intravenous drug users in Thailand. At regular intervals, the participants were screened for HIV to test whether the vaccine conferred any protection.

Both trials proved disappointing to the vaccine's creators. In February 2003, initial results from the first trial were released, followed in November 2003 by the initial results from the Thai trial. It was clear from the data that the HIV-infection rate for the volunteers who received AIDSVAX was not significantly different from the HIV-infection rate of those people who only received a placebo. Furthermore, the secondary goal of the vaccine—to slow the progression of AIDS in already infected individuals—also was not achieved. Both trials were halted.

Scientists now know why AIDSVAX failed. The vaccine was designed around gp120 because it was thought that this protein was essential to HIV and would stay fairly constant. As it turns out, the gp120 that is part of HIV can mutate into a number of forms, and the virus's ability to destroy the immune system is not impaired.

A young man who volunteered for one of two large-scale trials of AIDSVAX in 1999 displays a vial of the vaccine. Unfortunately, the vaccine proved ineffective in both trials.



Exploiting a Natural Immunity

While AIDSVAX was being tested, another very different vaccine was being developed. Doctors in Nairobi, Kenya, had noticed that about 5 percent of the two thousand prostitutes studied at an HIV clinic seemed to have developed a natural immunity against the virus. Though these women were repeatedly exposed to HIV, they remained uninfected. As the director of the clinic, Dr. Omu Anzale,

Researchers from the University of Nairobi in Kenya and Oxford University in England partnered to develop an AIDS vaccine. Here a Kenyan doctor conducts research at Oxford.

explained, "The very first exposure wasn't able to cause infection, but was able to prime their immune system."[41] In fact, T cell production in these women actually increased significantly. Somehow, these women's bodies were able to mount effective defenses against the initial onslaught of HIV. Furthermore, instead of being left with weakened immune systems that succumbed more readily to HIV upon the next exposure, these women seemed to be prepared for the virus and continued to win the battle against HIV.

Researchers at the United Kingdom's Oxford University and at the University of Nairobi, in partnership with the IAVI, developed a vaccine meant to mimic the resistance seen in the Nairobi women. The researchers designed the vaccine, named DNA-MVA, based on the A strain of HIV, the dominant strain found in Kenya and much of eastern Africa. DNA-MVA would introduce portions of HIV viral DNA into the recipient. Rather than using viral proteins directly as happened with AIDSVAX, with DNA-MVA, viral proteins are produced when the viral DNA enters the recipient's cells. The presence of these foreign proteins tricks the immune system into producing antibodies. This bit of trickery gives the immune system an advantage that might prevent real HIV from overpowering the immune system as efficiently.

To get around the problems caused by HIV's rapid mutation rate, the researchers picked twenty short DNA sequences that correspond to fragments of HIV proteins, rather than whole proteins. Smaller targets for the antibodies would presumably mutate to a lesser degree; furthermore, the variety of antibodies produced in response to the vaccine would ensure greater effectiveness in the long run.

Researchers noticed that some of the initially HIV-resistant prostitutes—if they stopped unsafe sexual practices for a time and then returned to work later—did develop HIV infection. From this, researchers concluded that constant exposure is key to HIV resistance. An effective vaccine, then, would probably include periodic booster treatment. All these observations were factored into the vaccine design.

Clinical trials using this vaccine began in 2000 in the United Kingdom and Kenya. In the first phase, the vaccine proved safe in

a small group of volunteers. By 2002, the second phase began, and the clinical trials had expanded to larger groups of volunteers. Preliminary results indicated that between 60 and 70 percent of the people injected with the vaccine show early signs that their immune systems might fend off HIV. If results continue to look promising, the final phase of clinical trials is slated to begin in Uganda, Kenya, and a third country not yet determined. If the final phase begins as planned, definitive results on whether the vaccine works or not would be expected at approximately the end of 2006.

A Single Solution

Even if DNA-MVA does prove effective, however, it will not have any effect on the spread of HIV in most of Europe and North America. This is because the DNA-MVA vaccine is specific for the A strain of HIV, whereas in Europe and North America, what is called the B strain of the virus is most common. In fact, there are five different strains of HIV altogether, and many of the vaccines in development are strain specific. Many of the vaccines currently in development are based on the B strain of HIV, but, as in the case of DNA-MVA, scientists around the globe have pushed ahead on vaccines for other HIV strains. For example, in India, where HIV research has yielded some positive results, officials announced in October 2003 that a vaccine specific for the form of HIV predominant in India, the C strain, had been developed and that human trials would follow.

Scientists think that either completely different vaccines would be needed to combat each of the other strains of HIV, or that the vaccine design would have to incorporate aspects of HIV that are not strain specific. To that end, some scientists, including Dr. Anne De Groot, chief executive officer of EpiVax, a vaccine development company in Providence, Rhode Island, are attempting to develop a vaccine that would train the immune system to target elements shared by all strains of HIV.

De Groot's plan takes the idea behind DNA-MVA—to use a large number of small protein fragments as templates for antibody production by the immune system—one step further: instead of lim-

A team of researchers works with bacterial cultures in their search for an effective AIDS vaccine.

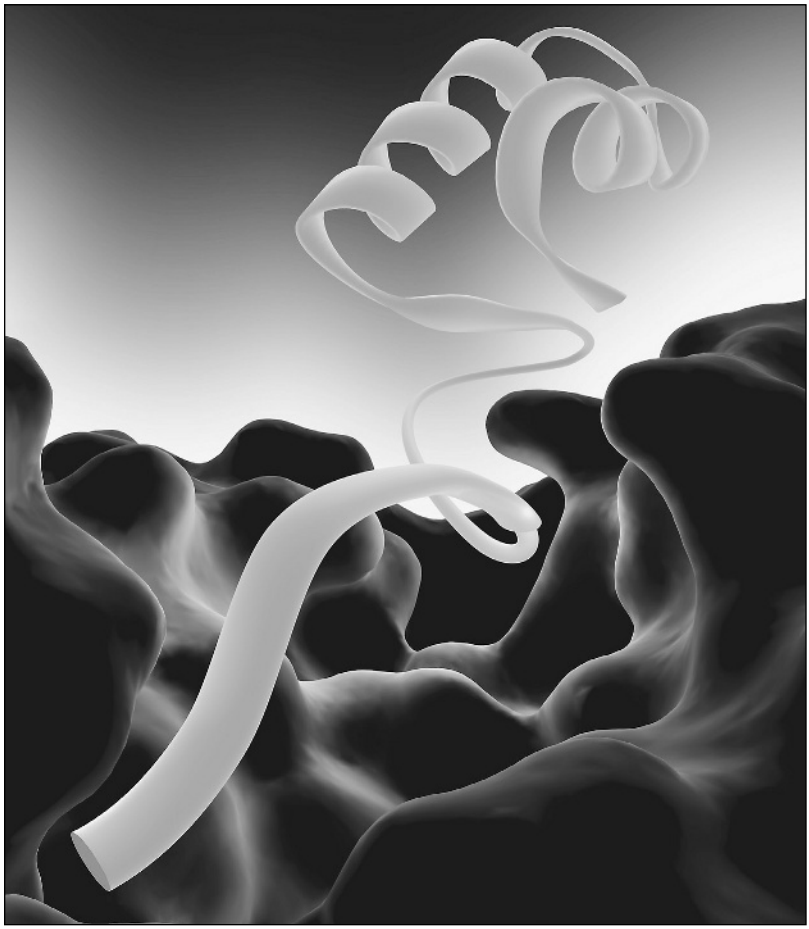
iting the protein fragments to one strain of HIV, De Groot plans to use those sequences that are common to all five HIV strains. According to De Groot, "There is something about these peptides [short protein fragments] the virus needs, something that really can't change very much, so they are conserved in all strains."[42]

De Groot's plan depends on a long-known fact about proteins. Proteins are long chains of amino acids that bend and curl to form three-dimensional structures. On the surface, the shape, or topography, of these three-dimensional structures is distinctive—though topography can be similar in related proteins, most of the time, different proteins take on different shapes. Antibodies are designed

to recognize specific topographies, so De Groot is attempting to design protein sequences that will fold to look like the topography of HIV. In this way, antibodies to HIV can be produced before actual infection takes place.

The process to find these sequences is long and tedious, mainly because it is not enough to identify short, shared protein fragments—the fragments must also assemble into a shape that can be recognized by the immune system. De Groot and her collaborators must

An illustration depicts a ribbon of protein. Some researchers are attempting to design protein sequences that look like HIV, thereby stimulating an immune response without actual infection.



find a handful of protein fragments that share structural similarities for the vaccine, but in the process, they must sort through more than sixty-five thousand potential fragments.

The fragments for De Groot's vaccine will be taken from an HIV protein called *env,* which is necessary for the virus to form the correct structure. When the prospective protein fragments are identified, DNA that codes for those fragments would be synthesized for the vaccine. In each molecule of vaccine, De Groot plans to put in at least one hundred fragments to enable an extensive immune response. Says De Groot, "There is a lot of evidence in HIV research that the broader the immune response you create, the better you will be able to contain the virus."[43]

In addition to a preventive application, De Groot envisions that this multistrain HIV vaccine could have a lot of benefit for people already infected with HIV. In research in animals, vaccination after antiretroviral drug therapy boosts the immune system. De Groot feels that this vaccine could help HIV-positive individuals build up their immune systems back to a level where therapy with antiretroviral drugs will no longer be necessary.

Many Paths

De Groot's efforts are being matched in other laboratories around the world. As of 2003, there were dozens of different HIV vaccines at different stages of clinical trials, with dozens more still in development, which altogether represented at least seven completely different scientific approaches to vaccine development. Scientists have found advantages and disadvantages to each approach, and no vaccine has yet been proven effective enough to proceed beyond clinical trials into actual usage. Said Dr. Wayne Koff, IAVI's senior vice president for research and development, "No one knows the magic recipe for an AIDS vaccine. The surest path is to try multiple approaches at once, comparing them against each other to see which are best."[44]

Indeed, scientists are hopeful that an HIV vaccine may finally be within reach. Even Gallo, whose earlier comments about an HIV vaccine were proven incorrect, is willing to voice his optimism. In 2002, he commented, "We'll solve this problem. I will never again

make specific predictions, but I believe that despite what some scientists think, we will find a vaccine. And I'll take on anyone with that bet."[45]

Still, the optimism is tempered with caution: Experts believe that, as of 2004, a usable HIV vaccine is still a decade away, and it is highly likely that the first vaccines will not be 100 percent effective. Additionally, as research into HIV and AIDS continues, scientists gain new understanding of the virus and its action mechanism. Through this greater knowledge, new and better solutions to the vaccine problem will be designed.

While the world waits for an HIV vaccine, scientists remain open to other alternatives. In fact, a great deal of research is aimed at other forms of prevention and treatment, as well as at clarifying the molecular characteristics of HIV. For example, when scientists finally understood the genetic diversity of HIV and its strains, a new focus was placed on the study of genetics—both of the virus and of the human victims—to find future treatments. Continued research designed to understand HIV more thoroughly is essential for improved treatment of HIV-positive individuals.

Chapter 6

The Future of AIDS

RESEARCH INTO HIV and AIDS has yielded many effective drugs and holds the promise for effective vaccines in the coming years. Experts fear, however, that the progress has resulted in one great disadvantage. The success of HAART and other treatment regimens in extending the lives of patients in developed countries has led to a complacency about HIV and AIDS. Says John Siegfried of the drug company industry group the Pharmaceutical Research and Manufacturers of America (PhRMA), "The fact that the death rate dropped 80 percent (in the United States) and the fact that people are living much longer is misinterpreted by many, many people as meaning AIDS is no longer a threat in the United States."[46] The problem of complacency is not limited to the United States. Said Derek Bodell, director of the National AIDS Trust in the United Kingdom, "I think we've now got a whole new generation who think that HIV is not the issue that it was for the generation before them."[47]

The truth, however, is that there is still no known cure for HIV infection, and even the drug regimens that have enjoyed a great deal of success have limitations. Between the potentially intolerable side effects and the possibility of a patient developing drug resistance, the current drug regimens are not universally effective. As far as the research has come since the beginning of the worldwide crisis, scientists continue to push forward down new avenues to contain and treat the disease. Some research is focused on the development of new classes of HAART drugs and new vaccines, while other studies aim to use gene therapy to treat HIV.

In addition, HIV education and prevention remain central issues, and many groups are trying to change the perception of HIV and the AIDS crisis around the world.

New and Better Antivirals

Through a global effort, the HAART drugs that have been successful in developed countries are now available in limited quantities in the developing world, with increased availability to come. Nevertheless, these drugs do not cure HIV infection or AIDS; in addition, up to 40 percent of HIV-positive individuals have either developed resistance to current multidrug cocktails or have had no success with the existing options. Said Ho, "Developing regimens that include anti-HIV drugs designed to attack the virus in new ways is one of the most pressing unmet medical needs in HIV therapeutics today."[48]

To that end, new classes of antiretroviral drugs are in development. One such class in particular, comprising drugs called entry inhibitors, shows the most promise. During HIV infection, the virus must first attach, or fuse, to a host cell. By preventing this fusion event, entry inhibitors block HIV from getting into cells and therefore prevent the infection from spreading.

The first drug in the entry inhibitor class is called Fuzeon, or T20. Fuzeon works by interfering with a protein called gp41, which is used by HIV to attach itself to proteins on the surface of a T cell. Normally, gp41 extends out from a virus particle to anchor the virus to the T cell's surface proteins. When Fuzeon is present, however, it binds those T cell surface proteins itself, thereby preventing gp41 from finding available targets and from entering the cell.

In July 2000, the results of a clinical trial of Fuzeon on seventy patients were revealed. HAART no longer worked in these patients, but of the forty-one who survived through the entire clinical trial, twenty-three of them saw their HIV levels cut to levels below detection. The drug's side effects also seemed tolerable, a major advantage over the toxicity of HAART. Later clinical trials that involved close to one thousand HIV-positive individuals worldwide confirmed Fuzeon's beneficial clinical effect. By March 2003, Fuzeon was approved by the FDA for use in the United States.

Though Fuzeon is beneficial to HIV-positive individuals at all stages of the disease, the drug is usually reserved for use after the immune system has become greatly damaged or other drug regimens have failed. A partial reason is that the drug requires high doses and patients can still suffer from such adverse side effects as injection site reactions, which both can lead to decreased patient compliance. The main reason, however, to hold off on Fuzeon is the drug's cost: According to Fuzeon's manufacturer, Roche Pharmaceuticals, the price of Fuzeon in the United States and Europe will exceed twenty thousand dollars annually per patient. This makes it the most expensive antiretroviral drug by far, and out of reach of many people even in the developed world. HIV victims in the developing world have little hope of being able to afford Fuzeon. Still, the drug represents success in a new area of HIV treatments and has already been joined by other prospective drugs

in the same class. Experts hope, as with previous HIV drugs, that the cost can be reduced with time and that entry inhibitors will become widely available, even in the developing world.

Turning HIV Against Itself

Entry inhibitors are but one of the new frontiers of HIV research. For the first time since AIDS was labeled a crisis, scientists have tools to use against HIV that promise significant breakthroughs—tools that were also completely unknown in the 1980s. For example, with the advent of advanced biotechnology, a new path to treat, and possibly cure, HIV infection has emerged in the form of gene therapy.

Gene therapy aims to treat illnesses by altering the genetics of diseased cells. The original goal of gene therapy was to treat diseases caused by specific defective genes by stimulating the body into incorporating new, working copies of the genes. However, VIRxSYS Corporation of Gaithersburg, Maryland, announced in 2003 that it would begin trying a drug called VRX496 that would work not by replacing a defective gene but by introducing a new gene that would neutralize one of HIV's key genes.

VRX496's developer, Dr. Boro Dropulic, realized that HIV's ability to integrate its own DNA into that of host cells meant that gene therapy might also work against this virus. His approach with VRX496 was to use a genetically engineered form of HIV in which the normal viral gene sequences were replaced by antisense DNA—sequences of DNA that are exactly opposite what they are in the normal virus—as well as DNA that coded for proteins called ribozymes. These ribozymes act like molecular scissors, cutting up and destroying genetic material from normal HIV but nothing else.

For VRX496 to work, T cells are harvested from a patient's body and infected with the therapeutic virus in the laboratory. T cells treated this way undergo the same processes as with HIV infection, except that VRX496 does not cause a disease. Eventually, the DNA of VRX496 is integrated into the host cells' DNA, and a VRX496 reservoir is created, just as it would be for HIV.

In theory, the presence of VRX496 turns T cells into "Trojan horses" that are ready to fight HIV. When these cells are returned

to the patient's body, some also get infected with HIV. Both the virus and VRX496 begin to replicate, one making normal HIV genetic material, and the other producing ribozymes to destroy that genetic material. As the process continues, HIV particles never properly form, and the disease progression is halted, perhaps permanently.

In trials in animals, VRX496 was proven safe, and scientists were able to deliver the therapeutic virus consistently to more than 90 percent of T cells harvested from humans. When the VRX496-infected T cells were tested in the laboratory, scientists observed a greater than 99 percent reduction in the replication of HIV.

In August 2003, VRX496 was administered to the first patient. By September, an independent data safety monitoring board declared that no adverse effects from the drug were detected in early clinical trials. Dropulic is optimistic and said in 2003 that "with the correct dose, it may be possible to cure patients with AIDS by creating an army of T cells that can inhibit and resist HIV infection."[49] Nevertheless, VRX496 faces many more hurdles and clinical trials before it can be used on a large scale. As seen with earlier therapies such as AIDSVAX, positive results from early trials do not guarantee success in large-scale clinical trials.

The Promise of Microbicides

Though Fuzeon and VRX496 are promising new therapies, the future of AIDS is not just about new treatments. As was true from the beginning, prevention and education remain vital to the efforts to contain this disease. The problem in much of the developing world remains that treatment with drugs does not prevent the transmission of HIV. This means that without changes in sexual

A University of Nairobi professor speaks to prostitutes about AIDS prevention. Researchers are working to develop a microbicide that would kill HIV during sexual activity.

behavior, HIV's spread will continue. The solution, at least in terms of reducing infection in women and therefore MTCT, seems to lie in developing preventive measures that are entirely within the control of women, who are at the greatest risk for contracting HIV. Said Gatell, "Prevention and therapy are no longer a dichotomy. They are complementary and should be implemented together and everywhere."[50]

One of these preventive measures, the female condom, has proven successful in some portions of the world in protecting women against HIV infection. Nevertheless, although it is an effective means of protection and can be obtained and used by women, the female condom still requires male cooperation in its use. Researchers have found that the same social and cultural barriers that prevent male condom use often come into play with female condoms.

To avoid the necessity of obtaining male cooperation, many researchers have turned to microbicides as a potential way to prevent HIV infection. Just as spermicides are topical solutions that kill sperm, microbicides work in similar ways to kill viruses and bacteria that cause a number of sexually transmitted diseases, including HIV.

Microbicides can be inserted into the vagina or rectum by women, and therefore do not require active cooperation from male partners. This is an advantage in societies where women lack the power to demand that their partners use protection. In addition, though spermicides by definition are contraceptives, many of the microbicides in development do not kill sperm. Women and couples who wish to conceive therefore need not risk HIV infection in order to have children.

Research into microbicides has yielded over fifty different products in various stages of clinical testing. Though the approach shows promise, some experts estimate that a $500 million investment will still be required to bring an effective microbicide to market. Moreover, extensive educational campaigns will be required to use the products successfully. The challenge for the future will be to provide these products to high-risk women in easy-to-use and affordable forms.

Combining Prevention and Therapy

Experts estimate that by 2010 there could be as many as 45 million additional people throughout the world who are HIV positive. The need for anti-HIV efforts therefore becomes even more pressing. In fact, by implementing safe sex practices and education about the virus, it is estimated that 29 million of these infections can be prevented. Says former American president Bill Clinton:

> It's pretty hard to justify or explain how we are on the verge of the worst epidemic in human history, that is preventable, where we have medicine that helps, replete with examples where the epidemic has been turned back. Some of the questions have to be answered by science, with continued progress in treatment therapies and the development of vaccines and cures. But the other questions have to be answered by politics and citizen action.[51]

Scientists urge that new forms of prevention must be actively investigated. For example, when sexually transmitted diseases other than HIV are aggressively treated, HIV infection rates seem to drop, as seen in the case of Tanzania where this approach has resulted in a 40 percent decrease in HIV infection. By simply giving people in rural areas of Tanzania access to a clinic with a trained staff and regular supply of drugs to treat STDs and encouraging people to visit the clinic regularly to receive health education, doctors were able to slow significantly the spread of HIV. Experts believe that similar programs in other areas are likely to achieve similar results.

Studies have also shown that promoting male circumcision reduces the risk of HIV infection by half. This is because the tissues of the foreskin include a type of cell that is particularly susceptible to HIV, and in an uncircumcised male, may provide an additional entry point for the virus. A similar situation exists among women, in that the cervix is particularly susceptible to HIV. In fact, cervical tissues are much more vulnerable to HIV than vaginal tissue; therefore, experts contend that women should be encouraged to use diaphragms as a protective measure against infection.

Current HAART drugs may also play a role in prevention of HIV infection, and these roles need to be investigated further. Some studies have suggested that the administration of certain antiretroviral

When Tanzania began a campaign to eradicate sexually transmitted diseases, HIV infection rates dropped. Sadly, this Tanzanian family, all HIV-positive, did not benefit from the program.

drugs after an individual has been exposed to HIV might inhibit infection. In essence, HAART drugs could be administered as a sort of "morning after" treatment after HIV exposure. Other studies are ongoing to determine whether antiretroviral drugs could block HIV transmission preemptively. According to Dr. Helene Gayle,

director of the HIV-AIDS program for the Bill and Melinda Gates Foundation, "HIV infection rates will drop when we implement programs based on sound scientific research and when prevention has the full backing of national leaders and is funded with adequate resources. . . . We must maintain a balance between biomedical options and behavioral prevention."[52]

Challenges

Part of the challenge that surrounds the AIDS crisis is to convince the world that the problem is not merely a medical issue or a public health issue—it has major implications on the economy, on crime, and on society. For example, 80 percent of those dying of AIDS are between twenty and fifty years old, the age group that normally holds the jobs, earns the money, and raises the families. As Bill Clinton says:

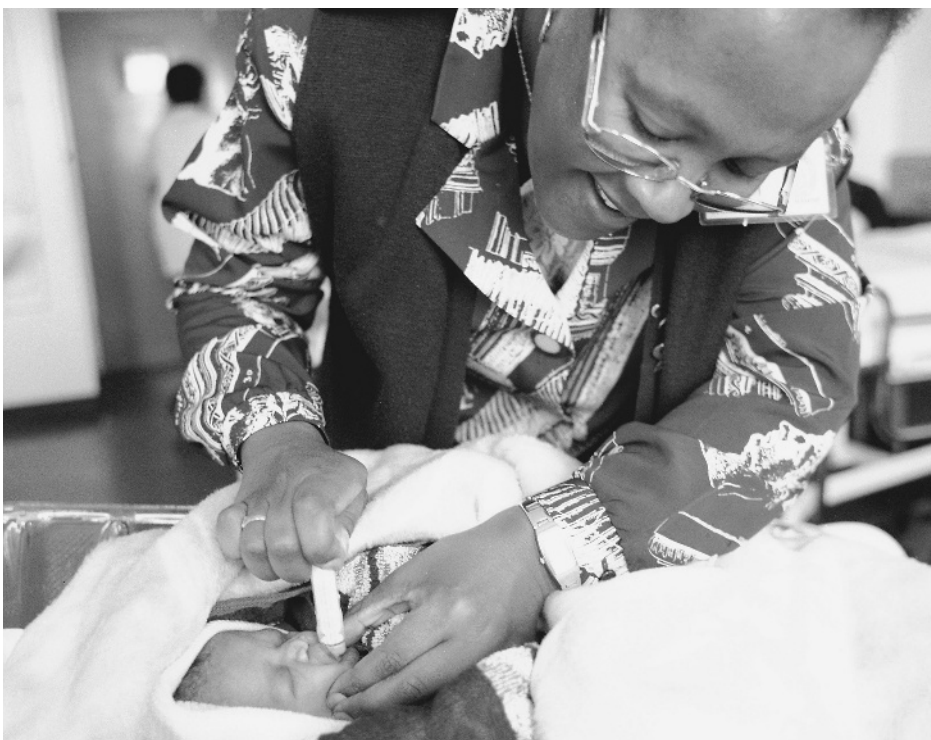
> In some nations, teachers, doctors, and nurses are dying faster than they can be trained, undermining health and education. In some places farmers and farm laborers are dying, cutting food production. Factory workers dying leads to reduction in productivity and growth. Police and military personnel dying undermines public order and safety. And most important, the mothers and fathers dying in droves undermines the fabric of families, social life, and civilization itself.[53]

The worldwide commitment to solving the problem of AIDS grows every day. Faced with the fact that as of 2003, only four hundred thousand people in developing countries had access to lifesaving antiretroviral drugs, on December 1, 2003, the World Health Organization (WHO) announced its "3 by 5" initiative, a commitment to provide antiretroviral treatments to 3 million additional people in developing countries by the year 2005. Initiatives of this magnitude would not be possible without the help of governments, private foundations, pharmaceutical companies, and researchers. Said Dr. Jack Chow, assistant director-general of WHO for HIV/AIDS, Tuberculosis, and Malaria, "The 3 by 5 framework is a plan for action by a broad alliance of nations, institutions, and committed people, including those living with HIV/AIDS. We urge all concerned to work to reach the 3 by 5 target as rapidly as possible."[54]

A key element of the 3 by 5 plan is that tens of thousands of community health care workers will be recruited to help with the administration of HIV drugs. By acknowledging that community involvement is vital for the success of an anti-HIV initiative, experts hope for greater adherence to treatment regimens and for more success in HIV prevention. In addition, the clear presence of HIV counselors in communities will presumably reduce the stigma for people living with the virus.

Still, it is important to keep in mind that though the 3 by 5 plan is an important step in achieving control over the AIDS crisis, it is not a complete solution. In 2003, the estimated number of people who needed but were not getting antiretroviral treatment was 5.9 million—nearly double the number covered by the WHO's plan. That number may even rise significantly by 2005. Furthermore, antiretroviral treatments must be taken for life, so the 3 by 5 plan cannot stop in 2005. As the WHO states in a 2003 report, "3 by 5 is just the beginning of antiretroviral therapy scale-up and strengthening of health systems."[55]

A baby whose mother is HIV-positive receives a dose of an anti-HIV drug shortly after birth. The worldwide commitment to solving the AIDS problem is growing daily.



These young AIDS patients wait in line for lunch at a Bangkok orphanage. The orphanage cares for HIV-positive babies abandoned by their parents.

Where Does the Solution Lie?

Even with the large amount of HIV research being conducted, it is still unclear whether any of the existing avenues of investigation will result in a definitive cure for this deadly disease. As experience has shown, even the most promising treatments may fail to realize their goals. Furthermore, many scientists feel that the AIDS crisis will get worse before it gets better and that this modern plague will remain deadly for several more generations.

The story of AIDS does not yet have an ending. Scientific authorities and global leaders continually work toward containing the spread of this disease and treating the victims more effectively. No one knows which approach will finally cure HIV infection or how long it will take to eradicate the disease; nevertheless, there is a great deal of hope in the twenty-first century that a cure for AIDS is not far off. Said Piot on World AIDS Day 2003, "There are few moral causes more important in the world today than to build the momentum which transforms scattered examples of success into a massive global movement to overcome AIDS. . . . We cannot delay."[56]

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Glossary

AIDS: Acquired immunodeficiency syndrome, the final and most severe stage of the disease caused by human immunodeficiency virus (HIV).

acute infection (also, acute stage of infection): The initial stage of HIV disease, characterized by mild flu-like symptoms as well as an initial decrease in helper T cell levels in the bloodstream.

antibodies: Proteins that play an active role in the immune response. Immune cells called B cells produce antibodies specific for a given infectious microbe, which then bind to the microbes in the bloodstream to flag them for destruction by other immune cells.

clinical latency: The second stage of HIV disease where the virus does not cause any harmful symptoms but continues to replicate.

clinical trial: Controlled tests of new drugs in development under strict government guidelines; typically, there are three phases of clinical trials: phase I, where the drug is tested on a small group for safety, phase II, where the drug is tested on a larger group for safety and effectiveness, and phase III, where the drug is tested on a large scale (typically thousands of volunteers) for effectiveness.

CMV: A type of infection caused by a virus called cytomegalovirus that can cause serious health complications in AIDS patients.

cryptococcosis: A fungus, commonly found in bird droppings, that can infect humans.

DNA: Deoxyribonucleic acid, the genetic material found in human cells.

entry inhibitors: A class of antiviral drug that prevents HIV from entering and infecting a host cell.

gene: A segment of DNA that codes for a particular protein.

gene therapy: A type of medical treatment in which deficiencies are corrected by replacing the defective gene in diseased cells.

HAART: Highly active antiretroviral therapy, formerly known as combination therapy; the practice of using a combination of antiretroviral drugs from different classes to control the progression of HIV disease. Administering more than one antiviral drug at once delays the occurrence of drug resistance.

hemophilia: An inherited disease in which the patient's blood lacks the proteins necessary for proper clotting.

HIV: Human immunodeficiency virus, the virus that causes AIDS.

immune deficiency: The condition in which the body's immune system is compromised or does not perform as well as it should.

immune system: The body's natural defense system against infection; includes T cells, B cells, macrophages, neutrophils, and other types of immune cells.

Kaposi's sarcoma: A normally benign cancer, characterized by lesions on the skin, which can cause serious health complications in AIDS patients.

microbicide: A topical solution that kills viruses and bacteria upon contact.

MTCT: Mother-to-child transmission, the transmission of HIV from a pregnant or nursing mother to her child through blood contact at birth or breast milk during feedings.

NNRTIs: Nonnucleoside reverse transcriptase inhibitors, a class of antiviral drug that interferes with the action of reverse transcriptase.

NRTIs: Nucleoside reverse transcriptase inhibitors, a class of antiviral drug that interferes with the action of reverse transcriptase by using chemicals that mimic nucleosides.

nucleoside: A building block of DNA.

opportunistic infection: An infection that occurs because the immune system is compromised.

PCP: *Pneumocystis carinii* pneumonia, a severe form of pneumonia often associated with AIDS cases.

protease inhibitors: A class of antiviral drug that interferes with a critical viral protein called protease.

resistance: The acquired ability of microorganisms to survive a drug that was formerly effective in killing them. Resistance occurs through mutations in the microorganisms' genes that result in a protection against the drug.

retrovirus: A class of virus characterized by the presence of reverse transcriptase; HIV belongs to this class of virus.

reverse transcriptase: An enzyme vital to the replication of HIV.

T cell: A type of immune cell. There are two types of T cells: killer T cells, which kill cells in the body that are diseased, and helper T cells, which make a template based on the way a foreign microbe looks to the body and present this template to B cells to use in the production of antibodies. Helper T cells are primarily affected by HIV infection.

toxoplasmosis: A rare parasitic disease that usually causes no negative symptoms in healthy people but can cause serious health complications in AIDS patients.

transfusion: The process by which blood from a donor is transferred intravenously to a recipient.

vaccine: A substance that, when administered into the body, elicits an immune response, usually against a particular disease-causing microorganism.

virus: An infective microorganism that only replicates inside a living host cell.

Organizations to Contact

AIDS Action
1906 Sunderland Pl. NW
Washington, DC 20036
(202) 530-8030
fax: (202) 530-8031
www.aidsaction.org

AIDS Action is composed of two distinct organizations: the AIDS Action Council and the AIDS Action Foundation. Together, these organizations brief public officials and lobby lawmakers on AIDS-related issues and support medical research and education efforts about HIV/AIDS.

AIDS Project Los Angeles (APLA)
The David Geffen Center 611 S. Kingsley Dr.
Los Angeles, CA 90005
(213) 201-1600
www.apla.org

AIDS Project Los Angeles (APLA) provides services, including prevention education, a food bank, professional dental care, housing assistance, mental health counseling, and case management, to men, women, and children living with HIV and AIDS in Los Angeles County. In addition, APLA provides bilingual information about HIV/AIDS to better serve the Hispanic community.

American Foundation for AIDS Research (amfAR)
120 Wall St. 13th Floor
New York, NY 10005-3908

(212) 806-1600
fax: (212) 806-1601
www.amfar.org

The American Foundation for AIDS Research supports HIV/AIDS research, AIDS prevention and treatment education, and advocates sound AIDS-related public policy. Since 1985, amfAR has invested close to $220 million in support of its mission and has funded grants to over two thousand research teams worldwide.

American Red Cross HIV/AIDS Education Office
1709 New York Ave. NW Suite 208
Washington, DC 20006
(202) 464-4077
www.redcross.org

The American Red Cross HIV/AIDS Education Office provides information about HIV/AIDS to all members of the community, including approaches designed to better educate minorities about this crisis.

AVERT
4 Brighton Rd. Horsham
West Sussex RH13 5BA UK
(+44) 01403 210202
www.avert.org

AVERT is a UK-based international charity that aims to "avert" HIV and AIDS around the world. The organization provides funding for medical research and comprehensive education materials, both in print and on the Internet.

Bill and Melinda Gates Foundation
PO Box 23350
Seattle, WA 98102
(206) 709-3140
e-mail: info@gatesfoundation.org
www.gatesfoundation.org

The Gates Foundation aims to improve health conditions throughout the world and to achieve equity in health care. The foundation's HIV/AIDS initiative provides funding to developing nations and to medical research to treat and contain the AIDS crisis more effectively.

CDC National Prevention Information Network (NPIN)
PO Box 6003
Rockville, MD 20849-6003
(800) 458-5231
fax: (888) 282-7681
e-mail: info@cdcnpin.org
www.cdcnpin.org

The CDC National Prevention Information Network pools, catalogs, and distributes information on HIV/AIDS, sexually transmitted diseases (STDs), and tuberculosis (TB) to organizations and individuals in international, national, state, and local settings.

International AIDS Trust
1627 K Street NW Suite 800
Washington, DC 20006
(202) 331-9622
fax: (202) 331-9765
e-mail: info@internationalaidstrust.org
www.aidstrust.org

The International AIDS Trust aims to mobilize global resources to prevent the spread of the AIDS crisis throughout the world. It provides public education, assists in the development and implementation of new AIDS policies, and brokers alliances between public and private resources to deal better with the problem of AIDS.

National Association of People with AIDS (NAPWA)
1413 K St. NW Suite 700
Washington, DC 20005
(202) 898-0414

fax: (202) 898-0435
e-mail: napwa@napwa.org
www.napwa.org

The goals of NAPWA are to represent all people living with and affected by HIV. The organization supports efforts to find a cure for HIV/AIDS and is involved in community AIDS education.

San Francisco AIDS Foundation
995 Market St. Suite 200
San Francisco, CA 94103
(415) 487-3000
fax: (415) 487-3009
www.sfaf.org

The San Francisco AIDS Foundation was founded in 1982 in response to the massive AIDS crisis in San Francisco. Its goals have grown from educating the community about HIV/AIDS to providing comprehensive services for people living with HIV, changing public policy to address the challenges posed by the AIDS crisis, and continuing AIDS education programs.

William J. Clinton Presidential Foundation HIV/AIDS Initiative
PO Box 1104
Little Rock, AR 72203
(501) 370-8000
fax: (501) 375-0512
e-mail: AIDS.info@clintonprograms.com
www.clintonpresidentialcenter.org

The Clinton Foundation HIV/AIDS Initiative assists developing nations to implement treatment and programs to prevent the spread of the AIDS epidemic. In particular, it partners with countries in Africa and the Caribbean to develop plans to increase HIV/AIDS care and treatment for underprivileged citizens.

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